Extracellular Vesicles from Human Adipose-Derived Mesenchymal Stem Cells: A Review of Common Cargos

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Accepted: 14 March 2021 / Published online: 26 April 2021
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Abstract
In recent years, the interest in adipose tissue mesenchymal cell–derived extracellular vesicles (AT-MSC-EVs) has increasingly grown. Numerous articles support the potential of human AT-MSC-EVs as a new therapeutic option for treatment of diverse diseases in the musculoskeletal and cardiovascular systems, kidney, skin, and immune system, among others. This approach makes use of the molecules transported inside of EVs, which play an important role in cell communication and in transmission of macromolecules. However, to our knowledge, there is no database where essential information about AT-MSC-EVs cargo molecules is gathered for easy reference. The aim of this study is to describe the different molecules reported so far in human AT-MSC-EVs, their main molecular functions, and biological processes in which they are involved. Recently, the presence of 591 proteins and 604 microRNAs (miRNAs) has been described in human AT-MSC-EVs. The main molecular function enabled by both proteins and miRNAs present in human AT-MSC-EVs is the binding function. Signal transduction and gene silencing are the biological processes in which a greater number of proteins and miRNAs from human AT-MSC-EVs are involved, respectively. In this review we highlight the therapeutics effects of AT-MSC-EVs related with their participation in relevant biological processes including inflammation, angiogenesis, cell proliferation, apoptosis and migration, among others.

Keywords Extracellular vesicles · Adipose-derived mesenchymal stem cells · miRNA · Proteomic · Exosome

Introduction

“Extracellular vesicle” (EV) is defined by the International Society for Extracellular Vesicles (ISEV) as the “generic term for particles naturally released from the cell that are delimited by a lipid bilayer and cannot replicate, i.e. do not contain a functional nucleus” [1, 2]. These particles contain a significant variety of proteins and RNAs that play important roles in cell-cell communication and in transmission of macromolecules between cells [3–6]. As this feature makes EVs a potential therapeutic approach for various diseases, interest in EV research has significantly increased over the last decade [4, 7]. Importantly, the profile of EV cargo depends on the cell type of origin [8]. In this sense, although a wide range of mammalian cells release EVs [4, 9], mesenchymal stem cells (MSC) are considered one of the most prolific producer cell types [10]. These vesicles are involved in the paracrine properties of MSCs [11–13].

MSCs can be harvested from different tissues, such as bone marrow (BM), adipose tissue (AT), dental pulp, and umbilical cord, among others [14, 15]. BM and AT are the most common sources of MSC for use in research [16–19]. Although BM-MSCs were the first identified MSC [20] type and have been extensively studied [21], AT-MSCs present remarkable advantages by comparison, including higher stability in culture conditions and lower senescence ratio [21]. In addition, the amount of MSC that can be obtained from this tissue, which is usually treated as waste material and discarded [22, 23], is significantly greater than that obtained from BM aspirates [21].

The interest in AT-MSC-EVs has increasingly grown, due to the wide range of AT sources and their relatively easy accessibility [9]. AT-MSC-EVs have been isolated not only from human cells, but also from mouse [24–32], rat [33, 34], pig [35–38], and rabbit [39, 40] cells. The main objective of
most published studies on AT-MSC-EVs was to evaluate their potential use as a new therapeutic approach to treat various diseases. Moreover, several of these publications did include an analysis of the molecules transported by the EVs, which is especially relevant to understanding their mechanism of action beyond their observable effects. Taken together, these studies have confirmed the presence of 591 proteins and 604 microRNA (miRNA) in the AT-MSC-EVs. Nevertheless, evaluation of effects of the molecules identified in the cargo focused solely on the disease or tissues under study. However, independent of the specific therapeutic use, the human AT-MSC-EVs are compositionally identical. Therefore, we anticipate that a review collecting together all available information about AT-MSC-EVs cargo and their function will be extremely useful for researchers working in this field.

ISEV recently published a guideline encouraging researchers to report their data to these field-specific databases to detect different studies describing the same molecules [1]. Thus, there is a great need for a well-organised review that collects all relevant information regarding molecules identified so far in AT-MSC-EVs cargo, and their biological activities. This will facilitate future research in this area. Currently, there are two online databases collecting the identified molecules in cargos of EVs derived from different cell types: http://microvesicles.org [41] (formerly http://www.exocarta.org [42]), and http://evpedia.info [43] (link currently unavailable). Both databases are good, reliable sources of information; however, the information available on AT-MSC-EVs cargo is still limited compared to that available on other cell types, such as T cells or prostate cancer cell EV cargos. Thus, this review will provide an updated source not only of identified AT-MSC-EVs cargo molecules, but also their functions and potential therapeutic applications.

Given the growing interest in the MSC-EVs, especially in those derived from AT, the purpose of this study is to provide the AT-MSC research community with a systematic review of publications reporting the cargo of AT-MSC-EVs, including an analysis of their molecular functions and the biological process in which they are involved.

Methods

A systematic literature search was conducted in the medical databases Pubmed and Web of Science, using the keywords “extracellular vesicles”, “exosome”, “adipose mesenchymal stem cells”, “cargo”, “protein” and “miRNA” without setting a time limit (last searched 6th September 2020). 112 articles published between 2006 and 2020 (inclusive) were reviewed. 48 of these articles were related to human AT-MSC-EV, and 17 to AT-MSC-EVs in other species. The remaining articles were about EVs in general and MSC-EVs from other sources. This study has included both articles that used the nomenclature recommended by ISEV (“EV”) [1] and those which used the terms “exosomes” and “microvesicles”. Given the number of publications that have used these terms during the past decades [2], we considered that the exclusion of them could lead to the loss of relevant information. In addition, although the isolation methods of EVs could have an impact on the cargo composition, it was not an exclusion criterion since there is no single optimal separation method [1].

Different nomenclatures such as adipose stem cells, adipose stromal cells, or adipose-derived stem cells, have been used to identify AT-MSCs. The keyword “adipose mesenchymal stem cells” allowed us to find articles in which authors used several of these nomenclatures. However, we may have missed some information due to this great variety of terms, and this may be a limitation of the present study.

Information regarding proteins (10 articles) and RNA (16 articles) detected in human AT-MSC-EVs was collected in two databases created in Excel (Microsoft Office Excel 2013; Microsoft Corporation, Redmond, WA, USA). Although an article was found in which the lipid content of human AT-MSC-ECs was measured, no more information about lipids was reported. Therefore, it was not possible to include a database of lipids in this review.

To standardise the data and facilitate the recognition of identified proteins, we used the recommended name and identifier code proposed by the Universal Protein Knowledgebase [44] (UniProtKB). This database includes additional information about the short and alternative names for some proteins, which allowed us to identify proteins described by certain authors with these terms. UniProtKB host institutions are the European Bioinformatics Institute (EMBL-EBI), the Swiss Institute of Bioinformatics, and the Protein Information Resource.

For RNA, we used the name of mature micro RNAs (miRNAs) and the code of identification recommended by the RNAcentral database [45] (https://rncentral.org/). This database is coordinated by EMBL-EBI and integrates information from 41 Expert Databases out of the 53 which constitute the RNAcentral Consortium. In addition, we used the miRBase database [46–51] to classify miRNAs by gene families. miRBase is one of the Expert Databases integrated in the RNAcentral database, and is managed by the University of Manchester. This database also includes information about the previous nomenclature of some miRNAs, which allowed us to correlate the previous mRNA name used by certain authors with the current recommended terminology.

Messenger RNA (mRNA) [52], transfer RNA (tRNA), small ribosomal RNA (rRNA), small nuclear RNA (snRNA), small nucleolar RNA (snoRNA) and small cytoplasmic RNA (scRNA) are also present in AT-MSC-EVs [53, 54]. However, there is less information available on these, therefore, it was possible to include the list of the main tRNAs and mRNA present in AT-MSC-EVs, but not the other types of RNA.
Finally, the web-based tool QuickGO [55] (https://www.ebi.ac.uk/QuickGO/), also managed by EMBL-EBI, was used to search the gene ontology (GO) terms of molecular functions and biological processes of detected proteins and miRNAs. An ontology consists of a set of specific concepts with well-defined relationships between them. The GO was developed by the GO Consortium, as a tool to unify the terminology used to describe the functions of genes and gene products [56].

Cargo of AT-MSC-EVs

Human AT-MSC-EVs transport different types of proteins [12, 52, 57–65], RNAs [11, 12, 53, 54, 59, 64–74] and lipids [58]. Due to this variety of cargo molecules, AT-MSC-EVs are involved in a wide range of biological functions including migration, immune regulation, cell proliferation, angiogenesis, osteocyte metabolism and nerve regeneration (for a comprehensive review see ref. 9) [9]. Their therapeutic potential is being tested for the treatment of diverse diseases in musculoskeletal [12, 52, 57, 65–67, 75–78] and cardiovascular systems [60, 72, 79–81], nephropathy [82, 83], skin [62, 68, 84–86] and immunology [71, 87], among others.

Surprisingly, we could only find one published study about the potential of human AT-MSC-EVs for the treatment of eye diseases [88], despite the fact that human AT-MSC and their conditioned media are being used in ophthalmology [89–99]. For instance, they are being used in 6 out of 403 registered clinical trials with these cells (ClinicalTrials.gov, NCT01808378, NCT02144103 and NCT02024269). In this study, human AT-MSC-EVs showed a protective effect both in vitro and in vivo in a mouse model of dry eye by suppressing the NLRP3 (NOD-like receptor family) inflammasome activation [88]. Moreover, the positive effects of mouse and rabbit AT-MSC-EVs have been demonstrated in in vivo models of laser-induced retinal injury [29] and diabetic retinopathy [40], respectively. In addition, rabbit AT-MSC-EVs seemed to take part in the viability regulation of cultured rabbit corneal stromal cells [39]. There are also several studies which have used human BM-MSC-EVs in ophthalmology, showing their beneficial effects in rat retinal and retinal ganglion cell cultures [100, 101] and in animal models of glaucoma [102, 103] and optic nerve crush [101]. As well as AT-MSC, BM-MSC have also been widely used in ophthalmology [104–113], including 8 out of 293 registered clinical trials with these cells (ClinicalTrials.gov, NCT01531348, NCT01562002, NCT01920867, NCT02325843, NCT02330978, NCT03011541, NCT03173638 and NCT03967275).

In the present review, we comprehensively describe the GO annotations of molecular functions and biological processes of each type of cargo reported in human AT-MSC-EVs.

Proteins

Proteomic analysis of EV cargo can enhance the knowledge of the functions and mechanisms of action in which these vesicles are involved [28]. To analyse AT-MSC-EV's protein content, researchers used a large variety of techniques such as mass spectrometry [12, 57, 59], antibody arrays [52, 60, 61, 65], Western Blotting [62, 63] and, to a lesser extent, rate immune nephelometry [58]. The EVs in those studies have been isolated by ultracentrifugation [12, 52, 57, 60, 65], filtration and ultracentrifugation [61, 63], commercial EV isolation kits [62], ultrafiltration [58], and affinity purification [59].

So far, 591 proteins have been identified (Table 1). Nevertheless, taking into account both the name and the gene or NCBI Reference Sequences mentioned in the articles, it was not possible to connect the proteins C-peptide, HCR/CRAM-A/B [52, 65], INSL3, macroglobulin [65], CA 19–9, MSHa, PPARg2, TGF-beta 5 and TRA-1-60/TRA-1-81, Pepsinogen I [52] with an UniprotKB code conclusively (Table 1). The presence of the protein families annexin, HSP 70 and HSP 90 has also been described [12] (Table 1). However, as the specific members of these three families were not reported, it was not possible to include them in the GO analyses.

The detailed molecular functions enabled by each protein are collected in Table 1S. The results showed that 577 proteins contribute to different molecular functions described by 710 GO terms. For the BMP-binding endothelial regulator protein, carcinoembryonic antigen-related cell adhesion molecule, coagulation factor XIII B chain and kremen protein 2, no GO annotations were found.

The main molecular functions enabled by the AT-MSC-EVs proteins are described by specific child terms (more specific terms) of binding: protein binding (80%), metal ion binding (20%), cytokine activity (18%), identical protein binding (17%), and signaling receptor binding (15%) (Fig. 1). Therefore, binding seems to be the most relevant molecular function of AT-MSC-EVs. The number of AT-MSC-EVs proteins involved in each molecular function is variable. Most described molecular functions are enabled by a limited number of proteins (less than 10), and only 11.6% of the functions are enabled by 10 or more proteins. They are related by specific terms of four molecular functions: binding, catalytic activity, structural molecular activity and molecular transducer activity (Fig. 2).

578 of the AT-MSC-EVs proteins identified play a role in different biological processes described by 3884 GO terms. For carcinoembryonic antigen-related cell adhesion molecule 7, layilin, and sex hormone-binding globulin, no GO annotations were found. The proteins involved in each process are...
| Protein                                                                 | Abbreviation          | UniProtKB | Gene       | Ref.    |
|-----------------------------------------------------------------------|-----------------------|-----------|------------|---------|
| 5'-AMP-activated protein kinase catalytic subunit alpha-1*            | AAPK1_HUMAN           | Q13131    | PRKAA1     | [65]    |
| 72 kDa type IV collagenase*                                           | MMP2_HUMAN            | P08253    | MMP2       | [52]    |
| A disintegrin and metalloproteinas with thrombospondin motifs 1*     | ATS1_HUMAN            | Q9UH18    | ADAMTS1    | [65]    |
| A disintegrin and metalloproteinas with thrombospondin motifs 2*     | ATS2_HUMAN            | O95450    | ADAMTS2    | [65]    |
| A disintegrin and metalloproteinas with thrombospondin motifs 4*     | ATS4_HUMAN            | Q75173    | ADAMTS4    | [52, 65]|
| A disintegrin and metalloproteinas with thrombospondin motifs 17*    | ATS17_HUMAN           | Q8TE56    | ADAMTS17   | [52]    |
| A disintegrin and metalloproteinas with thrombospondin motifs 18*    | ATS18_HUMAN           | Q8TE60    | ADAMTS18   | [65]    |
| A disintegrin and metalloproteinas with thrombospondin motifs 19*    | ATS19_HUMAN           | Q8TE59    | ADAMTS19   | [52, 65]|
| Acidic fibroblast growth factor intracellular-binding protein        | FIBP_HUMAN            | O43427    | FIBP       | [57]    |
| Activated CDC42 kinase 1*                                             | ACK1_HUMAN            | Q07912    | TNK2       | [52, 65]|
| Activin receptor type-1B*                                             | ACV1B_HUMAN           | P36896    | ACVR1B     | [65]    |
| Activin receptor type-2B*                                             | AVR2B_HUMAN           | Q13705    | ACVR2B     | [65]    |
| Adenomatous polyposis coli protein*                                   | APC_HUMAN             | P25054    | APC        | [52, 65]|
| Adhesion G protein-coupled receptor B1*                               | AGRB1_HUMAN           | O14514    | ADGRB1     | [52]    |
| Adhesion G protein-coupled receptor E5*                               | AGRE5_HUMAN           | P48960    | ADGRE5     | [52]    |
| ADP-ribosyl cyclase/cyclic ADP-ribose hydrolase 1*                    | CD38_HUMAN            | P28907    | CD38       | [65]    |
| Agouti-related protein*                                               | AGRP_HUMAN            | O00253    | AGRP       | [52, 65]|
| Alkaline phosphatase, placental type*                                 | PPB1_HUMAN            | P05187    | ALPP       | [52]    |
| Alpha-1-acid glycoprotein 1*                                          | A1AG1_HUMAN           | P02763    | ORM1       | [65]    |
| Alpha-1-antitrypsin                                                  | A1AT_HUMAN            | P01009    | SERPINA1   | [58]    |
| Alpha-1B-glycoprotein*                                                | A1BG_HUMAN            | P04217    | A1BG       | [52, 65]|
| Alpha-fetoprotein*                                                    | FETA_HUMAN            | P02771    | AFP        | [52, 59]|
| Alpha-lactalbumin                                                    | LALBA_HUMAN           | P00709    | LALBA      | [52, 65]|
| Aminopeptidase N*                                                    | AMPN_HUMAN            | P15144    | ANPEP      | [65]    |
| Angiopoietin-1                                                        | ANGP1_HUMAN           | Q15389    | ANGPT1     | [52, 65]|
| Angiopoietin-1 receptor*                                              | TIE2_HUMAN            | Q02763    | TEK        | [61]    |
| Angiopoietin-4                                                        | ANGP4_HUMAN           | Q9Y264    | ANGPT4     | [65]    |
| Angiopoietin-related protein 1*                                       | ANGL1_HUMAN           | Q95841    | ANGPTL1    | [52]    |
| Angiopoietin-related protein 2*                                       | ANGL2_HUMAN           | Q9UKU9    | ANGPTL2    | [65]    |
| Angiopoietin-related protein 7*                                       | ANGL7_HUMAN           | O43827    | ANGPTL7    | [60]    |
| Angiotatin (cleaved from plasminogen)                                 | PLMN_HUMAN            | P00747    | PLG        | [52, 60, 61]|
| Annexin*                                                              |                       |           | –          | [12]    |
| Annexin A5                                                            | ANXA5_HUMAN           | P08758    | ANXA5      | [59]    |
| Annexin A7                                                            | ANXA7_HUMAN           | P20073    | ANXA7      | [65]    |
| Antileukoproteinase*                                                  | SLPI_HUMAN            | P03973    | SLPI       | [52]    |
| Apelin receptor*                                                      | APLIN_HUMAN           | P35414    | APLIN      | [60]    |
| Apolipoprotein A-IV*                                                  | APOA4_HUMAN           | P06727    | APOA4      | [52, 65]|
| Apolipoprotein B-100*                                                 | APOB_HUMAN            | P04114    | APOB       | [59, 65]|
| Apolipoprotein C-1*                                                   | APOC1_HUMAN           | P02654    | APOC1      | [65]    |
| Apolipoprotein C-2*                                                   | APOC2_HUMAN           | P02655    | APOC2      | [65]    |
| Apolipoprotein E*                                                     | APOE_HUMAN            | P02649    | APOE       | [65]    |
| Apolipoprotein M*                                                     | APM_HUMAN             | O95445    | APM        | [65]    |
| Apoptosis regulator BAX*                                              | BAX_HUMAN             | Q07812    | BAX        | [52]    |
| Artemin                                                               | ARTN_HUMAN            | Q5T4W7    | ARTN       | [52, 60, 65]|

**Table 1** Proteins detected in human AT-MSC-EVs in alphabetical order
| Protein | Abbreviation | UniProtKB | Gene | Ref. |
|--------|--------------|-----------|------|-----|
| Aspartyl/asparaginyl beta-hydroxylase* | ASPH_HUMAN | Q12797 | ASPH | [52, 65] |
| Basal cell adhesion molecule | BCAM_HUMAN | P50895 | BCAM | [57] |
| BCL2/adenovirus E1B 19 kDa protein-interacting protein 2* | BNIP2_HUMAN | Q12982 | BNIP2 | [52, 65] |
| Beta-2-microglobulin* | B2MG_HUMAN | P61769 | B2M | [65] |
| Beta-Ala-His dipeptidase* | CNDP1_HUMAN | Q96KN2 | CNDP1 | [52, 65] |
| Beta-defensin 1* | DEFB1_HUMAN | P60022 | DEFB1 | [52] |
| Beta-defensin 4A | DEFB4A_HUMAN | O15263 | DEFB4A | [65] |
| Beta-endorphin (Pro-opiomelanocortin)* | COL1_HUMAN | P01189 | POMC | [52, 65] |
| BMP-binding endothelial regulator protein* | BMPER_HUMAN | Q8N8U9 | BMPER | [52, 60, 65] |
| Bone morphogenic protein 1 | BMP1_HUMAN | P13497 | BMP1 | [57] |
| Bone morphogenic protein 3* | BMP3_HUMAN | P12645 | BMP3 | [65] |
| Bone morphogenic protein 4* | BMP4_HUMAN | P12644 | BMP4 | [52, 65] |
| Bone morphogenic protein 5* | BMP5_HUMAN | P22003 | BMP5 | [52] |
| Bone morphogenic protein 6* | BMP6_HUMAN | P22004 | BMP6 | [65] |
| Bone morphogenic protein 7* | BMP7_HUMAN | P18075 | BMP7 | [52, 65] |
| Bone morphogenic protein 8B* | BMP8B_HUMAN | P34820 | BMP8B | [52] |
| Bone morphogenic protein receptor type-1A | BMR1A_HUMAN | P36894 | BMR1A | [57] |
| Bone morphogenic protein receptor type-1B* | BMR1B_HUMAN | O00238 | BMR1B | [65] |
| Bone morphogenic protein receptor type-2 | BMRP2_HUMAN | Q13873 | BMRP2 | [57] |
| Brain-derived neurotrophic factor* | BDNF_HUMAN | P23560 | BDNF | [65] |
| CA 19–9 | – | – | ST6GALNAC (partly synthesized by) | [52] |
| Cadherin-1 | CADH1_HUMAN | P12830 | CDH1 | [57] |
| Cadherin-2 | CADH2_HUMAN | P19022 | CDH2 | [57] |
| Cadherin-5 | CAD5_HUMAN | P33151 | CDH5 | [57] |
| Cadherin-11 | CAD11_HUMAN | P55287 | CDH11 | [57] |
| Cadherin-13 | CAD13_HUMAN | P55290 | CDH13 | [57] |
| Cadherin-related family member 2 | CDHR2_HUMAN | Q9BYE9 | CDHR2 | [57] |
| Cadherin-related family member 5 | CDHR5_HUMAN | Q9HBB8 | CDHR5 | [57] |
| Calbindin | CALB1_HUMAN | P05937 | CALB1 | [52, 65] |
| Calcitonin | CALC_HUMAN | P01258 | CALCA | [52] |
| Calreticulin | CALR_HUMAN | P27797 | CALR | [65] |
| Calsyntenin-1 | CSTN1_HUMAN | Q9G985 | CLSTN1 | [65] |
| Carboxypeptidase N subunit 2* | CPN2_HUMAN | P22792 | CPN2 | [52, 65] |
| Carcinoembryonic antigen-related cell adhesion molecule 7* | CEAM7_HUMAN | Q14002 | CEACAM7 | [65] |
| Caspase-3 | CASP3_HUMAN | P42574 | CASP3 | [65] |
| Caspase-8 | CASP8_HUMAN | Q14790 | CASP8 | [52] |
| Cathepsin B | CATB_HUMAN | P07858 | CTSB | [65] |
| Cathepsin D | CATD_HUMAN | P07339 | CTSD | [65] |
| C-C chemokine receptor type 1* | CCR1_HUMAN | P32246 | CCR1 | [52] |
| C-C chemokine receptor type 2* | CCR2_HUMAN | P41597 | CCR2 | [65] |
| C-C chemokine receptor type 3* | CCR3_HUMAN | P51677 | CCR3 | [52] |
| C-C chemokine receptor type 4* | CCR4_HUMAN | P51679 | CCR4 | [65] |
| C-C chemokine receptor type 5* | CCR5_HUMAN | P51681 | CCR5 | [65] |
| C-C chemokine receptor type 6* | CCR6_HUMAN | P51684 | CCR6 | [65] |
| C-C chemokine receptor type 7* | CCR7_HUMAN | P32248 | CCR7 | [65] |
| C-C chemokine receptor type 9* | CCR9_HUMAN | P51686 | CCR9 | [65] |
| C-C motif chemokine 1* | CCL1_HUMAN | P22362 | CCL1 | [61, 65] |
| C-C motif chemokine 2* | CCL2_HUMAN | P13500 | CCL2 | [52] |
| Protein                             | Abbreviation           | UniProtKB | Gene   | Ref.  |
|------------------------------------|------------------------|-----------|--------|-------|
| C-C motif chemokine 3*             | CCL3_HUMAN             | P10147    | CCL3   | [65]  |
| C-C motif chemokine 4*             | CCL4_HUMAN             | P13236    | CCL4   | [52]  |
| C-C motif chemokine 5*             | CCL5_HUMAN             | P13501    | CCL5   | [65]  |
| C-C motif chemokine 7*             | CCL7_HUMAN             | P80098    | CCL7   | [61]  |
| C-C motif chemokine 8*             | CCL8_HUMAN             | P80075    | CCL8   | [61, 65] |
| C-C motif chemokine 13*            | CCL13_HUMAN            | Q99616    | CCL13  | [61, 65] |
| C-C motif chemokine 14*            | CCL14_HUMAN            | Q16627    | CCL14  | [52, 60, 65] |
| C-C motif chemokine 16*            | CCL16_HUMAN            | O15467    | CCL16  | [65]  |
| C-C motif chemokine 18*            | CCL18_HUMAN            | P55774    | CCL18  | [52]  |
| C-C motif chemokine 19*            | CCL19_HUMAN            | Q99731    | CCL19  | [52]  |
| C-C motif chemokine 21*            | CCL21_HUMAN            | O00585    | CCL21  | [65]  |
| C-C motif chemokine 22*            | CCL22_HUMAN            | O00626    | CCL22  | [65]  |
| C-C motif chemokine 26*            | CCL26_HUMAN            | Q9Y258    | CCL26  | [65]  |
| C-C motif chemokine 27*            | CCL27_HUMAN            | Q9Y4X3    | CCL27  | [52]  |
| C-C motif chemokine 28*            | CCL28_HUMAN            | Q9NRJ3    | CCL28  | [52, 60] |
| CD166 antigen                      | CD166_HUMAN            | Q13740    | ALCAM  | [52, 65] |
| CD27 antigen                       | CD27_HUMAN             | P26842    | CD27   | [65]  |
| CD44 antigen                       | CD44_HUMAN             | P16070    | CD44   | [12, 57, 65] |
| CD59 glycoprotein*                 | CD59_HUMAN             | P13987    | CD59   | [52]  |
| CD63 antigen                       | CD63_HUMAN             | P08962    | CD63   | [12]  |
| Cdc42-interacting protein 4        | CIP4_HUMAN             | Q15642    | TRIP10 | [57]  |
| Cell division control protein 42 homolog | CDC42_HUMAN           | P60953    | CDC42  | [57]  |
| Cerberus                           | CER1_HUMAN             | O95813    | CER1   | [65]  |
| Ceruloplasmin                      | CERU_HUMAN             | P00450    | CP     | [52, 65] |
| Chitinase-3-like protein 1*        | CH3L1_HUMAN            | P36222    | CH3L1  | [52, 65] |
| Chordin-like protein 2*            | CRDL2_HUMAN            | Q6WN34    | CHRDL2 | [52]  |
| Ciliary neurotrophic factor receptor subunit alpha* | CNTFR_HUMAN           | P26992    | CNTFR  | [52]  |
| Ciliary neurotrophic factor*       | CNTF_HUMAN             | P26441    | CNTF   | [52, 65] |
| Clusterin                          | CLUS_HUMAN             | P10909    | CLU    | [52]  |
| Coagulation factor XIII A chain    | F13A_HUMAN             | P00488    | F13A1  | [52]  |
| Coagulation factor XIII B chain    | F13B_HUMAN             | P05160    | F13B   | [65]  |
| Collagen alpha-1(I) chain          | CO1A1_HUMAN            | P02452    | COL1A1 | [57]  |
| Collagen alpha-1(III) chain        | CO3A1_HUMAN            | P02461    | COL3A1 | [57]  |
| Collagen alpha-1(IV) chain         | CO4A1_HUMAN            | P02462    | COL4A1 | [57]  |
| Collagen alpha-1(V) chain          | CO5A1_HUMAN            | P20908    | COL5A1 | [57]  |
| Collagen alpha-1(VI) chain         | CO6A1_HUMAN            | P12109    | COL6A1 | [57]  |
| Collagen alpha-1(VII) chain        | CO7A1_HUMAN            | Q02388    | COL7A1 | [57]  |
| Collagen alpha-1(XII) chain        | COCA1_HUMAN            | Q99715    | COL12A1| [57]  |
| Collagen alpha-1(XV) chain         | COFA1_HUMAN            | P39059    | COL15A1| [57]  |
| Collagen alpha-2(2) chain          | CO1A2_HUMAN            | P08123    | COL1A2 | [57]  |
| Collagen alpha-2(IV) chain         | CO4A2_HUMAN            | P08572    | COL4A2 | [57]  |
| Collagen alpha-2(V) chain          | CO5A2_HUMAN            | P05997    | COL5A2 | [57]  |
| Collagen alpha-2(VI) chain         | CO6A2_HUMAN            | P12110    | COL6A2 | [57]  |
| Collagen alpha-3(3) chain          | CO6A3_HUMAN            | P12111    | COL6A3 | [57]  |
| Collagenase 3*                     | MMP13_HUMAN            | P45452    | MMP13  | [65]  |
| Complement C2*                     | CO2_HUMAN              | P06681    | C2     | [52, 65] |
| Complement C3*                     | CO3_HUMAN              | P01024    | C3     | [65]  |
| Complement C5*                     | CO5_HUMAN              | P01031    | C5     | [65]  |
| Complement factor H-related protein 2* | FHR2_HUMAN           | P36980    | CFHR2  | [65]  |
| Protein                               | Abbreviation | UniProtKB | Gene       | Ref. | |
|--------------------------------------|--------------|-----------|------------|------| |
| Corticosteroid 11-beta-dehydrogenase isozyme 1* | DH11_HUMAN   | P28845    | HSD11B1    | [65] |
| Corticosteroid-binding globulin      | CBG_HUMAN    | P08185    | SERPINA6   | [52] |
| C-peptide***                        | --           | --        | INS        | [52, 65] |
| C-reactive protein*                  | CRP_HUMAN    | P02741    | CRP        | [65] |
| Creatine kinase B-type*              | KCRB_HUMAN   | P12277    | CKB        | [52, 65] |
| CREB-binding protein*                | CBP_HUMAN    | Q92793    | CREBBP     | [52] |
| Cryptic protein                      | CFC1_HUMAN   | P0CG37    | CFC1       | [52, 65] |
| C-X-C chemokine receptor type 6*     | CXCR6_HUMAN  | O00574    | CXCR6      | [65] |
| C-X-C motif chemokine 2*             | CXCL2_HUMAN  | P19875    | CXCL2      | [52, 60, 65] |
| C-X-C motif chemokine 5*             | CXCL5_HUMAN  | P42830    | CXCL5      | [65] |
| C-X-C motif chemokine 9*             | CXCL9_HUMAN  | Q07325    | CXCL9      | [52] |
| C-X-C motif chemokine 10*            | CXL10_HUMAN  | P02778    | CXL10      | [65] |
| C-X-C motif chemokine 11*            | CXL11_HUMAN  | O14625    | CXL11      | [61, 65] |
| C-X-C motif chemokine 16*            | CXL16_HUMAN  | Q9H2A7    | CXL16      | [61, 65] |
| Cyclin-dependent kinase inhibitor 1* | CDN1A_HUMAN  | P38936    | CDKN1A     | [65] |
| Cystatin A                           | CYTA_HUMAN   | P01040    | CSTA       | [65] |
| Cytokine receptor common subunit gamma* | IL2RG_HUMAN | P31785    | IL2RG      | [52, 65] |
| Cytoplasmic tyrosine-protein kinase BMX* | BMX_HUMAN   | P51813    | BMX        | [65] |
| Cytoxic and regulatory T cell molecule* | CRTAM_HUMAN | O95727    | CRTAM      | [65] |
| Cytotoxic T lymphocyte protein 4*    | CTLA4_HUMAN  | P16410    | CTLA4      | [52, 65] |
| DAN domain family member 5*          | DAND5_HUMAN  | Q8N907    | DAND5      | [65] |
| Decorin                              | PG52_HUMAN   | P07585    | DCN        | [65] |
| Dentin matrix acidic phosphoprotein 1* | DMP1_HUMAN  | Q13316    | DMP1       | [65] |
| Dermcidin                            | DCD_HUMAN    | P81605    | DCD        | [59] |
| Dickkopf-related protein 1*          | DKK1_HUMAN   | O94907    | DKK1       | [65] |
| Dickkopf-related protein 3*          | DKK3_HUMAN   | Q9UBP4    | DKK3       | [65] |
| Dickkopf-related protein 4*          | DKK4_HUMAN   | Q9UBT3    | DKK4       | [52] |
| Discoidin domain-containing receptor 2* | DDR2_HUMAN  | Q16832    | DDR2       | [52] |
| Discoidin, CUB and LCCL domain-containing protein 2* | DCBD2_HUMAN | Q96PD2 | DCBLD2 | [65] |
| Echinoderm microtubule-associated protein-like 2* | EMAL2_HUMAN | O95834    | EML2       | [52, 65] |
| Ectodysplasin-A*                     | EDA_HUMAN    | Q92838    | EDA        | [60, 65] |
| Ectonucleotide pyrophosphatase/      | ENPP2_HUMAN  | Q13822    | ENPP2      | [52] |
| phosphodiesterase family member 2*  | ENIL3_HUMAN  | O43854    | ENIL3      | [57] |
| EGF-like repeat and discoidin 1-like domain-containing protein 3 | EF1A1_HUMAN | P68104 | EEF1A1 | [12] |
| Elongation factor 1-alpha 1          | EF2_HUMAN    | P13639    | EEF2       | [12] |
| Elongation factor 2*                 | EE2_HUMAN    | P13639    | EEF2       | [12] |
| Embryonic growth/differentiation factor 1* | GDF1_HUMAN  | P27539    | GDF1       | [52] |
| Endoglin                             | EGNL_HUMAN   | P17813    | ENG        | [52] |
| Endostatin (cleaved from Collagen alpha-1(XVIII) chain) | COIA1_HUMAN | P39060 | COL18A1 | [52, 57, 60, 65] |
| Endothelial cell-selective adhesion molecule* | ESAM_HUMAN  | Q96AP7    | ESAM       | [65] |
| Endothelin-1 receptor*               | EDNRA_HUMAN  | P25101    | EDNRA      | [52, 65] |
| Eotaxin                              | ECL11_HUMAN  | P51671    | CCL11      | [65] |
| Ephrin type-A receptor 4*            | EPHA4_HUMAN  | P54764    | EPHA4      | [52] |
| Ephrin type-A receptor 6*            | EPHA6_HUMAN  | Q9UF33    | EPHA6      | [65] |
| Ephrin type-A receptor 8*            | EPHA8_HUMAN  | P29322    | EPHA8      | [65] |
| Ephrin type-B receptor 4*            | EPHB4_HUMAN  | P54760    | EPHB4      | [65] |
| Epidermal growth factor receptor*     | EGFR_HUMAN   | P00533    | EGFR       | [57, 65] |
| Epidermal growth factor receptor substrate 15-like 1 | EP15R_HUMAN | Q9UBC2    | EPS15L1    | [57] |

* Denotes essential proteins.
| Protein                                                                 | Abbreviation   | UniProtKB | Gene   | Ref.  |
|------------------------------------------------------------------------|----------------|-----------|--------|-------|
| Epithelial cell adhesion molecule*                                      | EPCAM_HUMAN    | P16422    | EPCAM  | [65]  |
| Erythropoietin                                                          | EPO_HUMAN      | P01588    | EPO    | [52]  |
| Erythropoietin receptor                                                 | EPOR_HUMAN     | P19235    | EPOR   | [65]  |
| E-Selectin                                                             | LYAM2_HUMAN    | P16581    | SELE   | [52]  |
| EVI5-like protein                                                      | EVI5L_HUMAN    | Q96CN4    | EVI5L  | [52]  |
| FAS-associated death domain protein*                                   | FADD_HUMAN     | Q13158    | FADD   | [65]  |
| Fatty acid-binding protein 5                                            | FABP5_HUMAN    | Q01469    | FABP5  | [59]  |
| Ferritin light chain*                                                  | FRIL_HUMAN     | P02792    | FTL    | [65]  |
| Fetuin-B                                                               | FETUB_HUMAN    | Q9UGM5    | FETUB  | [65]  |
| Fibrinogen-like protein 1*                                              | FGL1_HUMAN     | Q08830    | FGL1   | [52, 65] |
| Fibrinopeptide A (cleaved from Fibrinogen alpha chain)                 | FIBA_HUMAN     | P02671    | FGA    | [52]  |
| Fibroblast growth factor 2*                                             | FGF2_HUMAN     | P09038    | FGF2   | [57, 65] |
| Fibroblast growth factor 4*                                             | FGF4_HUMAN     | P08620    | FGF4   | [61]  |
| Fibroblast growth factor 5*                                             | FGF5_HUMAN     | P12034    | FGF5   | [52]  |
| Fibroblast growth factor 6*                                             | FGF6_HUMAN     | P10767    | FGF6   | [65]  |
| Fibroblast growth factor 8*                                             | FGF8_HUMAN     | P55075    | FGF8   | [65]  |
| Fibroblast growth factor 10*                                            | FGF10_HUMAN    | O15520    | FGF10  | [52]  |
| Fibroblast growth factor 11*                                            | FGF11_HUMAN    | Q92914    | FGF11  | [52]  |
| Fibroblast growth factor 12*                                            | FGF12_HUMAN    | P61328    | FGF12  | [65]  |
| Fibroblast growth factor 13*                                            | FGF13_HUMAN    | Q92913    | FGF13  | [52]  |
| Fibroblast growth factor 16*                                            | FGF16_HUMAN    | O43320    | FGF16  | [52]  |
| Fibroblast growth factor 17*                                            | FGF17_HUMAN    | O60258    | FGF17  | [52, 65] |
| Fibroblast growth factor 18*                                            | FGF18_HUMAN    | O76093    | FGF18  | [52, 65] |
| Fibroblast growth factor 20*                                            | FGF20_HUMAN    | Q9NP95    | FGF20  | [52, 65] |
| Fibroblast growth factor 21*                                            | FGF21_HUMAN    | Q9NSA1    | FGF21  | [65]  |
| Fibroblast growth factor receptor 1                                     | FGFR1_HUMAN    | P11362    | FGFR1  | [57]  |
| Fibroblast growth factor receptor 3*                                    | FGFR3_HUMAN    | P22607    | FGFR3  | [65]  |
| Fibroblast growth factor receptor 4                                     | FGFR4_HUMAN    | P22455    | FGFR4  | [57]  |
| Fibroblast growth factor-binding protein 1*                            | FGFP1_HUMAN    | Q14512    | FGFBP1 | [65]  |
| Fibronectin                                                            | FINC_HUMAN     | P02751    | FN1    | [52, 57] |
| Filaggrin-2                                                            | FILA2_HUMAN    | Q5D862    | FLG2   | [59]  |
| Follistatin                                                            | FST_HUMAN      | P19883    | FST    | [52, 61, 65] |
| Follistatin-related protein 3*                                          | FSTL3_HUMAN    | O95633    | FSTL3  | [65]  |
| Forkhead box protein N3*                                                | FOXN3_HUMAN    | O00409    | FOXN3  | [52]  |
| Frizzled-1                                                              | FZD1_HUMAN     | Q9UP38    | FZD1   | [52, 57, 65] |
| Frizzled-3                                                              | FZD3_HUMAN     | Q9NPG1    | FZD3   | [52, 65] |
| Frizzled-6                                                              | FZD6_HUMAN     | O60353    | FZD6   | [57]  |
| Frizzled-7                                                              | FZD7_HUMAN     | O75084    | FZD7   | [65]  |
| Fructose-bisphosphate aldolase A*                                       | ALDOA_HUMAN    | P04075    | ALDOA  | [52]  |
| Fructose-bisphosphate aldolase B                                       | ALDOB_HUMAN    | P05062    | ALDOB  | [65]  |
| Fructose-bisphosphate aldolase C*                                      | ALDOC_HUMAN    | P09972    | ALDOC  | [52, 65] |
| Furin                                                                  | FURIN_HUMAN    | P09958    | FURIN  | [65]  |
| Galanin peptides                                                        | GALA_HUMAN     | P22466    | GAL    | [52]  |
| Galectin-10*                                                           | LEG10_HUMAN    | Q05315    | CLC    | [52, 65] |
| Galectin-3                                                             | LEG3_HUMAN     | P17931    | LGALS3 | [52, 65] |
| Gamma-Thrombin (cleaved from prothrombin)                              | THR8_HUMAN     | P00734    | F2     | [65]  |
| GATA-type zinc finger protein 1*                                        | ZGLP1_HUMAN    | P0C6A0    | ZGLP1  | [52]  |
| GDNF family receptor alpha-3*                                           | GFRA3_HUMAN    | O60609    | GFRA3  | [52]  |
| Geminin*                                                               | GEMI_HUMAN     | O75496    | GMNN   | [65]  |
| Protein                                                                 | Abbreviation       | UniProtKB | Gene  | Ref.    |
|------------------------------------------------------------------------|--------------------|-----------|-------|--------|
| Glial cell line-derived neurotrophic factor*                           | GDNF_HUMAN         | P39905    | GDNF  | [65]   |
| Glutathione peroxidase 1*                                              | GPX1_HUMAN         | P07203    | GPX1  | [65]   |
| Glutathione peroxidase 3*                                              | GPX3_HUMAN         | P22352    | GPX3  | [65]   |
| Glyceroldehyde 3-phosphate dehydrogenase                              | G3P_HUMAN          | P04406    | GAPDH | [12]   |
| Glycogen phosphorylase, brain form*                                    | PYGB_HUMAN         | P11216    | PYGB  | [65]   |
| Glycoprotein hormones alpha chain*                                     | GLHA_HUMAN         | P01215    | CGA   | [52]   |
| Glypican-3                                                             | GPC3_HUMAN         | P51654    | GPC3  | [60]   |
| Glypican-5                                                             | GPC5_HUMAN         | P78333    | GPC5  | [65]   |
| Granulocyte colony-stimulating factor*                                 | CSF3_HUMAN         | P09919    | CSF3  | [52, 60, 61, 65] |
| Granulocyte-macrophage colony-stimulating factor receptor subunit alpha* | CSF2R_HUMAN       | P15509    | CSF2RA| [52, 65] |
| Granulocyte-macrophage colony-stimulating factor*                     | CSF2_HUMAN         | P04141    | CSF2  | [52, 61] |
| Granzyme A                                                             | GRAA_HUMAN         | P12544    | GZMA  | [52, 65] |
| Gremlin-1                                                              | GREM1_HUMAN        | O60565    | GREM1 | [52]   |
| Growth arrest and DNA damage-inducible protein GADD45 alpha*           | GA45A_HUMAN        | P24522    | GNG12 | [52]   |
| Growth factor receptor-bound protein 2                                  | GRB2_HUMAN         | P62993    | GRB2  | [57]   |
| Growth/differentiation factor 2*                                       | GDF2_HUMAN         | Q9UK05    | GDF2  | [65]   |
| Growth/differentiation factor 3*                                       | GDF3_HUMAN         | Q9NR23    | GDF3  | [52, 65] |
| Growth/differentiation factor 5*                                       | GDF5_HUMAN         | P43026    | GDF5  | [52, 65] |
| Growth/differentiation factor 8*                                       | GDF8_HUMAN         | O14793    | MISTN | [52]   |
| Growth/differentiation factor 9*                                       | GDF9_HUMAN         | O60383    | GDF9  | [52, 65] |
| Growth/differentiation factor 11*                                      | GDF11_HUMAN        | O95390    | GDF11 | [52, 57, 65] |
| Guanine nucleotide-binding protein G(I)/G(S)/G(O) subunit gamma-12     | GBG12_HUMAN        | Q9UB16    | GNG12 | [57]   |
| Guanine nucleotide-binding protein subunit alpha-13                    | GNA13_HUMAN        | Q14344    | GNA13 | [57]   |
| Haptoglobin                                                            | HPT_HUMAN          | P00738    | HP    | [52]   |
| HCR / CRAM-A/B***                                                     | –                  | –         | CCHCR1| [52, 65] |
| Heat shock protein 70 kDa**                                            | –                  | –         | –     | [12]   |
| Heat shock protein 90 kDa**                                            | –                  | –         | –     | [12]   |
| Heat shock protein 105 kDa*                                           | HS105_HUMAN        | Q92598    | HSPH1 | [12]   |
| Heat shock protein beta-1*                                            | HSPB1_HUMAN        | P04792    | HSPB1_HUMAN | [12, 52, 65] |
| Hepatocyte growth factor activator                                     | HGFA_HUMAN         | Q04756    | HGFAC | [57]   |
| Hepatocyte growth factor receptor*                                     | MET_HUMAN          | P08581    | MET   | [52]   |
| Hepatocyte growth factor-like protein alpha chain (cleaved from hepatocyte growth factor-like protein)* | HGFL_HUMAN         | P26927    | MST1  | [52]   |
| Hepatocyte growth factor-regulated tyrosine kinase substrate           | HGS_HUMAN          | O14964    | HGS   | [57]   |
| Hepcidin                                                               | HEPC_HUMAN         | P81172    | HAMP  | [65]   |
| Histone H4                                                             | H4_HUMAN           | P62805    | H4C1  | [59]   |
| HLA class II histocompatibility antigen gamma chain*                   | HG2A_HUMAN         | P04233    | CD74  | [65]   |
| Homeobox protein NANOG*                                                | NANOG_HUMAN        | Q9H980    | NANOG | [65]   |
| Homerin                                                                | HORN_HUMAN         | Q86YZ3    | HRNR  | [59]   |
| Inhibin beta A chain*                                                  | INHBA_HUMAN        | P08476    | INHBA | [65]   |
| Inhibin beta B chain*                                                  | INHBB_HUMAN        | P09529    | INHBB | [65]   |
| Inhibin beta C chain*                                                  | INHBC_HUMAN        | P55103    | INHBC | [60]   |
| INSL3***                                                               | –                  | –         | –     | [65]   |
| Insulin receptor*                                                      | INSR_HUMAN         | P06213    | INSR  | [52, 65] |
| Insulin-degrading enzyme*                                              | IDE_HUMAN          | P14735    | IDE   | [65]   |
| Insulin-like growth factor 1 receptor                                  | IGF1R_HUMAN        | P08069    | IGF1R | [57]   |
| Insulin-like growth factor 1*                                          | IGF1_HUMAN         | P05019    | IGF1  | [65]   |
| Protein                                           | Abbreviation     | UniProtKB | Gene            | Ref.  |
|---------------------------------------------------|------------------|-----------|-----------------|-------|
| Insulin-like growth factor-binding protein 1*     | IBP1_HUMAN       | P08833    | IGFBP1          | [65]  |
| Insulin-like growth factor-binding protein 3      | IBP3_HUMAN       | P17936    | IGFBP3          | [57]  |
| Insulin-like growth factor-binding protein 4*     | IBP4_HUMAN       | P22692    | IGFBP4          | [52]  |
| Insulin-like growth factor-binding protein 5*     | IBP5_HUMAN       | P24593    | IGFBP5          | [65]  |
| Insulin-like growth factor-binding protein 7*     | IBP7_HUMAN       | Q16270    | IGFBP7          | [60, 65]|
| Insulin-like growth factor-binding protein complex acid labile subunit | ALS_HUMAN        | P35858    | IGFALS          | [57]  |
| Integrin alpha-1                                 | ITA1_HUMAN       | P56199    | ITGA1           | [57]  |
| Integrin alpha-2                                 | ITA2_HUMAN       | P17301    | ITGA2           | [57]  |
| Integrin alpha-3                                 | ITA3_HUMAN       | P26006    | ITGA3           | [57]  |
| Integrin alpha-4                                 | ITA4_HUMAN       | P13612    | ITGA4           | [57]  |
| Integrin alpha-5                                 | ITA5_HUMAN       | P08648    | ITGA5           | [57]  |
| Integrin alpha-6                                 | ITA6_HUMAN       | P23229    | ITGA6           | [57]  |
| Integrin alpha-7                                 | ITA7_HUMAN       | Q13683    | ITGA7           | [57]  |
| Integrin alpha-10                                | ITA10_HUMAN      | O75578    | ITGA10          | [57]  |
| Integrin alpha-11                                | ITA11_HUMAN      | Q9UKX5    | ITGA11          | [57]  |
| Integrin alpha-M*                                | ITAM_HUMAN       | P11215    | ITGAM           | [52]  |
| Integrin alpha-V                                 | ITAV_HUMAN       | P06756    | ITGAV           | [52, 57, 65]|
| Integrin beta-1                                  | ITB1_HUMAN       | P05556    | ITGB1           | [57]  |
| Integrin beta-1-binding protein 1                 | ITBPI1_HUMAN     | O14713    | ITGB1BP1        | [57]  |
| Integrin beta-3                                  | ITB3_HUMAN       | P05106    | ITGB3           | [57]  |
| Integrin beta-5                                  | ITB5_HUMAN       | P18084    | ITGB5           | [57]  |
| Integrin-linked protein kinase                    | ILK_HUMAN        | Q13418    | ILK             | [57]  |
| Inter-alpha-trypsin inhibitor heavy chain H2      | ITH2_HUMAN       | P19823    | ITH2            | [59]  |
| Intercellular adhesion molecule 1                 | ICAM1_HUMAN      | P05362    | ICAM1           | [57]  |
| Intercellular adhesion molecule 2*                | ICAM2_HUMAN      | P13598    | ICAM2           | [57, 65]|
| Interferon beta*                                 | IFNB_HUMAN       | P01574    | IFNB1           | [65]  |
| Interferon gamma*                                | IFNG_HUMAN       | P01579    | IFNG            | [52, 65]|
| Interferon lambda-1*                             | IFNLI1_HUMAN     | Q8IU54    | IFNL1           | [65]  |
| Interferon lambda-2*                             | IFNL2_HUMAN      | Q8IZJ0    | IFNL2           | [65]  |
| Interferon regulatory factor 6*                   | IRF6_HUMAN       | Q14896    | IRF6            | [52]  |
| Interleukin-1 alpha*                             | IL1A_HUMAN       | P01583    | IL1A            | [52, 60, 65]|
| Interleukin-1 beta*                              | IL1B_HUMAN       | P01584    | IL1B            | [61]  |
| Interleukin-1 family member 10*                   | IL1FA_HUMAN      | Q8WWZ1    | IL1F10          | [52, 65]|
| Interleukin-1 receptor accessory protein-like 1*  | IRPL1_HUMAN      | Q9NZN1    | IL1RPL1         | [52, 65]|
| Interleukin-1 receptor type 1*                    | IL1R1_HUMAN      | P14778    | IL1R1           | [52]  |
| Interleukin-1 receptor type 2*                    | IL1R2_HUMAN      | P27930    | IL1R2           | [52]  |
| Interleukin-1 receptor-like 1*                    | ILRL1_HUMAN      | Q01638    | IL1RL1          | [52]  |
| Interleukin-1 receptor-like 2*                    | ILRL2_HUMAN      | Q9HB29    | IL1RL2          | [52]  |
| Interleukin-2*                                   | IL2_HUMAN        | P60568    | IL2             | [52]  |
| Interleukin-2 receptor subunit alpha*             | IL2RA_HUMAN      | P01589    | IL2RA           | [65]  |
| Interleukin-2 receptor subunit beta*              | IL2RB_HUMAN      | P14784    | IL2RB           | [52]  |
| Interleukin-4*                                   | IL4_HUMAN        | P05112    | IL4             | [61]  |
| Interleukin-5*                                   | IL5_HUMAN        | P05113    | IL5             | [52]  |
| Interleukin-6*                                   | IL6_HUMAN        | P05231    | IL6             | [52, 62]|
| Interleukin-7*                                   | IL7_HUMAN        | P13232    | IL7             | [52, 65]|
| Interleukin-7 receptor subunit alpha*             | IL7RA_HUMAN      | P16871    | IL7R            | [65]  |
| Interleukin-8*                                   | IL8_HUMAN        | P10145    | CXCL8           | [52, 65]|
| Interleukin-9*                                   | IL9_HUMAN        | P15248    | IL9             | [52, 65]|

**Table 1 (continued)**
| Protein                                      | Abbreviation | UniProtKB | Gene    | Ref.  |
|----------------------------------------------|--------------|-----------|---------|-------|
| Interleukin-10*                              | IL10_HUMAN   | P22301    | IL10    | [52, 61] |
| Interleukin-10 receptor subunit alpha*        | I10R1_HUMAN  | Q13651    | IL10RA  | [52]   |
| Interleukin-11*                              | IL11_HUMAN   | P20809    | IL11    | [52]   |
| Interleukin-12 subunit alpha*                | IL12A_HUMAN  | P29459    | IL12A   | [61]   |
| Interleukin-12 subunit beta*                 | IL12B_HUMAN  | P29460    | IL12B   | [61]   |
| Interleukin-13 receptor subunit alpha-1*      | I13R1_HUMAN  | P78552    | IL13RA1 | [52, 65] |
| Interleukin-13 receptor subunit alpha-2*      | I13R2_HUMAN  | Q14627    | IL13RA2 | [65]   |
| Interleukin-13*                              | IL13_HUMAN   | P35225    | IL13    | [52]   |
| Interleukin-15*                              | IL15_HUMAN   | P40933    | IL15    | [52]   |
| Interleukin-17 receptor B*                    | I17RB_HUMAN  | Q9NRK6    | IL17RB  | [52, 65] |
| Interleukin-17 receptor C*                    | I17RC_HUMAN  | Q8NAC3    | IL17RC  | [52]   |
| Interleukin-17A*                              | IL17_HUMAN   | Q16552    | IL17A   | [52, 65] |
| Interleukin-17C*                              | IL17C_HUMAN  | Q9POF4    | IL17C   | [65]   |
| Interleukin-19*                              | IL19_HUMAN   | Q9UHD0    | IL19    | [65]   |
| Interleukin-20 receptor subunit alpha*        | I20RA_HUMAN  | Q9UHF4    | IL20RA  | [52]   |
| Interleukin-21 receptor*                      | I21R_HUMAN   | Q9HBE5    | IL21R   | [65]   |
| Interleukin-21*                              | IL21_HUMAN   | Q9HBE4    | IL21    | [52, 65] |
| Interleukin-23 receptor*                      | I23R_HUMAN   | Q5VWK5    | IL23R   | [65]   |
| Interleukin-23 subunit alpha*                 | IL23A_HUMAN  | Q9NPF7    | IL23A   | [52, 65] |
| Interleukin-24*                              | IL24_HUMAN   | Q13007    | IL24    | [65]   |
| Interleukin-27 subunit alpha*                 | IL27A_HUMAN  | Q8NEV9    | IL27    | [65]   |
| Interleukin-36 gamma*                         | IL36G_HUMAN  | Q9NZH8    | IL36G   | [65]   |
| Interleukin-36 receptor antagonist protein*    | I36RA_HUMAN  | Q9UBH0    | IL36RN  | [65]   |
| Intestinal collagenase*                       | MMP1_HUMAN   | P03956    | MMP1    | [52, 61] |
| Islet amyloid polypeptide*                    | IAPP_HUMAN   | P10997    | IAPP    | [52, 65] |
| Junctional adhesion molecule C                | JAM3_HUMAN   | Q9BX67    | JAM3    | [57]   |
| Junctional adhesion molecule-like*            | JAML_HUMAN   | Q86YT9    | JAML    | [65]   |
| Kallikrein 2                                 | KL2_HUMAN    | P20151    | KL2     | [52]   |
| Kallikrein 11                                | KLK11_HUMAN  | Q9UBX7    | KLK11   | [65]   |
| Keratin, type I cytoskeletal 19*              | K1C19_HUMAN  | P08727    | KRT19   | [52, 65] |
| Kremen protein 1*                            | KREM1_HUMAN  | Q96MU8    | KREMEN1 | [52]   |
| Kremen protein 2*                            | KREM2_HUMAN  | Q8NCW0    | KREMEN2 | [60, 65] |
| Lactadherin*                                 | MFGM_HUMAN   | Q08431    | MFGE8   | [60]   |
| Lactotransferrin*                            | TRFL_HUMAN   | P02788    | LTTF    | [52, 59] |
| Lactoylglutathione lyase*                    | LGUL_HUMAN   | Q04760    | GLO1    | [65]   |
| Laminin subunit alpha-1                      | LAMA1_HUMAN  | P25391    | LAMA1   | [57]   |
| Laminin subunit alpha-2                      | LAMA2_HUMAN  | P24043    | LAMA2   | [57]   |
| Laminin subunit alpha-4                      | LAMA4_HUMAN  | Q16363    | LAMA4   | [57]   |
| Laminin subunit alpha-5                      | LAMA5_HUMAN  | Q15230    | LAMA5   | [57]   |
| Laminin subunit beta-1                       | LAMB1_HUMAN  | P07942    | LAMB1   | [57]   |
| Laminin subunit beta-2                       | LAMB2_HUMAN  | P55268    | LAMB2   | [57]   |
| Laminin subunit gamma-1                      | LAMC1_HUMAN  | P11047    | LAMC1   | [57]   |
| Latent-transforming growth factor beta-binding protein 1 | LTBP1_HUMAN | Q14766    | LTBP1   | [57]   |
| Layilin                                      | LAYN_HUMAN   | Q6UX15    | LAYN    | [65]   |
| Leucine-rich alpha-2-glycoprotein*            | A2GL_HUMAN   | P02750    | LRG1    | [52, 65] |
| Leukocyte surface antigen CD47                | CD47_HUMAN   | Q08722    | CD47    | [57]   |
| Lipoilysaccharide-binding protein*            | LBP_HUMAN    | P18428    | LBP     | [65]   |
| L-lactate dehydrogenase A chain*             | LDHA_HUMAN   | P00338    | LDHA    | [12]   |
| Low affinity immunoglobulin epsilon Fc receptor* | FCER2_HUMAN | P06734    | FCER2   | [65]   |
| Protein                                                                 | Abbreviation       | UniProtKB   | Gene     | Ref.   |
|------------------------------------------------------------------------|--------------------|-------------|----------|--------|
| Low-density lipoprotein receptor*                                      | LDLR_HUMAN         | P01130      | LDLR     | [65]   |
| Low-density lipoprotein receptor-related protein 6*                    | LRP6_HUMAN         | O75581      | LRP6     | [60]   |
| L-Selectin                                                             | LYAM1_HUMAN        | P14151      | SEL      | [52]   |
| Lutropin-choriogonadotropin hormone receptor*                          | LSHR_HUMAN         | P22888      | LHCGR    | [52]   |
| Lymphocyte activation gene 3 protein*                                  | LAG3_HUMAN         | P18627      | LAG3     | [52]   |
| Lymphotoksin-alpha*                                                    | TNFB_HUMAN         | P01374      | LTA      | [52]   |
| Lymphotoksin-beta                                                      | TNFC_HUMAN         | Q06643      | LTB      | [65]   |
| Lysosome membrane protein 2*                                           | SCR82_HUMAN        | Q14108      | SCARB2   | [65]   |
| Lysosome-associated membrane glycoprotein 2*                           | LAMP2_HUMAN        | P13473      | LAMP2    | [12]   |
| Macrophage migration inhibitory factor*                                | MIF_HUMAN          | P14174      | MIF      | [65]   |
| Mammaglobin A                                                          | SG2A2_HUMAN        | Q13296      | SCGB2A2  | [52]   |
| Mast/stem cell growth factor receptor Kit                              | KIT_HUMAN          | P10721      | KIT      | [57]   |
| Matriptisin                                                            | MMP7_HUMAN         | P09237      | MMP7     | [65]   |
| Matrix metalloproteinase-9*                                            | MMP9_HUMAN         | P14780      | MMP9     | [61, 65] |
| Matrix metalloproteinase-14*                                           | MMP14_HUMAN        | P50281      | MMP14    | [65]   |
| Matrix metalloproteinase-19*                                           | MMP19_HUMAN        | Q99542      | MMP19    | [52]   |
| Matrix metalloproteinase-20*                                           | MMP20_HUMAN        | O60882      | MMP20    | [52, 60, 65] |
| Matrix metalloproteinase-24*                                           | MMP24_HUMAN        | Q9Y5R2      | MMP24    | [52, 65] |
| Megakaryocyte-associated tyrosine-protein kinase*                      | MATK_HUMAN         | P42679      | MATK     | [52]   |
| Metalloproteinase inhibitor 2                                          | TIMP2_HUMAN        | P16035      | TIMP2    | [60]   |
| Metalloproteinase inhibitor 3*                                         | TIMP3_HUMAN        | P35625      | TIMP3    | [65]   |
| MHC class I polypeptide-related sequence A*                            | MICA_HUMAN         | Q29983      | MICA     | [65]   |
| Microglobulin***                                                       |                    | –           | –        | [65]   |
| Microtubule-associated tumor suppressor 1*                             | MTUS1_HUMAN        | Q9ULD2      | MTUS1    | [65]   |
| Mitogen-activated protein kinase 1                                     | MK01_HUMAN         | P28482      | MAPK1    | [57]   |
| Mitogen-activated protein kinase 3                                     | MK03_HUMAN         | P27361      | MAPK3    | [57]   |
| Monocyte differentiation antigen CD14*                                  | CD14_HUMAN         | P08571      | CD14     | [65]   |
| MSHa***                                                                |                    | –           | –        | [52]   |
| Mucin-1*                                                               | MUC1_HUMAN         | P15941      | MUC1     | [65]   |
| Mucin-16*                                                              | MUC16_HUMAN        | Q8WXI7      | MUC16    | [52, 65] |
| Mucosal addressin cell adhesion molecule 1                             | MADCA_HUMAN        | Q13477      | MADCAM1  | [57]   |
| Muscle, skeletal receptor tyrosine-protein kinase*                      | MUSK_HUMAN         | O15146      | MUSK     | [52]   |
| Myeloid-derived growth factor                                          | MYDGF_HUMAN        | Q969H8      | MYDGF    | [57]   |
| Natriuretic peptides B*                                                | ANFB_HUMAN         | P16860      | NPPB     | [52]   |
| Natural killer cell receptor 2B4*                                      | CD244_HUMAN        | Q9BZW8      | CD244    | [65]   |
| Nephrilysin                                                            | NEP_HUMAN          | P08473      | MME      | [63]   |
| Netrin-1*                                                              | NET1_HUMAN         | O95631      | NTN1     | [52]   |
| Netrin-G2                                                              | NTNG2_HUMAN        | Q96CW9      | NTNG2    | [52]   |
| Neural cell adhesion molecule 1*                                       | NCAM1_HUMAN        | P13591      | NCAM1    | [65]   |
| Neural cell adhesion molecule L1-like protein                          | NCHL1_HUMAN        | O00533      | CHL1     | [57]   |
| Neuregulin-1 (cleaved form pro-neuregulin-1, membrane-bound isof orm)  | NRG1_HUMAN         | Q02297      | NRG1     | [52]   |
| Neuregulin-2 (cleaved pro-neuregulin-2, membrane-bound isof orm)*      | NRG2_HUMAN         | O14511      | NRG2     | [52]   |
| Neuregulin-3 (cleaved pro-neuregulin-3, membrane-bound isof orm)*      | NRG3_HUMAN         | P56975      | NRG3     | [52]   |
| Neurofibromin*                                                         | NF1_HUMAN          | P21359      | NF1      | [52]   |
| Neurogenic differentiation factor 1*                                    | NDF1_HUMAN         | Q13562      | NEUROD1  | [65]   |
| Neuronal pentraxin-1                                                   | NPTX1_HUMAN        | Q15818      | NPTX1    | [52]   |
Table 1 (continued)

| Protein                                             | Abbreviation   | UniProtKB | Gene       | Ref.   |
|-----------------------------------------------------|----------------|-----------|------------|--------|
| Neuropeptide Y (cleaved form pro-neuropeptide Y)    | NPY_HUMAN      | P01303    | NPY        | [65]   |
| Neurosecretory protein VGF*                          | VGF_HUMAN      | Q015240   | VGF        | [52]   |
| Neuroserpin*                                        | NEUS_HUMAN     | Q99574    | SERPIN1    | [65]   |
| Neurturin                                           | NRTN_HUMAN     | Q99748    | NRTN       | [65]   |
| Neutrophil collagenase*                              | MMP8_HUMAN     | P22894    | MMP8       | [52]   |
| Neutrophil-activating peptide 2 (cleaved from Platelet basic protein)* | CXCL7_HUMAN | P02775    | PPBP       | [65]   |
| Non-receptor tyrosine-protein kinase TYK2*           | TYK2_HUMAN     | P29597    | TYK2       | [65]   |
| Nucleoside diphosphate kinase A                      | NDKA_HUMAN     | P15531    | NME1       | [65]   |
| Orexin receptor type 1*                              | OX1R_HUMAN     | O43613    | HCRTR1     | [65]   |
| OX-2 membrane glycoprotein*                          | OX2G_HUMAN     | P41217    | CD200      | [65]   |
| Pentraxin-related protein PTX3                       | PTX3_HUMAN     | P26022    | PTX3       | [59, 60]|
| Peptide YY                                           | PYH_HUMAN      | P10082    | PYY        | [65]   |
| Periostin                                            | POSTN_HUMAN    | Q15063    | POSTN      | [59]   |
| Phosphatidylinositol 3-kinase regulatory subunit beta*| P85B_HUMAN     | O00549    | PIK3R2     | [52]   |
| Phosphoglycerate Kinase 1                            | PGK1_HUMAN     | P00558    | PGK1       | [12]   |
| Plakophilin-1                                        | PKP1_HUMAN     | Q13835    | PKP1       | [59]   |
| Plasma protease C1 inhibitor*                        | SCI_HUMAN      | P05155    | SERPING1   | [52]   |
| Platelet endothelial cell adhesion molecule*         | PECA1_HUMAN    | P16284    | PECAM1     | [61]   |
| Platelet glycoprotein 4*                             | CD36_HUMAN     | P16671    | CD36       | [65]   |
| Platelet-derived growth factor D*                   | PDGF_D_HUMAN   | Q99ZP0    | PDGF       | [65]   |
| Platelet-derived growth factor receptor alpha*       | PGFRA_HUMAN    | P16234    | PDGFRA     | [52, 57, 65]|
| Platelet-derived growth factor receptor beta*        | PGFRB_HUMAN    | P09619    | PDGFRB     | [52, 57]|
| Platelet-derived growth factor subunit B             | PDGF_B_HUMAN   | P01127    | PDGFB      | [57]   |
| Polyubiquitin-B*                                     | UBB_HUMAN      | P0CG47    | UBB        | [52, 65]|
| PPARg2***                                           | –              | –         | PPARG      | [52]   |
| Probetaclulin*                                       | BTC_HUMAN      | P35070    | BTC        | [52, 65]|
| Pro-epidermal growth factor*                         | EGF_HUMAN      | P01133    | EGF        | [61]   |
| Progesterone receptor                                | PRGR_HUMAN     | P06401    | PGR        | [52]   |
| pro-Glucagon                                         | GLUC_HUMAN     | P01275    | GCG        | [65]   |
| Progranulin                                          | GRN_HUMAN      | P28799    | GRN        | [65]   |
| Proheparin-binding EGF-like growth factor*           | HBEGF_HUMAN    | Q99075    | HBEGF      | [65]   |
| Prokinetin-1*                                        | PROK1_HUMAN    | P58294    | PROK1      | [65]   |
| ProSAAS                                              | PCSN1_HUMAN    | Q9UHG2    | PCSK1N     | [52]   |
| Prostaglandin D2 receptor 2*                         | PD2R2_HUMAN    | Q9Y5Y4    | PTGDR2     | [65]   |
| Protein AMBP*                                        | AMBP_HUMAN     | P02760    | AMBP       | [65]   |
| Protein FAM3B                                        | FAM3B_HUMAN    | P158499   | FAM3B      | [52, 65]|
| Protein S100-A6                                      | S10A6_HUMAN    | P06703    | S100A6     | [65]   |
| Protein S100-A8                                      | S10A8_HUMAN    | P05109    | S100A8     | [65]   |
| Protein S100-A10                                     | S10AA_HUMAN    | P60903    | S100A10    | [65]   |
| Protein S100-A12                                     | S10AC_HUMAN    | P80511    | S100A12    | [65]   |
| Protein Wnt-5a                                       | WNT5A_HUMAN    | P41221    | WNT5A      | [57]   |
| Protein Wnt-5b                                       | WNT5B_HUMAN    | Q9H1J7    | WNT5B      | [57]   |
| Protein wntless homolog                              | WLS_HUMAN      | Q5T9L3    | WLS        | [57]   |
| Protocadherin Fat 1                                  | FAT1_HUMAN     | Q14517    | FAT1       | [57]   |
| Protocadherin Fat 4                                  | FAT4_HUMAN     | Q6V017    | FAT4       | [57]   |
| Protocadherin gamma-C3                               | PCDGK_HUMAN    | Q9UN70    | PCDHG3C    | [57]   |
| Protocadherin-7                                      | PCDH7_HUMAN    | O60245    | PCDH7      | [57]   |
| Protocadherin-9                                      | PCDH9_HUMAN    | Q9HC56    | PCDH9      | [57]   |

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| Protein                                                                 | Abbreviation | UniProtKB | Gene | Ref.   |
|------------------------------------------------------------------------|--------------|-----------|------|--------|
| Protocadherin-18                                                       | PCD18_HUMAN  | Q9HCL0    | PCDH18 | [57]   |
| Proto-oncogene tyrosine-protein kinase Ret*                             | RET_HUMAN    | P07949    | RET  | [65]   |
| P-selectin                                                              | LYM3_HUMAN   | P16109    | SELP | [52]   |
| Ras-related protein R-Ras                                              | RRAS_HUMAN   | P10301    | RRAS | [57]   |
| Ras-related protein R-Ras2                                              | RRAS2_HUMAN  | P62070    | RRAS2| [57]   |
| Receptor tyrosine-protein kinase erbB-2*                               | ERBB2_HUMAN  | P04626    | ERBB2| [65]   |
| Receptor tyrosine-protein kinase erbB-4*                               | ERBB4_HUMAN  | Q15303    | ERBB4| [65]   |
| Receptor-interacting serine/threonine-protein kinase 1a*               | RIPK1_HUMAN  | Q13546    | RIPK1| [65]   |
| Receptor-type tyrosine-protein kinase FLT3*                             | FLT3_HUMAN   | P36888    | FLT3 | [65]   |
| Receptor-type tyrosine-protein phosphatase delta*                      | PTPRD_HUMAN  | P23468    | PTPRD| [52]   |
| Rho family-interacting cell polarization regulator 1                   | RIPR1_HUMAN  | Q6ZS17    | RIPOR1| [57]   |
| Rho GTPase-activating protein 1                                         | RHG01_HUMAN  | Q07960    | ARHGAP1| [57]  |
| Rho guanine nucleotide exchange factor 1                               | ARHG1_HUMAN  | Q92888    | ARHGEF1| [57]  |
| Rho guanine nucleotide exchange factor 7                                | ARHG7_HUMAN  | Q14155    | ARHGEF7| [57]  |
| Rho-associated protein kinase 1a*                                       | ROCK1_HUMAN  | Q13464    | ROCK1| [52, 57]|
| Rho-associated protein kinase 2                                         | ROCK2_HUMAN  | Q75116    | ROCK2| [57]   |
| Rho-related GTP-binding protein RhoB                                    | RHOB_HUMAN   | P62745    | RHOB | [57]   |
| Rho-related GTP-binding protein RhoE                                    | RND3_HUMAN   | P61587    | RND3 | [57]   |
| Rho-related GTP-binding protein RhoG                                    | RHOG_HUMAN   | P84095    | RHOG | [57]   |
| Ribosomal oxygenase 2*                                                 | RIOX2_HUMAN  | Q8IU8     | RIOX2| [52]   |
| Scavenger receptor cysteine-rich type 1 protein M130*                   | C163A_HUMAN  | Q86V7B    | CD163 | [52]   |
| Sclerostin*                                                            | SOST_HUMAN   | Q9BQ84    | SOST | [65]   |
| Secreted frizzled-related protein 1*                                    | SFRP1_HUMAN  | Q8N474    | SFRP1| [65]   |
| Serum amyloid A-1 protein*                                              | SAA1_HUMAN   | P0DIJ8    | SAA1 | [52]   |
| Secreted frizzled-related protein 3*                                    | SFRP3_HUMAN  | Q92765    | FRZB | [65]   |
| Secreted frizzled-related protein 4*                                    | SFRP4_HUMAN  | Q6FH7     | SFRP4| [60]   |
| Serine/threonine-protein kinase MRCK alpha                               | MRCKA_HUMAN  | Q5VT25    | CDC42BPA| [57]  |
| Serine/threonine-protein kinase MRCK beta                               | MRCKB_HUMAN  | Q9YS52    | CDC42BBP| [57] |
| Serotransferrin                                                        | TRFE_HUMAN   | P02787    | TF    | [59]   |
| Sex hormone-binding globulin*                                           | SHBG_HUMAN   | P04278    | SHBG  | [52]   |
| Sialic acid-binding Ig-like lectin 5*                                   | SIGL5_HUMAN  | Q15389    | SIGLEC5| [65]  |
| Sialic acid-binding Ig-like lectin 9a*                                  | SIGL9_HUMAN  | Q9Y336    | SIGLEC9| [52]  |
| Signal peptide, CUB and EGF-like domain-containing protein 3            | SCUB3_HUMAN  | Q8IX30    | SCUBE3| [57]   |
| Signal transducer CD24*                                                | CD24_HUMAN   | P25063    | CD24 | [65]   |
| SLIT-ROBO Rho GTPase-activating protein 1                               | SRGP1_HUMAN  | Q7Z6B7    | SRGAP1| [57]  |
| SLIT-ROBO Rho GTPase-activating protein 2                               | SRGP2_HUMAN  | Q75044    | SRGAP2| [57]  |
| Solute carrier family 2, facilitated glucose transporter 1a*            | GTR1_HUMAN   | P11166    | SLC2A1| [52, 65]|
| Solute carrier family 2, facilitated glucose transporter 2a*            | GTR2_HUMAN   | P11168    | SLC2A2| [52]   |
| Solute carrier family 2, facilitated glucose transporter 2b*            | GTR3_HUMAN   | P11169    | SLC2A3| [65]   |
| Solute carrier family 2, facilitated glucose transporter 3a*            | GTR5_HUMAN   | P22732    | SLC2A5| [52, 65]|
| Somatotropin*                                                          | SOMA_HUMAN   | P01241    | GH1  | [52]   |
| Sonic hedgehog protein*                                                | SHH_HUMAN    | Q15465    | SHH  | [52]   |
| SPARC                                                                  | SPRC_HUMAN   | P09486    | SPARC| [60]   |
| Sphingosine 1-phosphate receptor 1a*                                    | S1PR1_HUMAN  | P21453    | S1PR1| [52, 65]|

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| Protein                                                                 | Abbreviation | UniProtKB | Gene          | Ref.  |
|------------------------------------------------------------------------|--------------|-----------|---------------|------|
| Stromal cell-derived factor 1*                                         | SDF1_HUMAN   | P48061    | CXCL12        | [52] |
| Stromelysin-2*                                                         | MMP10_HUMAN  | P09238    | MMP10         | [65] |
| Stromelysin-3                                                          | MMP11_HUMAN  | P24347    | MMP11         | [52, 65] |
| SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily E member 1* | SMCE1_HUMAN | Q969G3    | SMARCE1       | [65] |
| TGF-beta 5***                                                          | –            | –         | TGFBR5        | [52] |
| TGF-beta receptor type-2                                               | TGFR2_HUMAN  | P37173    | TGFBR2        | [57] |
| Thioredoxin-interacting protein*                                       | TXNIP_HUMAN  | Q9H3M7    | TXNIP         | [52, 65] |
| Thrombopoietin                                                         | TPO_HUMAN    | P40225    | TPO           | [65] |
| Thrombospondin-1                                                       | TSP1_HUMAN   | P07996    | THBS1         | [59, 60] |
| Thrombospondin-2                                                       | TSP2_HUMAN   | P35442    | THBS2         | [52] |
| Thyroid peroxidase*                                                    | PERT_HUMAN   | P07202    | TPO           | [52] |
| Thyrotropin subunit beta*                                              | TSHB_HUMAN   | P01222    | TSHB          | [52] |
| T lymphocyte activation antigen CD80*                                   | CD80_HUMAN   | P33681    | CD80          | [60, 65] |
| Toll-like receptor 2*                                                  | TLR2_HUMAN   | O60603    | TLR2          | [65] |
| Toll-like receptor 4*                                                  | TLR4_HUMAN   | O00206    | TLR4          | [65] |
| TRA-1-60 and TRA-1-81***                                               | –            | –         | PODXL         | [52] |
| Transcription factor SOX-2*                                            | SOX2_HUMAN   | P48431    | SOX2          | [65] |
| Transcription initiation factor TFIIID subunit 4*                      | TAF4_HUMAN   | O00268    | TAF4          | [65] |
| Transferrin receptor protein 1*                                        | TFR1_HUMAN   | P02786    | TFRC          | [52, 65] |
| Transforming growth factor alpha (cleaved from Protransforming growth factor alpha) | TGFA_HUMAN   | P01135    | TGFA          | [61] |
| Transforming growth factor beta receptor type 3*                       | TGBR3_HUMAN  | Q03167    | TGFBR3        | [65] |
| Transforming growth factor beta-1 (cleaved from Transforming growth factor beta-1 proprotein) | TGBF1_HUMAN  | P01137    | TGFBR1        | [52, 57, 65] |
| Transforming growth factor beta-3* (cleaved form Transforming growth factor beta-3 proprotein) | TGBF3_HUMAN  | P10600    | TGFBR3        | [61] |
| Transforming growth factor-beta-induced protein ig-h3                  | BGH3_HUMAN   | Q15582    | TGFBI         | [57, 59] |
| Transforming protein RhoA                                               | RHOA_HUMAN   | P61586    | RHOA          | [57] |
| Transient receptor potential cation channel subfamily M member 7*      | TRPM7_HUMAN  | Q96QT4    | TRPM7         | [65] |
| Triggering receptor expressed on myeloid cells 1*                      | TREM1_HUMAN  | Q9NP99    | TREM1         | [61] |
| Troponin C, slow skeletal and cardiac muscles*                         | TNUNC1_HUMAN | P63316    | TNNC1         | [52] |
| Tumor necrosis factor ligand superfamily member 10*                    | TNF10_HUMAN  | P5091    | TNFSF10       | [65] |
| Tumor necrosis factor ligand superfamily member 11*                    | TNF11_HUMAN  | O14788   | TNFSF11       | [65] |
| Tumor necrosis factor ligand superfamily member 13*                    | TNF13_HUMAN  | O75888   | TNFSF13       | [60] |
| Tumor necrosis factor ligand superfamily member 15*                    | TNF15_HUMAN  | O95150   | TNFSF15       | [65] |
| Tumor necrosis factor ligand superfamily member 4*                     | TNFL4_HUMAN  | P23510   | TNFSF4        | [65] |
| Tumor necrosis factor ligand superfamily member 6*                     | TNFL6_HUMAN  | P48023   | FASLG         | [65] |
| Tumor necrosis factor ligand superfamily member 8*                     | TNFL8_HUMAN  | P32971   | TNFRSF8       | [52, 65] |
| Tumor necrosis factor receptor superfamily member 10A*                 | TR10A_HUMAN  | O00220   | TNFRSF10A     | [52] |
| Tumor necrosis factor receptor superfamily member 10B*                 | TR10B_HUMAN  | O14763   | TNFRSF10B     | [52] |
| Tumor necrosis factor receptor superfamily member 11B*                 | TR11B_HUMAN  | O00300   | TNFRSF11B     | [60] |
| Tumor necrosis factor receptor superfamily member 13B*                 | TR13B_HUMAN  | O14836   | TNFRSF13B     | [52] |
| Tumor necrosis factor receptor superfamily member 13C*                 | TR13C_HUMAN  | Q96JR3   | TNFRSF13C     | [52, 60, 65] |
| Tumor necrosis factor receptor superfamily member 6B*                  | TNF6B_HUMAN  | O95407   | TNFRSF6B      | [65] |
| Tumor necrosis factor receptor superfamily member 14B*                 | TNR14_HUMAN  | Q92956   | TNFRSF14      | [65] |
| Tumor necrosis factor receptor superfamily member 17B*                 | TNR17_HUMAN  | Q02223   | TNFRSF17      | [65] |
| Tumor necrosis factor receptor superfamily member 19B*                 | TNR19_HUMAN  | Q9NS68   | TNFRSF19      | [65] |
| Tumor necrosis factor receptor superfamily member 25B*                 | TNR25_HUMAN  | Q93038   | TNFRSF25      | [52, 65] |
| Tumor necrosis factor receptor superfamily member 27B*                 | TNR27_HUMAN  | Q9HAV5   | EDA2R         | [52, 65] |
reported in Table 2S. The biological processes in which a relatively large number of proteins are involved are: developmental process, signaling and cell communication, cell adhesion, immune system process, cellular component organization, response to stimulus, regulation of cellular process, apoptotic process, cellular protein metabolic process, viral process, regulation of molecular function, locomotion, and positive regulation of cell population proliferation, immune system process (17% immune response) and developmental processes (17% multicellular organism development) (Fig. 4).

Therapeutic Approaches of AT-MSC-EV Proteins

These results illustrate the role of AT-MSC-EVs in cell-cell communication [3–6], and the promising therapeutic effects observed in different research fields. Regarding the musculoskeletal system, AT-MSC-EVs have shown protective effects against cartilage degeneration, promotion of cell proliferation and migration of osteoarthritis chondrocytes, and antisenescence effects in osteoarthritis osteoblasts in vitro and in vivo [66, 78]. They have also shown protective properties on muscle damage in an in vivo model of hindlimb...
ischemia and in an in vitro model of ischemia/reperfusion [52]. These effects may be a consequence of the presence of proteins such as lactotransferrin, C-X-C motif chemokine 16, protein Wnt-5a, and transforming protein RhoA, which are involved in positive regulation of chondrocyte proliferation, positive regulation of cell migration, regulation of inflammatory response and regulation of osteoblast proliferation, respectively. The complete list of proteins involved in these processes is reported in Table 2S.

With regard to cardiology and vascular system, AT-MSC-EVs are involved in a wide range of biological processes, including heart development, contraction and morphogenesis, positive regulation of cardiac muscle cell proliferation and hypertrophy, regulation of cardiac muscle cell apoptotic process and proliferation, blood vessel maturation, remodeling and morphogenesis, regulation of blood vessel diameter and angiogenesis, among others (Table 2S). Hence, numerous proteins detected in AT-MSC-EVs could account for the protective effects observed in cardiac function and cardiomyocytes after their injection in an in vivo model of myocardial infarction [79]. In addition, the effects of AT-MSC-EVs in angiogenesis have been also studied in vitro and in vivo [60, 72, 80]. Proteins detected in AT-MSC-EVs such as IL-1 alpha and apelin receptor are proangiogenic, while SPARC is antiangiogenic (Table 2S).

Human AT-MSC-EVs also have an inhibitory effect on vein graft neointima formation, as observed in a mouse model of vein grafting [81]. This effect correlated with decreased macrophage infiltration, attenuated inflammatory cytokine expression, and reduced activation of MAPK and phosphatidylinositol-3 kinase signaling pathways [81]. EV proteins potentially involved in these processes are thrombospondin-1 (inflammatory response), IL-4 (negative regulation of macrophage activation), growth factor receptor-bound protein 2 (regulation of MAPK cascade) and MAP kinase 1 (regulation of phosphatidylinositol 3-kinase signaling) (Table 2S).

The effects of AT-MSC-EVs proteins in the vascular system may also be related to the cardio-renal protection observed in a deoxycorticosterone acetate-salt hypertensive animal model [82]. Thus, the administration of AT-MSC-EVs in this in vivo model protected against renal damage, preserved renal function, reduced inflammatory response, prevented fibrosis in the kidney and in cardiac tissue, and conserved normal blood pressure [82]. The administration of AT-MSC-EVs also showed a renal protective effect in an in vivo model of acute kidney injury [83]. Proteins detected in AT-MSC-EVs such as integrin alpha-3, IL-4, IL-10, collagen alpha-2(I) chain or periostin could be implicated in these outcomes (Table 2S).

Finally, the action of AT-MSC-EVs in skin diseases has also been studied [62, 68, 84, 85]. Human AT-MSC-EVs enhanced cutaneous repair and regeneration, both in vitro and in vivo, by the promotion of cell migration and proliferation, the inhibition of cell apoptosis and the regulation of fibroblast differentiation during skin wound healing [68, 84, 85]. This is unsurprising, considering that the main biological
**Fig. 2** Simplified outline of the main molecular functions enabled by proteins detected in EVs derived from human AT-MSC. For a complete review of the relationships between gene ontology terms see the chart view in the web-based tool QuickGO (https://www.ebi.ac.uk/QuickGO/).
processes of proteins described previously include response to stimulus (wound healing) and regulation of cellular processes (cell proliferation and migration) and apoptotic processes (Fig. 3, Table 2S). Proteins involved in these biological processes, along with those previously described in the vascular system, could support the protective effect of skin flaps against ischemia/reperfusion injury [62]. Although several proteins may be involved, in this study the observed effect was ascribed to the promotion of angiogenesis via IL-6, along with other mechanisms [62].

miRNA

AT-MSC-EVs cargo also contains several types of RNA, mainly miRNA, tRNA, mRNA, rRNA, snRNA, snoRNA and scRNA [53, 54]. AT-MSC-EVs are rich in miRNA [12, 54, 69, 70], which represents approximately 44% of all small, non-coding RNA detected in AT-MSC [53]. Currently, 604 miRNAs have been identified in AT-MSC-EVs (Table 2). The methods used for RNA analysis were sequencing systems [11, 53, 54, 59, 66, 67, 71, 74], quantitative real-time PCR [64, 65, 68, 72, 73], OpenArray systems [69, 70] and GeneChip RNA array [12], among others. The isolation methods of EVs used in those studies were centrifugation and/or ultracentrifugation [12, 64, 65, 67–69, 72, 74], commercial EV isolation kits [11, 53, 54, 59, 71, 73] and multi-filtration [66].

In this review, we present a comprehensive analysis of miRNAs currently identified in human AT-MSC-EVs. 489 miRNAs from 255 gene families were classified. The mir-515 and mir-10 families have the greatest numbers of miRNAs (Table 2). However, there was no information available about which gene families the other 115 miRNAs belonged to. In addition, hsa-miR-320a-3p and hsa-miR-375-3p were identified by the sequence and the precursor reported by Reza et al. [54], since the actual names used in the reference, hsa-miR-320a and hsa-miR-375, respectively, were not found for mature miRNA in any of the databases. Hsa-miR-1273a [54, 66] was included in the miRBase database as a dead miRNA entry. It was eventually removed due to lack of consistency between the patterns of mapped reads from RNA-sequencing experiments and the gene being processed as a miRNA. hsa-miR-1274a, hsa-miR-1274b, hsa-miR-1300 and hsa-miR-720 [65] were also included in the miRBase database as dead miRNA entries. They were removed because it is likely that they are fragments of tRNAs and mRNA. This could be the reason for their absence from
the RNAcentral database. 44 miRNAs were not found in any of the databases (Table 2). Other special cases included hsa-
mir-548aa and hsa-mir-548 t-3p [66] – there is a specific entry for each one in the miRBase database, however, both entries showed the same sequence and RNAcentral link. Therefore, in the present review they are treated as the same miRNA. The same applies to hsa-miR-199b-3p and hsa-miR-
199a-3p [53, 65, 66, 72].

The variety of miRNAs present in AT-MSC-EVs may play a role in the different therapeutic effects based on the paracrine properties of MSC [13]. Regardless, to confirm the involvement of miRNAs in these effects, it is necessary to take into consideration not only the presence of a specific miRNA, but also other factors such as concentration, structure, and availability of accessory proteins [13].

Only 199 miRNA showed GO annotations for molecular function when using the QuickGO database [55]. The molecular functions enabled by these miRNAs are mRNA binding involved in post-transcriptional gene silencing (95%), mRNA 3’-UTR binding (22%), RNA polymerase II complex binding (6%), single-stranded RNA binding and high-density lipoprotein particle binding (2% each), protein binding, transcription regulatory region sequence-specific DNA binding and sequence-specific single stranded DNA binding (1% each) (Fig. 5). All of these functions are specific child terms of the binding function (Fig. 6) which is also the most relevant molecular function of AT-MSC-EV proteins, as previously described. The specific molecular functions enabled by each miRNA are detailed in Table 3S.

The number of miRNAs with GO annotations of biological processes in QuickGO [55] was 212. These miRNAs take part in biological processes described by 577 different GO terms. The biological processes in which the greatest number of miRNA are involved are: negative regulation of gene expression, response to stimulus, regulation of cellular process, developmental process, locomotion, signaling, and cell communication (Fig. 7). The specific miRNAs involved in each process are detailed in Table 4S. 89% of these miRNAs are involved in gene silencing (Fig. 8). Other relevant GO terms in which a large number of miRNAs are included are mRNA mediated inhibition of translation (28%) negative regulation of gene expression (17%), negative regulation of angiogenesis (14%), negative regulation of inflammatory response (13%) and negative regulation of cell migration involved in sprouting angiogenesis (11%) (Fig. 8).

**Therapeutic approaches of AT-MSC-EV miRNAs**

Based on the data, miRNAs present in AT-MSC-EV cargo support their potential use as new treatments in various research fields. Similar to proteins, different miRNAs are involved in inflammatory response (hsa-let-7 g-5p, hsa-miR-16-5p, hsa-miR-92a-3p), negative regulation of macrophage activation (hsa-miR-124-3p), regulation of MAPK cascade...
| Family | Name | RNAcental | Sequence | Ref. |
|--------|------|-----------|----------|------|
| let-7  | hsa-let-7a-3p | URS000004F5D8_9606 | CUAAUACAAUCUACUGUCUUUC | [53] |
|        | hsa-let-7a-5p (hsa-let-7a) | URS0000416056_9606 | UGAGGUAGGUAGGUAGUAAGUU | [11, 12, 53, 54, 65, 66, 69] |
|        | hsa-let-7b-3p (hsa-let-7b) | URS00005918D5_9606 | CUAAUACACCUACUGCUUCCCC | [53, 65] |
|        | hsa-let-7b-5p (hsa-let-7b) | URS0000324096_9606 | UGAGGUAGGUAGGUAGUGGUUGGGU | [12, 53, 54, 65] |
|        | hsa-let-7c-3p | URS00000A07C1_9606 | AGAGGUAGGUAGGUAGGCAUAGGGU | [54, 65] |
|        | hsa-let-7c-5p (hsa-let-7c) | URS00004AFF8D_9606 | UGAGGUAGUAGGUAGGUACAGUU | [54, 65] |
|        | hsa-let-7g-3p (hsa-let-7g) | URS0000237CBD_9606 | CUGCGCAAGCUACUGCCUUGCU | [65] |
|        | hsa-let-7g-5p (hsa-let-7g) | URS00004023EA_9606 | UGAGGUAGGUAGGUAGGUUGCGUUG | [53, 54, 72] |
|        | hsa-let-7h-3p (hsa-let-7h) | URS00002F4762_9606 | CAAGCUUGUAUCUAUAGGUAGA | [65] |
|        | hsa-let-7h-5p (hsa-let-7h) | URS000016D2D4_9606 | UACCCUGUAGAACCGAAUUUGUG | [11, 53, 54, 65, 67] |
|        | hsa-let-7i-3p (hsa-let-7i) | URS00001C308D_9606 | CCACCCGUAGAACCGACCUUGCGC | [65] |
|        | hsa-let-7i-5p | URS00001925C1_9606 | UCACAAGUCAGGCUCUUGGGGAC | [65] |
|        | hsa-let-7j-3p (hsa-let-7j) | URS00001230A0_9606 | UACCAUACUGUAUACUGUAGA | [54, 65, 69] |
|        | hsa-let-7j-5p (hsa-let-7j) | URS0000476BE1_9606 | AGCAGCAUUGUACAGGGCUAUGA | [54, 65, 69] |
|        | hsa-let-7k-3p (hsa-let-7k) | URS0000209905_9606 | UCCUGAGACCACUAACUGUGA | [12, 53, 54, 65, 66, 72] |
|        | hsa-let-7k-5p (hsa-let-7k) | URS00005C62FC_9606 | CAAGCUUCGUACUACGUAGGCG | [65] |
|        | hsa-miR-98-3p (hsa-miR-98) | URS0000157026_9606 | AACCCGUAGAUCCGAUCUUGUG | [54, 65] |
|        | hsa-miR-98-5p (hsa-miR-98) | URS00001230A0_9606 | UACCAUACUGUAUACUGUAGA | [54, 65, 69] |
|        | hsa-miR-99a-3p (hsa-miR-99a*) | URS0000209905_9606 | UCCUGAGACCACUAACUGUGA | [12, 53, 54, 65, 66, 72] |
|        | hsa-miR-99a-5p (hsa-miR-99a) | URS00005C62FC_9606 | CAAGCUUCGUACUACGUAGGCG | [65] |
|        | hsa-miR-99b-3p (hsa-miR-99b*) | URS0000157026_9606 | UCCUGAGACCACUAACUGUGA | [54, 65] |
|        | hsa-miR-99b-5p (hsa-miR-99b) | URS00001925C1_9606 | UCACAAGUCAGGCUCUUGGGGAC | [65] |
|        | hsa-miR-99c-3p (hsa-miR-99c) | URS000004AC389_9606 | ACAGAUUCCGAUUCUGGAGAAU | [53, 65, 70] |
|        | hsa-miR-99c-5p (hsa-miR-99c) | URS000058760A_9606 | UACCUGUAGAACCGAAUUGUG | [11, 53, 54, 65, 67] |
|        | hsa-miR-99d-3p (hsa-miR-99d) | URS00002F4762_9606 | CAACUGUACUAGGGAAUA | [65] |
|        | hsa-miR-99d-5p (hsa-miR-99d) | URS00001230A0_9606 | UACCAUACUGUAUACUGUAGA | [54, 65, 69] |
|        | hsa-miR-99e-3p (hsa-miR-99e) | URS00005C62FC_9606 | CAAGCUUCGUACUACGUAGGCG | [65] |
|        | hsa-miR-99e-5p (hsa-miR-99e) | URS0000157026_9606 | UCCUGAGACCACUAACUGUGA | [54, 65] |
|        | hsa-miR-99f-3p (hsa-miR-99f) | URS0000157026_9606 | UCCUGAGACCACUAACUGUGA | [54, 65] |
|        | hsa-miR-99f-5p (hsa-miR-99f) | URS0000157026_9606 | UCCUGAGACCACUAACUGUGA | [54, 65] |
|        | hsa-miR-99g-3p (hsa-miR-99g) | URS0000476BE1_9606 | AGCAGCAUUGUACAGGGCUAUGA | [12, 53, 54, 65, 69] |
|        | hsa-miR-99g-5p (hsa-miR-99g) | URS00005C62FC_9606 | CAAGCUUCGUACUACGUAGGCG | [65] |
|        | hsa-miR-99h-3p (hsa-miR-99h) | URS0000157026_9606 | UCCUGAGACCACUAACUGUGA | [54, 65] |
|        | hsa-miR-99h-5p (hsa-miR-99h) | URS0000157026_9606 | UCCUGAGACCACUAACUGUGA | [54, 65] |
Table 2 (continued)

| Family | Name           | RNAcentral | Sequence                  | Ref.     |
|--------|----------------|------------|---------------------------|----------|
| mir-122| hsa-miR-122-5p | URS00003380CC_9606 | UGGAGUGUGACAAGUGUGUUG   | [59, 65] |
|        | (hsa-miR-122)  |            |                           |          |
| mir-1225| hsa-miR-1225-3p | URS000075D62D_9606 | UGAGGCGGCGGAGGCGGCGGAGG | [65]     |
|        | hsa-miR-1225-5p | URS000075D0F5_9606 | GGAGGCGGCGGAGGCGGCGGAGG | [72]     |
| mir-1226| hsa-miR-1226-5p | URS000075EAB0_9606 | GUGAGGCGGCGGAGGCGGCGGAGG | [65]     |
| mir-1227| hsa-miR-1227-3p | URS000075CFA8_9606 | CGUGCCACCCUUUCUCCAGCAGG | [65]     |
| mir-1228| hsa-miR-1228-5p | URS00004F1E01_9606 | GUGGGCCCGGCGGAGGCGGCGGAGG | [65, 67] |
|        | (hsa-miR-1228*)|            |                           |          |
| mir-1233| hsa-miR-1233-3p| URS000075D36A_9606 | UGAGGCGGCGGAGGCGGCGGAGG | [65]     |
| mir-1238| hsa-miR-1238-3p| URS000075E57E_9606 | UGAGGCGGCGGAGGCGGCGGAGG | [65]     |
| mir-124 | hsa-miR-124-3p | URS000075D0F5_9606 | GUGAGGCGGCGGAGGCGGCGGAGG | [72]     |
| mir-1244| hsa-miR-1244  | URS000075D0F5_9606 | GUGAGGCGGCGGAGGCGGCGGAGG | [65]     |
| mir-1246| hsa-miR-1246-3p| URS000075D0F5_9606 | GUGAGGCGGCGGAGGCGGCGGAGG | [65]     |
| mir-1247| hsa-miR-1247-3p| URS000075D0F5_9606 | GUGAGGCGGCGGAGGCGGCGGAGG | [65]     |
|        | (hsa-miR-1247) |            |                           |          |
| mir-1249| hsa-miR-1249-3p| URS000075D0F5_9606 | GUGAGGCGGCGGAGGCGGCGGAGG | [65]     |
|        | (hsa-miR-1249) |            |                           |          |
| mir-1253| hsa-miR-1253   | URS000075B58F_9606 | GAAGGAUCAGUUAACUGAGCUACG | [65]     |
| mir-1254| hsa-miR-1254   | URS000075B58F_9606 | GAAGGAUCAGUUAACUGAGCUACG | [65]     |
| mir-1255| hsa-miR-1255b-5p| URS000075B58F_9606 | GAAGGAUCAGUUAACUGAGCUACG | [65]     |
|        | (hsa-miR-1255b) |            |                           |          |
| mir-1256| hsa-miR-1256   | URS000075B58F_9606 | GAAGGAUCAGUUAACUGAGCUACG | [65]     |
| mir-126 | hsa-miR-126-3p | URS000075B58F_9606 | GAAGGAUCAGUUAACUGAGCUACG | [65]     |
|        | (hsa-miR-126)  |            |                           |          |
| mir-1260a| hsa-miR-1260a| URS000075B58F_9606 | GAAGGAUCAGUUAACUGAGCUACG | [65]     |
| mir-1260b| hsa-miR-1260b| URS000075B58F_9606 | GAAGGAUCAGUUAACUGAGCUACG | [65]     |
| mir-1262| hsa-miR-1262   | URS000075B58F_9606 | GAAGGAUCAGUUAACUGAGCUACG | [65]     |
| mir-1267| hsa-miR-1267   | URS000075B58F_9606 | GAAGGAUCAGUUAACUGAGCUACG | [65]     |
| mir-1268| hsa-miR-1268a  | URS000075B58F_9606 | GAAGGAUCAGUUAACUGAGCUACG | [65]     |
| mir-127 | hsa-miR-127-3p | URS000075B58F_9606 | GAAGGAUCAGUUAACUGAGCUACG | [65]     |
|        | (hsa-miR-127)  |            |                           |          |
| mir-1270| hsa-miR-1270   | URS000075B58F_9606 | GAAGGAUCAGUUAACUGAGCUACG | [65]     |
| mir-1271| hsa-miR-1271-5p| URS000075B58F_9606 | GAAGGAUCAGUUAACUGAGCUACG | [65]     |
|        | (hsa-miR-1271) |            |                           |          |
| mir-1272| hsa-miR-1272   | URS000075B58F_9606 | GAAGGAUCAGUUAACUGAGCUACG | [65]     |
| mir-1273| hsa-miR-1273a  | URS000075B58F_9606 | GAAGGAUCAGUUAACUGAGCUACG | [65]     |
|        | hsa-miR-1273d  | URS000075B58F_9606 | GAAGGAUCAGUUAACUGAGCUACG | [65]     |
|        | hsa-miR-1273e  | URS000075B58F_9606 | GAAGGAUCAGUUAACUGAGCUACG | [65]     |
|        | hsa-miR-1273f  | URS000075B58F_9606 | GAAGGAUCAGUUAACUGAGCUACG | [65]     |
| mir-1275| hsa-miR-1275   | URS000075B58F_9606 | GAAGGAUCAGUUAACUGAGCUACG | [65]     |
|        | hsa-miR-128-1-5p| URS000075B58F_9606 | GAAGGAUCAGUUAACUGAGCUACG | [65]     |
|        | (hsa-miR-128a) |            |                           |          |
| mir-128 | hsa-miR-128-3p | URS000075B58F_9606 | GAAGGAUCAGUUAACUGAGCUACG | [65]     |
|        | (hsa-miR-128a) |            |                           |          |
| mir-1285| hsa-miR-1285-3p| URS000075B58F_9606 | GAAGGAUCAGUUAACUGAGCUACG | [65]     |
|        | (hsa-miR-1285) |            |                           |          |
| mir-1285| hsa-miR-1285-5p| URS000075B58F_9606 | GAAGGAUCAGUUAACUGAGCUACG | [65]     |
|        | (hsa-miR-1285) |            |                           |          |
| mir-129 | hsa-miR-129-2-3p| URS000075B58F_9606 | GAAGGAUCAGUUAACUGAGCUACG | [65]     |
| Family      | Name                        | RNAcental | Sequence                                                                 | Ref.   |
|------------|-----------------------------|-----------|--------------------------------------------------------------------------|--------|
| hsa-miR-129-5p | URS00004E1410_9606         | CUUUUUGGGCGUGGGCUGUUCGCU         | [54]                           |
| mir-1290    | URS000043F369_9606          | UGGAAUUUGGAUCAGGGGCG            | [54, 65, 66]                   |
| mir-1291    | URS000047E28E_9606          | UGGCUCUGCACGAGCGAGCCAGGCAU       | [54, 65]                       |
| mir-1292    | URS000055860D_9606          | UGGGAACGGGUGUGCCAGCGCGUUGGCU            | [67]                           |
| mir-130     | URS0000315338_9606          | CAGUGCAAGUGUUAAGGGCAU           | [65]                           |
| mir-1303    | URS000032FC1A_9606          | UUUAGAGACGGGCUUCUUCGCU         | [54, 65]                       |
| mir-1305    | URS000040EC3B_9606          | UUUUCAACUCUAUGGGAAGGA           | [65]                           |
| mir-1306    | URS0000500449_9606          | CCACCUCCCUGAAGACGCUCA           | [67]                           |
| mir-1307    | URS00000EEF5F_9606          | UCGACCGGACUCGCAGCGCU            | [54]                           |
| mir-132     | URS00006054DA_9606          | UAACAGUCUCAAGCCUAGUGCU          | [65]                           |
| mir-133     | URS00001D6BAE_9606          | UAACAGUCUCCAGUCCGACG           | [65]                           |
| mir-134     | URS0000272A92_9606          | UGUACUGUGUACAGUGACCGG           | [65]                           |
| mir-135     | URS00000759B67_9606         | UGGGGAGCGGCCCCGUGGGG           | [67]                           |
| mir-136     | URS000000204177_9606        | CAUCAUCUGUCUAAUGAGUCU          | [54, 65]                       |
| mir-137     | URS00004EAB18_9606          | ACUCCAUUGUUGUGUGAUGAG           | [65]                           |
| mir-138     | URS000075AA94_9606          | GCUGAUCAGCAGCAGUCGGU           | [65]                           |
| mir-139     | URS000040780F_9606          | AGUUGGGCGUAAGCGCAUGG           | [54, 65]                       |
| mir-140     | URS0000023BE29_9606         | UGAGACGGCGGCGUGUUGCUGG         | [65]                           |
| mir-142     | URS00002620A7_9606          | UGUUGAGGUUUCUCAUUUAUGGA        | [65]                           |
| mir-143     | URS00001E0AEA_9606          | CAUAAAGUUGAAGAAGCAGCUA         | [65]                           |
| mir-144     | URS000005C2A6D_9606         | UGAGAAGUGACUGACAGUGC           | [11, 53, 54, 65]               |
| mir-145     | URS0000037C5A8_9606         | UACAGUAUAGAUGAUGUAC           | [53, 54, 65]                   |
| mir-146     | URS000002E92A8_9606         | GGAUAAUAUCAUAAUCAGUAAG        | [65]                           |
| mir-147     | URS0000052F380_9606         | GGAUUGUGGAUGAAUGUUCGUCU        | [65]                           |
| mir-148     | URS0000052F89_9606          | GUCCAGUUUUCCCAGGAUCCCU         | [12, 65, 66]                   |
| mir-149     | URS000050B527_9606          | UGAGAUCGAAUUUCAUGG             | [11, 65, 69–71]                |
| mir-150     | URS000050CCE0_9606          | UGCCCGUGACUGACUGUUCG            | [65]                           |
| mir-151     | URS000061B694_9606          | UGAGAAGUAGUAUCUAGG             | [11, 65]                  |
| Family | Name | RNAcental | Sequence | Ref. |
|--------|------|-----------|----------|------|
| mir-1468 | hsa-miR-1468-5p | URS00002ECEE4_9606 | CUCGUUUUGCCUGUUUCGCU | [54] |
| mir-148 | hsa-miR-148a-3p | URS00003BBF48_9606 | UCAGUAGCUCAGAAGCUUUGU | [54, 64, 65, 74] |
| | (hsa-miR-148a) | | | [63, 64, 70] |
| | hsa-miR-148b-3p | | | [65] |
| | (hsa-miR-148b) | | | [65] |
| | hsa-miR-148b-5p | | | [65] |
| | (hsa-miR-148b*) | | | [65] |
| mir-149 | hsa-miR-149-3p | URS00001C770D_9606 | UUGCUUUCUUGCUUUCGCU | [65] |
| | hsa-miR-149-5p | | | [65] |
| mir-15 | hsa-miR-15a-3p | URS00001C94E0_9606 | CAGGCCAUAUAUUGCUUCUCA | [65] |
| | (hsa-miR-15a*) | | | [65] |
| | hsa-miR-15b-3p | | | [65] |
| | (hsa-miR-15b) | | | [65] |
| | hsa-miR-15b-5p | | | [65] |
| | (hsa-miR-15b) | | | [65] |
| | hsa-miR-16-1-3p | | | [65] |
| | (hsa-miR-16-1*) | | | [65] |
| | hsa-miR-16-2-3p | | | [65] |
| | (hsa-miR-16-2*) | | | [65] |
| | hsa-miR-16-5p | | | [65] |
| | (hsa-miR-16) | | | [65] |
| | hsa-miR-195-3p | | | [65] |
| | hsa-miR-195-5p | | | [65] |
| | (hsa-miR-195) | | | [65] |
| | hsa-miR-150-5p | | | [65] |
| | (hsa-miR-150) | | | [65] |
| | hsa-miR-153-3p | | | [54] |
| | hsa-miR-1538 | | | [67] |
| | hsa-miR-154-3p | | | [65] |
| | (hsa-miR-154) | | | [65] |
| | hsa-miR-323a-3p | | | [65] |
| | (hsa-miR-323) | | | [65] |
| | hsa-miR-323b-5p | | | [65] |
| | (hsa-miR-453) | | | [65] |
| | hsa-miR-369-3p | | | [65] |
| | hsa-miR-369-5p | | | [65] |
| | (hsa-miR-377) | | | [65] |
| | hsa-miR-381-3p | | | [54] |
| | hsa-miR-382-5p | | | [65] |
| | (hsa-miR-382) | | | [65] |
| | hsa-miR-409-3p | | | [54] |
| | hsa-miR-409-5p | | | [54] |
| | hsa-miR-410-3p | | | [54] |
| | hsa-miR-539-5p | | | [65] |
| | (hsa-miR-539) | | | [65] |
| mir-155 | hsa-miR-155-5p | | | [65] |
| | (hsa-miR-155) | | | [65] |
| mir-17 | hsa-miR-106a-5p | | | [65] |
| | (hsa-miR-106a) | | | [65] |
| | hsa-miR-106b-3p | | | [65] |
| | (hsa-miR-106b*) | | | [65] |
Table 2 (continued)

| Family | Name | RNAcental | Sequence | Ref. |
|--------|------|-----------|----------|------|
| hsa-miR-106b-5p (hsa-miR-106b) | URS00004449AE_9606 | UAAAGUGCUAGCAGACUGA | [65] |
| hsa-miR-17-3p (hsa-miR-17*) | URS00004636A3_9606 | ACUGCAGUGAACACUGCUAG | [65] |
| hsa-miR-17-5p (hsa-miR-17) | URS00002075FA_9606 | CAAAGUGCUAAGCAGAUG | [65] |
| hsa-miR-18a-3p (hsa-miR-18a*) | URS00004311FE_9606 | ACUGCCCUAAGCUCUCUUCUG | [65] |
| hsa-miR-18a-5p (hsa-miR-18a) | URS000035CC3E_9606 | UAAAGUGCUAUCAGACUGA | [65] |
| hsa-miR-18b-5p (hsa-miR-18b) | URS00004565E5_9606 | UAAAGUGCUAUCAGACUGA | [65] |
| hsa-miR-20a-3p (hsa-miR-20a*) | URS0000042E1F_9606 | UAAAGUGCUAUCAGACUGA | [65] |
| hsa-miR-20a-5p (hsa-miR-20a) | URS00000754A2C_9606 | UAAAGUGCUAUCAGACUGA | [65, 72] |
| mir-17 | hsa-miR-20b-5p (hsa-miR-20b) | URS000002B378_9606 | CAAAGUGCUAUCAGACUGA | [65] |
| hsa-miR-93-3p (hsa-miR-93*) | URS0000149452_9606 | AACAUUCAACGCUGUGGUG | [54, 59] |
| hsa-miR-93-5p (hsa-miR-93) | URS00004565E5_9606 | UAAAGUGCUAUCAGACUGA | [65] |
| hsa-miR-181a-2-3p (hsa-miR-181a-2*) | URS000003F252_9606 | ACCAUCGACCGUGUAACUAC | [65] |
| mir-181 | hsa-miR-181a-3p (hsa-miR-181a-1) | URS00003DA300_9606 | AACAUUCAACGCUGUGGUG | [54, 65] |
| hsa-miR-181b-5p (hsa-miR-181b) | URS0000605E00_9606 | AACAUUCAACGCUGUGGUG | [54] |
| hsa-miR-181c-3p (hsa-miR-181c*) | URS0000244A71_9606 | AACAUUCAACGCUGUGGUG | [65] |
| hsa-miR-181c-5p (hsa-miR-181c) | URS000018C928_9606 | AACAUUCAACGCUGUGGUG | [54, 65] |
| mir-182 | hsa-miR-182-5p (hsa-miR-182) | URS00001CC379_9606 | UUUGCGAAAGUGUAGAACUCA | [65] |
| mir-1825 | hsa-miR-1825 | URS0000754A4A_9606 | UCAGUCGUCCUCUCUCUCUC | [65] |
| hsa-miR-183-3p (hsa-miR-183) | URS0000528C96_9606 | UAGCAUUCGAGAGGGGAUA | [65] |
| hsa-miR-183-5p (hsa-miR-183) | URS0000528C96_9606 | UAGCAUUCGAGAGGGGAUA | [65] |
| mir-184 | hsa-miR-184 | URS0000543D82_9606 | UGGACGAGAAACUGUAAAGGGG | [65] |
| hsa-miR-185-3p | URS00002367FA_9606 | AGGGCGUUGCUUUCCUCUGUCG | [67] |
| hsa-miR-185-5p (hsa-miR-185) | URS00004176D4_9606 | UGGAGAGAAAGGCAGUUCCUG | [65, 70] |
| mir-186 | hsa-miR-186-5p (hsa-miR-186) | URS000040DCFF_9606 | CAAAGAAUCUCCUUUUGGCU | [54, 65, 70] |
| hsa-miR-188-3p (hsa-miR-188) | URS00004B4B85_9606 | CCUCACACACCCAGGCUUGCU | [65, 67] |
| hsa-miR-332-3p (hsa-miR-332) | URS00004636A3_9606 | ACUGCAGUGAACACUGCUAG | [65, 70] |
| hsa-miR-660-5p (hsa-miR-660) | URS00000116A0_9606 | UACCCAGUCAUGCAUGGAGGU | [65, 70] |
| mir-19 | hsa-miR-19a-3p (hsa-miR-19a) | URS000006FD4D_9606 | UGGUGGAUUCAUAGCAAAACUGA | [65, 70] |
| hsa-miR-19b-1-5p (hsa-miR-19b-1) | URS000018C928_9606 | AACAUUCAACGCUGUGGUG | [54, 65] |
| hsa-miR-19b-3p (hsa-miR-19b) | URS000019D317_9606 | UGGCAUACCUAGGAAAACUGA | [65, 66, 70, 72] |
| mir-190 | hsa-miR-190a-5p (hsa-miR-190) | URS0000520927_9606 | UGGCAUACCUAGGAAAACUGA | [65] |
| mir-1908 | hsa-miR-1908-3p | URS0000754A4A_9606 | CCCGCGCGCGCGCGCGCGCGC | [54] |
| hsa-miR-1908-5p | URS00002373FD_9606 | CGCGCGCGCGCGCGCAUG | [67] |
| Family | Name | RCental | Sequence | Ref. |
|--------|------|---------|----------|------|
| mir-191 | hsa-miR-191-3p (hsa-miR-191*) | URS00002B2B5C_9606 | GCUUGCGCUUUGAUUUCGUCCCC | [65] |
| | hsa-miR-191-5p (hsa-miR-191) | URS00005C2E31_9606 | CAACCGAAACCACAAAGCAGCUG | [11, 54, 65, 66, 70] |
| mir-1914 | hsa-miR-1914-3p | URS000075E34C_9606 | GAGGGGGUCGGCGACUGGGGAGG | [67] |
| mir-1915 | hsa-miR-1915-3p (hsa-miR-192*) | URS000039BF2D_9606 | CCCAGGGCGAGCGCGCGGGA | [12, 72] |
| mir-192 | hsa-miR-192-3p (hsa-miR-192**) | URS00005B9A2_9606 | UCGCAGAUUCCAGUGAGCACAG | [65] |
| | hsa-miR-192-5p (hsa-miR-192) | URS0000155642_9606 | UGCAGAACUACAGGCAUGGU | [54, 65, 66] |
| mir-193 | hsa-miR-193a-3p | URS00005DBAF3_9606 | AACUGCCCUAAGAGCACUGGA | [54, 65] |
| | hsa-miR-193a-5p (hsa-miR-193b) | URS0000367985_9606 | UGGGUCUUUGCGGGCGAGAUGA | [54, 65, 66] |
| | hsa-miR-193b-3p (hsa-miR-193b*) | URS00001E1DC5_9606 | CGGGGUUUUGAGGGCGAGAUGA | [53, 65] |
| mir-194 | hsa-miR-194-5p (hsa-miR-194) | URS000029C2DC_9606 | UGUAAACGCAACUCAGUGGA | [65] |
| mir-196 | hsa-miR-196a-5p | URS0000D6AAG7_9606 | UAGGUAUUUGAAGACUGGGA | [53, 59] |
| | hsa-miR-196b-5p (hsa-miR-196b) | URS0000611746_9606 | UAGGUAUUUGAAGACUGGGA | [53, 65] |
| mir-197 | hsa-miR-197-3p (hsa-miR-197) | URS000061E740_9606 | UUCACCACCUCCACCCGACG | [65] |
| | hsa-miR-197-5p (hsa-miR-197) | URS00002E2DD_9606 | CGGGUGAAGAGGCACUGGGAGG | [67] |
| mir-1972 | hsa-miR-1972 | URS000042A1A2_9606 | UACGGCCAGCAACAGUGGCUCA | [54, 66] |
| mir-198 | hsa-miR-198 | URS000075ACA3_9606 | GUUGCAGAGGGGAGAUGGUUC | [65] |
| mir-199 | hsa-miR-199a-5p (hsa-miR-199a) | URS0000554A4F_9606 | CCCAGUGUUCAGAACCACUCAGC | [53, 54, 65] |
| | hsa-miR-199b-3p (hsa-miR-199b) | URS00003F2D94_9606 | ACAGUAUGUCGCAUAGUGUUA | [53, 65, 66, 72] |
| | hsa-miR-199b-5p (hsa-miR-199b) | URS000029EBD_9606 | CCCAGUGUUAAGACUACUGUCU | [53, 65, 67] |
| mir-203 | hsa-miR-203a-3p (hsa-miR-203) | URS00004DA9DB_9606 | GUGAAGUUGUUGAAGGACACUAG | [65] |
| mir-204 | hsa-miR-204-3p (hsa-miR-204) | URS000059A01D_9606 | GCUGGGAAGCGCAAGGAGCUG | [54] |
| | hsa-miR-204-5p (hsa-miR-204) | URS000029DF9F1_9606 | UUCCGCUUGUGCAUCCAGCU | [54, 65] |
| mir-205 | hsa-miR-205-3p (hsa-miR-205) | URS0000446722_9606 | UCCUUCUUCACCCGAGACUCUG | [54, 65, 68] |
| | hsa-miR-205-5p (hsa-miR-205) | URS000009262D_9606 | CAACACGUGACGUGUCGUGU | [54, 65] |
| mir-21 | hsa-miR-21-3p (hsa-miR-21+) | URS000039ED8D_9606 | UAGCUAAUCAGACUGAGUUGA | [53, 54, 65] |
| | hsa-miR-21-5p (hsa-miR-21) | URS000009262D_9606 | CAACACGUGACGUGUCGUGU | [54, 65] |
| | hsa-miR-21 (hsa-miR-21) | URS000039ED8D_9606 | UAGCUAAUCAGACUGAGUUGA | [53, 54, 65] |
| | hsa-miR-21 (hsa-miR-21) | URS000009262D_9606 | CAACACGUGACGUGUCGUGU | [54, 65] |
| mir-210 | hsa-miR-210-5p | URS000009262D_9606 | CAACACGUGACGUGUCGUGU | [54, 65] |
| mir-214 | hsa-miR-214-3p (hsa-miR-214) | URS000020DF8A_9606 | UAGCUAAUCAGACUGAGUUGA | [53, 54, 65] |
| | hsa-miR-214-5p (hsa-miR-214) | URS000009262D_9606 | CAACACGUGACGUGUCGUGU | [54, 65] |
| mir-216 | hsa-miR-216a-5p (hsa-miR-216a) | URS0000318E24_9606 | UAGCUAAUCAGACUGAGUUGA | [53, 54, 65] |
| mir-218 | hsa-miR-218-2-3p (hsa-miR-218-2*) | URS00001F9A0F_9606 | CAUGGCUUGUGCAAGCAGCAGCUG | [65] |
| | hsa-miR-218-5p (hsa-miR-218) | URS000020DF8A_9606 | UAGCUAAUCAGACUGAGUUGA | [53, 54, 65] |
| mir-219 | hsa-miR-219a-5p (hsa-miR-219) | URS0000568C8D_9606 | UAGCUAAUCAGACUGAGUUGA | [53, 54, 65] |
| mir-22 | hsa-miR-22-3p (hsa-miR-22) | URS0000096022_9606 | AAGCUUGCGACUGAAGAAGCUG | [11, 12, 53, 54, 65] |
| Family | Name | RNAcental | Sequence | Ref. |
|--------|------|-----------|----------|------|
|        |      | hsa-miR-22-5p | AGUUUCUUGAGGCAAGCUUUA | [65, 70] |
| mir-221|      | hsa-miR-22-3p * | AGCUCAUUGCUUGCUUGGG | [12, 54, 59, 65, 66, 69] |
|        |      | hsa-miR-221-3p * | AGCUCAUUGCUUGCUUGGG | [11, 12, 54, 59, 64, 65, 70] |
|        |      | hsa-miR-222-3p | AGCUCAUUGCUUGCUUGGG | [12, 54, 65] |
| mir-222|      | hsa-miR-222-5p | AGCUACAUUGCUUGCUUGGG | [65] |
|        |      | hsa-miR-223-3p | AGCUACAUUGCUUGCUUGGG | [65] |
| mir-223|      | hsa-miR-223-5p | AGCUACAUUGCUUGCUUGGG | [65] |
|        |      | hsa-miR-224-3p | AGCUACAUUGCUUGCUUGGG | [65] |
|        |      | hsa-miR-224-5p | AGCUACAUUGCUUGCUUGGG | [65] |
| mir-23 |      | hsa-miR-23a-3p | AGCUACAUUGCUUGCUUGGG | [12, 54, 59, 66, 69, 72] |
|        |      | hsa-miR-23b-3p | AGCUACAUUGCUUGCUUGGG | [12, 54, 66] |
| mir-24 |      | hsa-miR-24-1-5p | AGCUACAUUGCUUGCUUGGG | [65] |
|        |      | hsa-miR-24-2-5p | AGCUACAUUGCUUGCUUGGG | [65] |
|        |      | hsa-miR-24-3p | AGCUACAUUGCUUGCUUGGG | [65] |
|        |      | hsa-miR-25-3p | AGCUACAUUGCUUGCUUGGG | [65] |
|        |      | hsa-miR-25-5p | AGCUACAUUGCUUGCUUGGG | [65] |
| mir-25 |      | hsa-miR-25a-3p | AGCUACAUUGCUUGCUUGGG | [64, 65] |
|        |      | hsa-miR-25a-5p | AGCUACAUUGCUUGCUUGGG | [65] |
|        |      | hsa-miR-25b-3p | AGCUACAUUGCUUGCUUGGG | [54, 65] |
|        |      | hsa-miR-25b-5p | AGCUACAUUGCUUGCUUGGG | [65] |
| mir-26 |      | hsa-miR-26a-3p | AGCUACAUUGCUUGCUUGGG | [65] |
|        |      | hsa-miR-26a-5p | AGCUACAUUGCUUGCUUGGG | [65] |
|        |      | hsa-miR-26b-3p | AGCUACAUUGCUUGCUUGGG | [65] |
|        |      | hsa-miR-26b-5p | AGCUACAUUGCUUGCUUGGG | [65] |
|        |      | hsa-miR-26a-1-3p | AGCUACAUUGCUUGCUUGGG | [65] |
|        |      | hsa-miR-26a-1-5p | AGCUACAUUGCUUGCUUGGG | [65] |
| mir-27 |      | hsa-miR-27a-3p | AGCUACAUUGCUUGCUUGGG | [12, 53, 65] |
|        |      | hsa-miR-27a-5p | AGCUACAUUGCUUGCUUGGG | [65, 70] |
|        |      | hsa-miR-27b-3p | AGCUACAUUGCUUGCUUGGG | [54, 65] |
|        |      | hsa-miR-27b-5p | AGCUACAUUGCUUGCUUGGG | [65] |
| mir-28 |      | hsa-miR-28a-3p | AGCUACAUUGCUUGCUUGGG | [11, 54, 65] |
|        |      | hsa-miR-28a-5p | AGCUACAUUGCUUGCUUGGG | [54, 65] |
|        |      | hsa-miR-28b-3p | AGCUACAUUGCUUGCUUGGG | [54, 65] |
|        |      | hsa-miR-28b-5p | AGCUACAUUGCUUGCUUGGG | [65] |
| mir-2861|      | hsa-miR-2861 | AGCUACAUUGCUUGCUUGGG | [72] |
| mir-29 |      | hsa-miR-29a-3p | AGCUACAUUGCUUGCUUGGG | [54, 65] |
| Family | Name | RNAcentral | Sequence | Ref. |
|--------|------|------------|----------|-----|
| hsa-miR-29a-5p | URS0000076995_9606 | ACUGAUUUUCUUGGGUGUGUCAG | [65, 70] |
| hsa-miR-29b-1-5p | URS00001123BD_9606 | GCUGUUUUCAUGGGUUGUUAAGA | [65] |
| hsa-miR-29b-2-5p | URS0000403C02_9606 | CUGGUUUCACAGGUGGCUUAG | [65] |
| hsa-miR-29b-3p | URS000024463E_9606 | UAGCACAAUUGAUAUGAGUUA | [54, 65] |
| hsa-miR-29c-3p | URS000024463E_9606 | UAGCACAAUUGAUAUGAGUUA | [54, 65] |
| hsa-miR-296 | URS00001C3AC1_9606 | AGGGCCCCCUCAUCUCCUCUCAGU | [65, 67] |
| hsa-miR-299 | URS000003B1F5C_9606 | UAUGUUGGAUGGUAACCCCUU | [54, 65] |
| hsa-miR-30a-3p | URS000043D1A9_9606 | UGUAAACAUCCUCAGUGAAG | [54, 65] |
| hsa-miR-30a-5p | URS000017DBB8_9606 | UGGUUUACCGUCCCACACAAU | [65] |
| hsa-miR-30b-5p | URS00005165DA_9606 | UGUAAACAUCCUACACUCAG | [65, 70] |
| hsa-miR-30c-5p | URS000019907A_9606 | UGUAAACAUCCUACACUCUCAG | [54, 65] |
| hsa-miR-30d-3p | URS0000070CD2_9606 | UAAGUGCUUCCAUGUUUUGGUGA | [65] |
| hsa-miR-30d-5p | URS0000070CD2_9606 | UAAGUGCUUCCAUGUUUUGGUGA | [65] |
| hsa-miR-31 | URS00002A291B_9606 | AGGCAAGAUGCUGGCAUAGCU | [12, 59, 65] |
| hsa-miR-320-3p | URS00004390F6_9606 | ACUGCCACGUGUGCUGUG | [65, 70] |
| hsa-miR-320-5p | URS00004390F6_9606 | ACUGCCACGUGUGCUGUG | [65, 70] |
| hsa-miR-320a-3p | URS000003C02_9606 | CUGGUUUCACAGGUGGCUUAG | [65] |
| hsa-miR-320b | URS000058BF17_9606 | UGUAAACAUCCUCAGUGAAG | [54, 65] |
| hsa-miR-320c | URS0000010D30_9606 | AAAACGUGGGUGAGGCUAAGC | [54] |
| hsa-miR-320d | URS0000010D30_9606 | AAAACGUGGGUGAGGCUAAGC | [54] |
| hsa-miR-32 | URS0000017DBB8_9606 | UGGUUUACCGUCCCACACAAU | [65] |
| hsa-miR-320a-5p | URS000003C02_9606 | CUGGUUUCACAGGUGGCUUAG | [65] |
| hsa-miR-320b | URS000003C02_9606 | CUGGUUUCACAGGUGGCUUAG | [65] |
| hsa-miR-320c | URS000003C02_9606 | CUGGUUUCACAGGUGGCUUAG | [65] |
| hsa-miR-320d | URS000003C02_9606 | CUGGUUUCACAGGUGGCUUAG | [65] |
| hsa-miR-324 | URS00004390F6_9606 | ACUGCCACGUGUGCUGUG | [65, 70] |
| hsa-miR-326 | URS000003C02_9606 | CUGGUUUCACAGGUGGCUUAG | [65] |
| hsa-miR-329 | URS000003C02_9606 | CUGGUUUCACAGGUGGCUUAG | [65] |
| hsa-miR-33 | URS000017DBB8_9606 | UGGUUUACCGUCCCACACAAU | [65] |
| hsa-miR-330 | URS0000070CD2_9606 | UAAGUGCUUCCAUGUUUUGGUGA | [65] |
| hsa-miR-330-3p | URS0000070CD2_9606 | UAAGUGCUUCCAUGUUUUGGUGA | [65] |
| Family   | Name           | RNAcentral | Sequence                                                                 | Ref.   |
|----------|----------------|------------|--------------------------------------------------------------------------|--------|
| miR-330  | hsa-miR-330    | URS00003380 | UCUCUGGGCCUGUGCUUAGGC                                                   [65]   |
| miR-331  | hsa-miR-331-3p | URS00003DDE | GCCCGUGGGCCUAUCCUGAGA                                                    [65]   |
| miR-335  | hsa-miR-335-3p | URS00005092 | CAGCUAGCGUAGAGUGGAGGAGGAGGAGGAGGAGGAC                                   [65]   |
| miR-337  | hsa-miR-337-3p | URS0000564D | CAGCUAGCGUAGAGUGGAGGAGGAGGAGGAGGAC                                   [65]   |
| miR-338  | hsa-miR-338-3p | URS0000254A | CAGCUAGCGUAGAGUGGAGGAGGAGGAGGAGGAC                                   [65]   |
| miR-339  | hsa-miR-339-3p | URS0000306C | CAGCUAGCGUAGAGUGGAGGAGGAGGAGGAGGAC                                   [65]   |
| miR-34   | hsa-miR-34-3p  | URS00000EED | CAGCUAGCGUAGAGUGGAGGAGGAGGAGGAGGAC                                   [65]   |
| miR-340  | hsa-miR-340-3p | URS00004852 | CAGCUAGCGUAGAGUGGAGGAGGAGGAGGAGGAC                                   [65]   |
| miR-341  | hsa-miR-341    | URS000007FA | CAGCUAGCGUAGAGUGGAGGAGGAGGAGGAGGAC                                   [65]   |
| miR-342  | hsa-miR-342-3p | URS0000148B | CAGCUAGCGUAGAGUGGAGGAGGAGGAGGAGGAC                                   [65]   |
| miR-343  | hsa-miR-343-3p | URS00005A80 | CAGCUAGCGUAGAGUGGAGGAGGAGGAGGAGGAC                                   [65]   |
| miR-344  | hsa-miR-344-3p | URS000005D4 | CAGCUAGCGUAGAGUGGAGGAGGAGGAGGAGGAC                                   [65]   |
| miR-345  | hsa-miR-345-3p | URS0000016E | CAGCUAGCGUAGAGUGGAGGAGGAGGAGGAGGAC                                   [65]   |
| miR-346  | hsa-miR-346-3p | URS00003E72 | CAGCUAGCGUAGAGUGGAGGAGGAGGAGGAGGAC                                   [65]   |
| miR-347  | hsa-miR-347-3p | URS000032A9 | CAGCUAGCGUAGAGUGGAGGAGGAGGAGGAGGAC                                   [65]   |
| miR-348  | hsa-miR-348-3p | URS00003AD2 | CAGCUAGCGUAGAGUGGAGGAGGAGGAGGAGGAC                                   [65]   |
| miR-349  | hsa-miR-349-3p | URS00005E65 | CAGCUAGCGUAGAGUGGAGGAGGAGGAGGAGGAC                                   [65]   |
| miR-350  | hsa-miR-350-3p | URS00004204 | CAGCUAGCGUAGAGUGGAGGAGGAGGAGGAGGAC                                   [65]   |
| miR-351  | hsa-miR-351-3p | URS00003F30 | CAGCUAGCGUAGAGUGGAGGAGGAGGAGGAGGAC                                   [65]   |
| miR-352  | hsa-miR-352-3p | URS000003EA | CAGCUAGCGUAGAGUGGAGGAGGAGGAGGAGGAC                                   [65]   |
| miR-353  | hsa-miR-353-3p | URS00004852 | CAGCUAGCGUAGAGUGGAGGAGGAGGAGGAGGAC                                   [65]   |
| miR-354  | hsa-miR-354-3p | URS000007FA | CAGCUAGCGUAGAGUGGAGGAGGAGGAGGAGGAC                                   [65]   |
| miR-355  | hsa-miR-355-3p | URS0000148B | CAGCUAGCGUAGAGUGGAGGAGGAGGAGGAGGAC                                   [65]   |
| miR-356  | hsa-miR-356-3p | URS00003E72 | CAGCUAGCGUAGAGUGGAGGAGGAGGAGGAGGAC                                   [65]   |
| miR-357  | hsa-miR-357-3p | URS000032A9 | CAGCUAGCGUAGAGUGGAGGAGGAGGAGGAGGAC                                   [65]   |
| miR-358  | hsa-miR-358-3p | URS00005E65 | CAGCUAGCGUAGAGUGGAGGAGGAGGAGGAGGAC                                   [65]   |
| miR-359  | hsa-miR-359-3p | URS00004204 | CAGCUAGCGUAGAGUGGAGGAGGAGGAGGAGGAC                                   [65]   |
| miR-360  | hsa-miR-360-3p | URS00003F30 | CAGCUAGCGUAGAGUGGAGGAGGAGGAGGAGGAC                                   [65]   |
| miR-361  | hsa-miR-361-3p | URS000003E7 | CAGCUAGCGUAGAGUGGAGGAGGAGGAGGAGGAC                                   [65]   |
| miR-362  | hsa-miR-362-3p | URS0000148B | CAGCUAGCGUAGAGUGGAGGAGGAGGAGGAGGAC                                   [65]   |
| miR-363  | hsa-miR-363-3p | URS00003F30 | CAGCUAGCGUAGAGUGGAGGAGGAGGAGGAGGAC                                   [65]   |
| miR-364  | hsa-miR-364-3p | URS000003E7 | CAGCUAGCGUAGAGUGGAGGAGGAGGAGGAGGAC                                   [65]   |
| miR-365  | hsa-miR-365a-3p| URS000003E7 | CAGCUAGCGUAGAGUGGAGGAGGAGGAGGAGGAC                                   [65]   |
| miR-366  | hsa-miR-366-3p | URS000003E7 | CAGCUAGCGUAGAGUGGAGGAGGAGGAGGAGGAC                                   [65]   |
| miR-367  | hsa-miR-367-3p | URS000003E7 | CAGCUAGCGUAGAGUGGAGGAGGAGGAGGAGGAC                                   [65]   |
| miR-368  | hsa-miR-368-3p | URS000003E7 | CAGCUAGCGUAGAGUGGAGGAGGAGGAGGAGGAC                                   [65]   |
| miR-369  | hsa-miR-369-3p | URS000003E7 | CAGCUAGCGUAGAGUGGAGGAGGAGGAGGAGGAC                                   [65]   |
| miR-370  | hsa-miR-370-3p | URS000003E7 | CAGCUAGCGUAGAGUGGAGGAGGAGGAGGAGGAC                                   [65]   |
| miR-371  | hsa-miR-371-3p | URS000003E7 | CAGCUAGCGUAGAGUGGAGGAGGAGGAGGAGGAC                                   [65]   |
| miR-372  | hsa-miR-372-3p | URS000003E7 | CAGCUAGCGUAGAGUGGAGGAGGAGGAGGAGGAC                                   [65]   |
| miR-373  | hsa-miR-373-3p | URS000003E7 | CAGCUAGCGUAGAGUGGAGGAGGAGGAGGAGGAC                                   [65]   |
| miR-374  | hsa-miR-374-3p | URS000003E7 | CAGCUAGCGUAGAGUGGAGGAGGAGGAGGAGGAC                                   [65]   |
| miR-375  | hsa-miR-375-3p | URS000003E7 | CAGCUAGCGUAGAGUGGAGGAGGAGGAGGAGGAC                                   [65]   |
| miR-376  | hsa-miR-376-3p | URS000003E7 | CAGCUAGCGUAGAGUGGAGGAGGAGGAGGAGGAC                                   [65]   |
| miR-377  | hsa-miR-377-3p | URS000003E7 | CAGCUAGCGUAGAGUGGAGGAGGAGGAGGAGGAC                                   [65]   |
| miR-378  | hsa-miR-378-3p | URS000003E7 | CAGCUAGCGUAGAGUGGAGGAGGAGGAGGAGGAC                                   [65]   |

(continues)
| Family | Name         | RNAcentral        | Sequence                                                                 | Ref. |
|--------|--------------|-------------------|--------------------------------------------------------------------------|------|
| mir-379| hsa-miR-380-5p | URS000075BE5F_9606 | UGGUUGACCAUAAGAACAUGGC | [65] |
|        | hsa-miR-411-3p | URS000037DAEA_9606 | UAUUGUACACGGUUCCACUAACC | [65] |
| (hsa-miR-411*) |           | URS00000C5BAA_9606 | UAUUGACCAUAAGGCUAC ACC | [54, 65] |
|        | hsa-miR-758-3p | URS000024B619_9606 | UUGUGACCUCCACUACC | [65] |
| mir-384| hsa-miR-384 | URS000075DD0E_9606 | AUUUCAGAAGUUCUCAUA | [65] |
| mir-3934| hsa-miR-3934-5p | URS00003ACE11_9606 | UCAGGCUCCACACCAGCGAC | [72] |
|        | hsa-miR-411-5p | URS00001C8A86_9606 | UGAAGGCCCCAGACAGAGACCUUU | [54, 65, 66, 69, 70] |
| mir-3940| hsa-miR-411* | URS000056B04E_9606 | AUCGGGAAUGUCGUCGCCGCG | [65] |
|        | hsa-miR-425-5p | URS00003CC245_9606 | ACUGGACUUAGGGUCAGAAGGC | [65] |
| mir-425| hsa-miR-425-3p | URS00003CC245_9606 | ACUGGACUUAGGGUCAGAAGGC | [65] |
| (hsa-miR-425*) |           | URS00001C8A86_9606 | UGAAGGCCCCAGACAGAGACCUUU | [54, 65, 66, 69, 70] |
| mir-431| hsa-miR-431-5p | URS000043908D_9606 | UGGCAGUCAGUACACCCCUUG | [65, 69] |
| mir-432| hsa-miR-432-5p | URS00001C406A_9606 | UCUUUGAGAUAGAUAAGGUGG | [65] |
|        | (hsa-miR-432) | URS00001C406A_9606 | UCUUUGAGAUAGAUAAGGUGG | [65] |
| mir-4446| hsa-miR-4446-3p | URS00000EFOB_9606 | CAGGGCUCCAGCAGACAGACAGG | [67] |
| mir-4449| hsa-miR-4449 | URS00004DE2FC_9606 | CGUCCGCCGUGCGCGCGCGCA | [54, 67] |
| mir-4488| hsa-miR-4488 | URS00001C8A86_9606 | UGAAGGCCCCAGACAGAGACCUUU | [54, 65, 66, 69, 70] |
| mir-449| hsa-miR-449a | URS0000477FED_9606 | UAGUGCAAUAGUUGUAGCGGG | [65] |
| (hsa-miR-449) |           | URS0000477FED_9606 | UAGUGCAAUAGUUGUAGCGGG | [65] |
| mir-450| hsa-miR-450-5p | URS00001F5B39_9606 | UGGCAGUGUAUUGUGUAGCGG | [65] |
| (hsa-miR-449b) |           | URS00001F5B39_9606 | UGGCAGUGUAUUGUGUAGCGG | [65] |
| mir-450| hsa-miR-450a-5p | URS00001BCACA5_9606 | UUGAAAGGCUCUUUCUUUGGC | [65] |
| (hsa-miR-450b) |           | URS00001BCACA5_9606 | UUGAAAGGCUCUUUCUUUGGC | [65] |
| mir-452| hsa-miR-452-5p | URS00004BF1DC_9606 | UCCUGUACUGAGCUCGCCGAG | [65] |
| (hsa-miR-452*) |           | URS00004BF1DC_9606 | UCCUGUACUGAGCUCGCCGAG | [65] |
| mir-454| hsa-miR-454-5p | URS000039A052_9606 | GAGGCUCCGUCCACUACC | [65] |
| (hsa-miR-454*) |           | URS000039A052_9606 | GAGGCUCCGUCCACUACC | [65] |
| mir-455| hsa-miR-455-5p | URS0000022A78C_9606 | GCAGGUCCAGGCAUAUCAC | [65] |
| (hsa-miR-455) |           | URS0000022A78C_9606 | GCAGGUCCAGGCAUAUCAC | [65] |
| mir-483| hsa-miR-483-3p | URS000000EA063_9606 | UCACUCCUCUCUCUCUCCUCU | [65] |
| mir-484| hsa-miR-484 | URS00003573B_9606 | UAGACCGGGGAAAGAAGGGAG | [65] |
| mir-485| hsa-miR-485-3p | URS0000597BED_9606 | UUGUGAAGCCACUCUCUCUCUCU | [54, 65, 67] |
| mir-485| hsa-miR-485-5p | URS00006372A_9606 | GCACAUGAGCUCGGCUCUUCUCU | [65] |
| mir-486| hsa-miR-486-5p | URS00001935FA_9606 | AGAGGCUGCGGCCUGAGUAAUC | [65] |
| (hsa-miR-486) |           | URS00001935FA_9606 | AGAGGCUGCGGCCUGAGUAAUC | [65] |
| mir-488| hsa-miR-488-3p | URS000001BCAC5_9606 | UUGAAAGGCUCUUUCUUUGGUC | [65] |
| (hsa-miR-488) |           | URS000001BCAC5_9606 | UUGAAAGGCUCUUUCUUUGGUC | [65] |
| mir-492| hsa-miR-492 | URS000032599B_9606 | AGGACCUGGCGGAAAGAAGGAG | [65] |
| mir-493| hsa-miR-493-3p | URS00005E7CB2_9606 | UUAAGGACUACUGUAGCCAGG | [65] |
| (hsa-miR-493) |           | URS00005E7CB2_9606 | UUAAGGACUACUGUAGCCAGG | [65] |
| mir-497| hsa-miR-497-5p | URS00001BC212_9606 | CAGCAGCACACUUGGGUUUGU | [65] |
| (hsa-miR-497) |           | URS00001BC212_9606 | CAGCAGCACACUUGGGUUUGU | [65] |
| mir-500| hsa-miR-500a-5p | URS000039A052_9606 | GAGGCUCCGUCCACUACC | [65] |
|        | hsa-miR-500a-5p | URS000039A052_9606 | GAGGCUCCGUCCACUACC | [65] |
| Family | Name | RNAcental | Sequence | Ref. |
|--------|------|-----------|----------|-----|
| (hsa-miR-500) | URS000000E35_9606 | AAUGCACCCGGGCAAGGAUUCU | [65] |
| hsa-miR-501-3p | URS00001E2DBC_9606 | AAUCCUUUGGCGCCUGGGAGGA | [65] |
| (hsa-miR-501) | URS0000601CC4_9606 | AAUGCACCCGGGCAAGGAUUCU | [65] |
| hsa-miR-502-3p | URS00000F6E49_9606 | AAUCCUUUGGCGCCUGGGAGGA | [65] |
| mir-503 | hsa-miR-503-5p | URS00001E2DBC_9606 | AAUGCACCCGGGCAAGGAUUCU | [65] |
| hsa-miR-505-3p | URS00000E2E6A_9606 | UGGUGGGCACAGAAUCUGGACU | [65] |
| (hsa-miR-505) | URS00001E2DBC_9606 | AAUGCACCCGGGCAAGGAUUCU | [65] |
| hsa-miR-505-5p | URS00001E2DBC_9606 | AAUGCACCCGGGCAAGGAUUCU | [65] |
| hsa-miR-505* | URS00001E2DBC_9606 | AAUGCACCCGGGCAAGGAUUCU | [65] |
| mir-506 | hsa-miR-508-3p | URS00000F6E49_9606 | AAUGCACCCGGGCAAGGAUUCU | [65] |
| (hsa-miR-508) | URS00001E2DBC_9606 | AAUGCACCCGGGCAAGGAUUCU | [65] |
| hsa-miR-512-3p | URS00000E2E6A_9606 | UGGUGGGCACAGAAUCUGGACU | [65] |
| (hsa-miR-512) | URS00001E2DBC_9606 | AAUGCACCCGGGCAAGGAUUCU | [65] |
| hsa-miR-512-5p | URS00001E2DBC_9606 | AAUGCACCCGGGCAAGGAUUCU | [65] |
| hsa-miR-513a-3p | URS00001E2DBC_9606 | AAUGCACCCGGGCAAGGAUUCU | [65] |
| (hsa-miR-513-5p) | URS00001E2DBC_9606 | AAUGCACCCGGGCAAGGAUUCU | [65] |
| mir-515 | hsa-miR-517c-3p | URS00001F8E9B_9606 | AAUGCACCCGGGCAAGGAUUCU | [65] |
| (hsa-miR-517c) | URS00001E2DBC_9606 | AAUGCACCCGGGCAAGGAUUCU | [65] |
| hsa-miR-518b | URS00001E2DBC_9606 | AAUGCACCCGGGCAAGGAUUCU | [65] |
| hsa-miR-518d-3p | URS00001F8E9B_9606 | AAUGCACCCGGGCAAGGAUUCU | [65] |
| (hsa-miR-518d) | URS00001E2DBC_9606 | AAUGCACCCGGGCAAGGAUUCU | [65] |
| hsa-miR-518f-3p | URS00001F8E9B_9606 | AAUGCACCCGGGCAAGGAUUCU | [65] |
| (hsa-miR-518f) | URS00001E2DBC_9606 | AAUGCACCCGGGCAAGGAUUCU | [65] |
| mir-541 | hsa-miR-541-3p | URS00000F6E49_9606 | AAUGCACCCGGGCAAGGAUUCU | [65] |
| (hsa-miR-541) | URS00001E2DBC_9606 | AAUGCACCCGGGCAAGGAUUCU | [65] |
| hsa-miR-542-3p | URS00000F6E49_9606 | AAUGCACCCGGGCAAGGAUUCU | [65] |
| (hsa-miR-542) | URS00001E2DBC_9606 | AAUGCACCCGGGCAAGGAUUCU | [65] |
| mir-548 | hsa-miR-548a-3p | URS00000F6E49_9606 | AAUGCACCCGGGCAAGGAUUCU | [65] |
| (hsa-miR-548a) | URS00001E2DBC_9606 | AAUGCACCCGGGCAAGGAUUCU | [65] |
| hsa-miR-548b-3p | URS00000F6E49_9606 | AAUGCACCCGGGCAAGGAUUCU | [65] |
| (hsa-miR-548b) | URS00001E2DBC_9606 | AAUGCACCCGGGCAAGGAUUCU | [65] |
| mir-549 | hsa-miR-549a-3p | URS00000F6E49_9606 | AAUGCACCCGGGCAAGGAUUCU | [65] |
| Family     | Name                  | RNAcental | Sequence                                                                 | Ref.  |
|------------|-----------------------|-----------|--------------------------------------------------------------------------|-------|
| mir-550    | (hsa-miR-549)         | URS00003FFA6C_9606 | AGUGCCUGAGGGAGUAAGAGCCC                                                  | [65]  |
| mir-551    | (hsa-miR-550a-5p)     | URS00002E99CB_9606 | GCGACCCACUCUUGGAGGUUCCA                                                  | [65]  |
| mir-556    | (hsa-miR-550)         | URS00001D6605_9606 | AUAAUACUAUGCUACACCUUU                                                    | [65]  |
| mir-561    | (hsa-miR-556-3p)      | URS000075D1DD_9606 | CAAAGUUAAAGAUCCUCUGAGAGAG                                               | [65]  |
| mir-564    | (hsa-miR-551)         | URS000075ED17_9606 | AGGCAAGUGUGCCAGCAGGC                                                    | [65]  |
| mir-571    | (hsa-miR-551a)        | URS000075C61C_9606 | UGAGUUUUGCCACUAGUGAGAG                                                  | [65]  |
| mir-572    | (hsa-miR-552)         | URS000075CEB8_9606 | GUCUGCUGGCGGUGGCGCCA                                                    | [65]  |
| mir-574    | (hsa-miR-554-3p)      | URS000075CF056_9606 | CACGCUAUCAGCACACCACA                                                      | [65, 66, 72] |
| mir-582    | (hsa-miR-554-5p)      | URS000057466C_9606 | UGAGUGUGUGAGUGAGAGAGG                                                 | [65, 66, 72] |
| mir-584    | (hsa-miR-555-3p)      | URS00002573C3_9606 | UAACUGUGUAAACAACACGAC                                                    | [65]  |
| mir-589    | (hsa-miR-555-5p)      | URS0000272039_9606 | UAAUUAUAUGUAAGCUAGC                                                     | [65]  |
| mir-590    | (hsa-miR-556)         | URS000025E3F32_9606 | GAAGUGUGCCGUGGUGCAGG                                                    | [65]  |
| mir-592    | (hsa-miR-557)         | URS00004F507C_9606 | UUGGUGUAAUGCGAAGAGG                                                    | [65]  |
| mir-593    | (hsa-miR-557-3p)      | URS000075D407_9606 | UGUCUCUGGCGGUGGUGC                                                      | [65]  |
| mir-595    | (hsa-miR-558-3p)      | URS000075B75E_9606 | GAAAGUGUAGCAGCAGG                                                      | [65]  |
| mir-596    | (hsa-miR-558-5p)      | URS000075B35F_9606 | AACGCUCCGCGCGCUCUCGG                                                    | [65]  |
| mir-6089   | (hsa-miR-560-3p)      | URS000075B63F_9606 | GGGAGCGCGGGCGGCGGCGG                                                    | [12]  |
| mir-615    | (hsa-miR-561-3p)      | URS00003D5391_9606 | UCCAGGCGCCUGGUCUCUCUCUU                                                  | [53, 54] |
| mir-616    | (hsa-miR-561-5p)      | URS00004D8280_9606 | GGGGCGCCGCGGUCGCAGG                                                     | [65, 67] |
| mir-618    | (hsa-miR-562)         | URS00005E3F32_9606 | AGUCUAUGGAGGUGGUGAGC                                                    | [65]  |
| mir-619    | (hsa-miR-562-3p)      | URS0000450P92_9606 | AAAAAAAAAAAUCAUGCCAGAGG                                                  | [65]  |
| mir-622    | (hsa-miR-563)         | URS000075B584_9606 | GCUUGGAAUAAAAGCAGGACC                                                    | [54, 66] |
| mir-623    | (hsa-miR-563-3p)      | URS000075E944_9606 | AAGCUAGCAGAGAGGUGGAGG                                                  | [65]  |
| mir-625    | (hsa-miR-563-5p)      | URS000075DB1_9606  | AUCCACUCGAGGCGGCGGCGG                                                     | [65]  |
| mir-628    | (hsa-miR-563-5p)      | URS0000475E09_9606 | GACUAUAGAAGCUUUCCCCCCCUCA                                                 | [65]  |
| mir-629    | (hsa-miR-564)         | URS000061BE3B_9606 | UCUAGUAAAGAGUGCGAGG                                                     | [65]  |
| mir-636    | (hsa-miR-564-3p)      | URS00002F3336_9606 | UGGGUGUGAGUUGGAGAACC                                                    | [65]  |
| mir-638    | (hsa-miR-565)         | URS000075A79D_9606 | UGUGCUUGCUUGGCGGCGGCGGCGG                                               | [65]  |
| mir-639    | (hsa-miR-566)         | URS000075DB2F_9606 | AGAAGGCUAGGCGGCGGCGGCGG                                                 | [12, 65, 70, 72] |
| mir-641    | (hsa-miR-567)         | URS000075B8B8_9606 | AUCGUCGAGGCGUGAAGGAGG                                                  | [65]  |
| mir-642    | (hsa-miR-567-3p)      | URS00003D9790_9606 | AAAGACAUAGAUAAGACAGC                                                     | [65]  |
| mir-649    | (hsa-miR-568)         | URS000075B1CE_9606 | GGUUCCCCUCUCAAUUGGAGC                                                   | [73]  |
| mir-650    | (hsa-miR-569)         | URS000075D5BB_9606 | AAACCUAUCUGGCAGG                                                       | [65]  |
| mir-6511   | (hsa-miR-570)         | URS000075AO9C_9606 | AAAAAACUGUGAGZCAGG                                                      | [65]  |
| hsa-miR-571 | (hsa-miR-570-3p)      | URS000075C82B_9606 | AAAAAACGGAAGGCGGCGGAGGAGG                                                | [67]  |
| hsa-miR-572 | (hsa-miR-570-5p)      | URS0000759CCE_9606 | CCCCCCACCCCCUCCUCCGCGCGA                                                  | [67]  |
| mir-652    | (hsa-miR-571)         | URS00001D3D8_9606  | AAAAAACUGGAGCAGG                                                        | [64]  |
| mir-654    | (hsa-miR-571-3p)      | URS00002F40E9_9606 | UAAUUCGUAGUGACAGG                                                        | [65]  |
| hsa-miR-572 | (hsa-miR-571-5p)      | URS00002B0B46_9606 | UGGUGGGCGCAGAAGAAGGC                                                      | [65]  |
Table 2 (continued)

| Family | Name | RNAcental | Sequence | Ref. |
|--------|------|-----------|----------|------|
| (hsa-miR-654) | URS000075C4C7_9606 | GGCAGGUUCCACCCUCUCUAGG | [65] |
| mir-657 | hsa-miR-657 | URS00004929F1_9606 | AGGCCGGCGCCGCCGCCGCCGCC | [54, 66, 67] |
| mir-661 | hsa-miR-661 | URS000075C3F6_9606 | GGGUGGCCGCAGCCGUGUGGAG | [54, 65, 67] |
| mir-663 | URS00004929F1_9606 | AGGCCGGCGCCGCCGCCGCCGCC | [54, 66, 67] |
| mir-664 | hsa-miR-664a-3p | URS000029AE45_9606 | UAUUCUAUUACCCCAAGCUACA | [65, 66] |
| mir-665 | hsa-miR-665 | URS0000572E11_9606 | AGGAGCUUACCAUCUAGCUGG | [65] |
| mir-671 | hsa-miR-671 | URS00002FB368_9606 | AGGAAGCCUCAGGAGGUGGAGG | [67] |
| mir-671-3p | hsa-miR-671 | URS00002FB368_9606 | AGGAAGCCUCAGGAGGUGGAGG | [67] |
| mir-6724 | hsa-miR-6724-5p | URS00007777B8_9606 | CUGGAGCCGGCGCCGGCGGGG | [67] |
| mir-675 | hsa-miR-675-5p | URS00004E5112_9606 | UGGUGCGGAGGGCCACAGUG | [67] |
| mir-760 | hsa-miR-760 | URS0000512C88_9606 | CGGCUCUGGGUCUGUGGGGA | [67] |
| mir-761 | hsa-miR-761 | URS0000327AFF_9606 | GGGGCGGGGCGGGCGGGCGGGG | [72] |
| mir-7641 | hsa-miR-7641 | URS000075B793_9606 | UUGAACUCCGAGAAGCUAACG | [54, 66, 67] |
| mir-766 | hsa-miR-766-3p | URS00001012BC_9606 | ACUCAGCCCACAGCCUCAGC | [65] |
| mir-769 | hsa-miR-769-5p | URS00004E008F_9606 | UGAGACUCUCCGUGUCUGACG | [54, 65, 67] |
| mir-770 | hsa-miR-770-5p | URS000075A169_9606 | UCCAGUACCAGUUCUGAGGCCCA | [65] |
| mir-8 | (hsa-miR-141-3p) | URS000003E1A9_9606 | UAAACACUGUCCUGUAAGAGG | [65] |
| mir-8069 | hsa-miR-8069 | URS0000575E1C1_9606 | GGAUGUUGGGGCGGCGGGCGGG | [12] |
| mir-874 | (hsa-miR-874-3p) | URS00005609ED_9606 | UCCGAGGGCCAGGAGGACC | [67] |
| mir-875 | hsa-miR-875-5p | URS0000312ECD_9606 | UGAAAGACUCCAGUUUAACAGGUG | [65] |
| mir-876 | hsa-miR-876-5p | URS0000470305_9606 | UGGAAUUUCCUGGUGAAUCACCA | [65] |
| mir-885 | hsa-miR-885-5p | URS0000246356_9606 | UCCAUUACAUCCUGUCCUCUC | [65] |
| mir-9 | (hsa-miR-9-3p) | URS00004208C5_9606 | UCUUUGUUUAACUUGAGCUAUGA | [54, 65, 67] |
| mir-R922 | hsa-miR-9-3p | URS0000575D3F5_9606 | GCAGCAGCAGAUAAGGCAUCAGUC | [65] |
| mir-R935 | hsa-miR-9-3p | URS0000312ECD_9606 | UGAUCUACUGUAUCAGC | [65] |
| mir-R937 | hsa-miR-9-3p | URS0000553F81_9606 | AUCCGGCCUGUCAUCUGUCC | [65] |
| mir-R938 | hsa-miR-9-3p | URS000075DF80_9606 | UCCGGCCAAAGGGAACCCAG | [65] |
### Table 2 (continued)

| Family | Name                          | RNAcental     | Sequence                           | Ref. |
|--------|-------------------------------|---------------|------------------------------------|------|
|        | hsa-miR-939-5p                | URS00005A31EB_9606 | UGGGGAGGCUGAGGCUUGGGGUGG           | [65] |
|        | (hsa-miR-939)                 |               |                                    |      |
| mir-941| hsa-miR-941                   | URS000050E4BA_9606 | CACCCGCGUGUGGACAGUG              | [65] |
| mir-95 | hsa-miR-545-3p                | URS00002E1509_9606 | UCAGAAAACUUAAUUGUGGU             | [65] |
|        | (hsa-miR-545)                 |               |                                    |      |
|        | hsa-miR-545-5p                | URS00004C4520_9606 | UCAGAUAAGUUAUUGAGAUG            | [65] |
|        | (hsa-miR-545*)               |               |                                    |      |
|        | hsa-let-7c                    | –             | –                                  | [65] |
|        | hsa-miR-1                     | –             | –                                  | [65] |
|        | hsa-miR-10                    | URS00005D8C46_9606 | UACCCUGUAAGAACCGAUUG          | [74] |
|        | hsa-miR-10395-3p              | URS00005D2042_9606 | AUGUAUUCGUACUGUGUCG          | [59] |
|        | hsa-miR-10395-5p              | URS0000D53F1E_9606 | GUGAUUGAGAGCAAUACC          | [59] |
|        | hsa-miR-1180                  | –             | –                                  | [65] |
|        | hsa-miR-1234-5p               | –             | –                                  | [72] |
|        | hsa-miR-1274a                 | –             | –                                  | [65] |
|        | hsa-miR-1274b                 | –             | –                                  | [65] |
|        | hsa-miR-1298                  | –             | –                                  | [65] |
|        | hsa-miR-1300                  | –             | –                                  | [65] |
|        | hsa-miR-133a                  | –             | –                                  | [65] |
|        | hsa-miR-152                   | –             | –                                  | [65] |
|        | hsa-miR-190b                  | –             | –                                  | [65] |
|        | hsa-miR-199                   | URS000027FB26_9606 | CCCAGUGUUUAAGACUAUGC          | [74] |
|        | hsa-miR-210                   | –             | –                                  | [65] |
|        | hsa-miR-215                   | –             | –                                  | [65] |
|        | hsa-miR-219-2-3p              | –             | –                                  | [65] |
|        | hsa-miR-2277-5p               | URS00000D6C3F_9606 | AGCGCGGCGUGACGCGUCGCAGUC   | [67] |
|        | hsa-miR-23-3p                 | –             | –                                  | [73] |
|        | hsa-miR-26                    | –             | –                                  | [74] |
|        | hsa-miR-3178                  | URS0000365675_9606 | GGGGCGCGGCGCCGGAUCG         | [12] |
|        | hsa-miR-3195                  | URS000004DB7E_9606 | CGCGCGGCGCGCCGGUU         | [54] |
|        | hsa-miR-3196                  | URS000033B548_9606 | CGGGCGCGACGGGCUCUC     | [12] |
|        | hsa-miR-328                   | –             | –                                  | [65] |
|        | hsa-miR-329                   | –             | –                                  | [64, 65] |
|        | hsa-miR-3614-5p               | URS00003D4175_9606 | CACUUUGAUCUGAGCUGCC       | [54] |
|        | hsa-miR-3653-3p               | URS000009AF54_9606 | CUAAGAUGUACUGAAG          | [54] |
|        | hsa-miR-3656                  | URS0000514CEC_9606 | GGGCGGGUCCGCGGGUUG  | [12, 72] |
|        | hsa-miR-3665                  | URS000075AFFF_9606 | AGCGUGUCGCGGGCGCG     | [12] |
|        | hsa-miR-370                   | –             | –                                  | [65] |
|        | hsa-miR-375                   | –             | –                                  | [65] |
|        | hsa-miR-378c                  | URS000025307A_9606 | ACUGGACUUGAGUACAGAGAUGUG | [54] |
|        | hsa-miR-383                   | –             | –                                  | [65] |
|        | hsa-miR-3944-3p               | URS0000446855_9606 | UUCGGGCGUGGCUGCUCUCCCG   | [67] |
|        | hsa-miR-410                   | –             | –                                  | [65] |
|        | hsa-miR-412                   | –             | –                                  | [65] |
|        | hsa-miR-4284                  | URS00001FC26E_9606 | GGGCUCACUACACCCCA     | [72] |
|        | hsa-miR-433                   | –             | –                                  | [65] |
|        | hsa-miR-4443                  | URS00004D84DB_9606 | UUGGAGCCGUGGGUUUUUU     | [72] |
|        | hsa-miR-4448                  | URS00005F305A_9606 | GGGCUCUCUUGCUAGGGGUA    | [54] |
|        | hsa-miR-4454                  | URS00005D12AC_9606 | GGAUCCGAGUCACGCACCA    | [12, 54, 66] |
|        | hsa-miR-4461                  | URS000028425A_9606 | GAUUGAGACUAGUAGGGCUAGGC | [54] |
| Family | Name | RNAcentral | Sequence | Ref. |
|--------|------|------------|----------|-----|
| hsa-miR-4466 | URS00001DC1D3_9606 | GGGUGCGGCGCGCGCGG | [12, 54, 72] |
| hsa-miR-4485-3p | URS000038446A_9606 | UAACGGCAGCGAGCGAGC | [11] |
| hsa-miR-4492 | URS000045ED38_9606 | GGGGUGCGGCGCGCGCGG | [54] |
| hsa-miR-4497 | URS00000A2C49_9606 | CUGGGGAGAGCGAGCGGC | [12] |
| hsa-miR-4505 | URS000075EBEE_9606 | AGGCCAGGCAGCGAGCGGA | [72] |
| hsa-miR-4508 | URS000045E78D3_9606 | GGGGUGCGGCGCGCGCGG | [12, 54] |
| hsa-miR-4516 | URS00000BF7F9_9606 | GGGGAGAAGGGUCGGGGC | [54, 66] |
| hsa-miR-4532 | URS000013A349_9606 | CCCCGGGGAGCGCGCGG | [54, 66, 67] |
| hsa-miR-4649-5p | URS000044FB51_9606 | UGGGCGAGGGGUGGGCUCAGAG | [67] |
| hsa-miR-4665-5p | URS00004E78D3_9606 | CUGGGGAGAGCGAGCGGC | [67] |
| hsa-miR-4668-5p | URS0000A17E7_9606 | AGGGAAAGAAAAAGGAUUGGUC | [12] |
| hsa-miR-4678-3p | URS000047996E_9606 | GGGGAGAAGGGUCGGGGC | [72] |
| hsa-miR-4707-5p | URS00003EB443_9606 | GGGGAGAAGGGUCGGGGC | [12] |
| hsa-miR-4708-3p | URS00004F4FFB_9606 | AGCAAGGCGGCAUCUCUCUGAU | [73] |
| hsa-miR-4722-5p | URS0000475996E_9606 | GGCGAGGAGGGUCGAGCU | [67] |
| hsa-miR-4741 | URS0000547F6A_9606 | CGGGCUGUCCGGAGGGUCGGCU | [67] |
| hsa-miR-4763-3p | URS00004A40D8_9606 | AGGCGAGGCGUGUCCGUGGGGCGG | [67, 72] |
| hsa-miR-4787-5p | URS0000521832_9606 | GGGGAGAAGGGUCGGGGC | [12, 54] |
| hsa-miR-4792 | URS00005B6542_9606 | CUGUGAGCGCUCGUAGC | [54, 66] |
| hsa-miR-487a | – | – | [65] |
| hsa-miR-487b | – | – | [65] |
| hsa-miR-489 | – | – | [65] |
| hsa-miR-494 | – | – | [65] |
| hsa-miR-5088-5p | URS00002F0130_9606 | CAGGGCUCAGGAUGGAGTAGG | [67] |
| hsa-miR-5095 | URS00002E1785_9606 | UUACAGGCGUGAACCACCGGC | [54] |
| hsa-miR-5096 | URS00001F8B82_9606 | GUUUCACCAUGUUGGUCAGG | [54, 66] |
| hsa-miR-5100 | URS000007F978_9606 | UUACAGAUCGCCACGGGUGCUCU | [12] |
| hsa-miR-5191 | URS000075CB1C_9606 | AGGAUAGGAAGAAUGAAGUC | [54] |
| hsa-miR-520b | – | – | [65] |
| hsa-miR-520f | – | – | [65] |
| hsa-miR-520g | – | – | [65] |
| hsa-miR-5585-3p | URS00003E6EFA_9606 | CUGAAUAGCGAGGAGCUACAGGU | [54, 66] |
| hsa-miR-5566 | URS00000FDSFE_9606 | GGGGCGGCGUGUAACCCACGG | [65] |
| hsa-miR-5787 | URS000075CA3A_9606 | GGCGUGGGGCAGCGGGAGG | [12, 72] |
| hsa-miR-597 | – | – | [65] |
| hsa-miR-598 | – | – | [65] |
| hsa-miR-605 | – | – | [65] |
| hsa-miR-6068 | URS000075E142_9606 | CCUGCGAGUCUCGGCGGUGG | [72] |
| hsa-miR-6087 | URS000075EF8B_9606 | UGAGCGCGCGGGCGGAGG | [12, 54, 66, 67] |
| hsa-miR-6088 | URS000075EC34_9606 | AGAGAUCGAGGGGCGGAGG | [12, 72] |
| hsa-miR-6090 | URS000075F58_9606 | GGAGCGAGGGGCGGAGG | [12] |
| hsa-miR-6124 | URS000075CC26_9606 | GGAGAGGGAAGGGGAGG | [72] |
| hsa-miR-6125 | URS000075F0F0_9606 | GCGGAAGGGCGAGCCGCGAGA | [12] |
| hsa-miR-6126 | URS000075D118_9606 | GUGAGCCCGCGGCGGAGA | [66] |
| hsa-miR-627 | – | – | [65] |
| hsa-miR-655 | – | – | [65] |
| hsa-miR-656 | – | – | [65] |
| hsa-miR-659-3p | URS000075C04A_9606 | CUUGGUUCAGGGAGGGUCCCA | [65] |
Numerous miRNAs are involved in the positive regulation of angiogenesis, such as hsa-miR-126-3p, hsa-miR-143-3p, hsa-miR-1908-5p, hsa-miR-199a-5p, hsa-miR-199b-3p, hsa-miR-20a-5p, hsa-miR-21-5p, hsa-miR-27b-3p, hsa-miR-29a-3p and hsa-miR-31-5p, among others (Table 4S). They may play a role in the promotion of angiogenesis, as observed both in vitro and in vivo [60, 72, 80]. However, it should be noted that there are also numerous miRNAs involved in the negative regulation of angiogenesis (see Table 4S for a complete list).

Finally, although there are less miRNAs than proteins involved in regulation of cellular processes such as proliferation (hsa-miR-155-5p) and proliferation (hsa-miR-199a-5p), and regulation of cardiac conduction (hsa-miR-19a-3p), among others (Table 4S). AT-MSC-EV proteins are also implicated in some of these biological processes. Therefore, both types of molecules, proteins and miRNAs, may present a synergistic action, supporting the cardioprotection observed in an in vivo model of myocardial infarction after the administration of AT-MSC-EVs [79].

Table 2 (continued)

| Family       | Name       | RNAcental | Sequence                  | Ref.   |
|--------------|------------|-----------|---------------------------|--------|
| (hsa-miR-659)| hsa-miR-668|           |                           | [65]   |
| hsa-miR-672  | URS000075A9AA_9606 CUCGGGGCAGGCGGCUGGGAGCG            | [12, 67] |
| hsa-miR-6729-5p |             |           |                           | [65]   |
| hsa-miR-6739-5p |             |           |                           | [66]   |
| hsa-miR-6746-5p |             |           |                           | [67]   |
| hsa-miR-6789-5p |             |           |                           | [67]   |
| hsa-miR-6821-5p |             |           |                           | [67]   |
| hsa-miR-6858-5p |             |           |                           | [67]   |
| hsa-miR-6869-5p |             |           |                           | [12]   |
| hsa-miR-6891-5p |             |           |                           | [67]   |
| hsa-miR-720   | URS000028F729_9606 CGGGGUCGGCGGCGACGUG            | [12, 54, 66] |
| hsa-miR-7704  | URS000075A1F7_9606 UUCCCCAGCCAACCGACACCA            | [12]   |
| hsa-miR-8061  | URS000075E23B_9606 CUUAGAUUAGGAGAUUGUU            | [54]   |
| hsa-miR-8845  | URS000076B539_9606 CACACACACACACACACUA            | [66]   |
| hsa-miR-874   | URS000028F729_9606 CGGGGUCGGCGGCGACGUG            | [12, 54, 66] |
| hsa-miR-886-3p |             |           |                           | [65]   |
| hsa-miR-886-5p |             |           |                           | [65]   |
| hsa-miR-887   |             |           |                           | [65]   |
| hsa-miR-889   |             |           |                           | [65]   |
| hsa-miR-891a  |             |           |                           | [65]   |
| hsa-miR-942   |             |           |                           | [65]   |
| hsa-miR-95    |             |           |                           | [65]   |

## The two names corresponded to the same sequence
# Identified by the sequence and the precursor. The referred article uses a name not found in the databases

(hsa-miR-126-3p, hsa-miR-21-5p, hsa-miR-26a-5p, hsa-miR-29b-3p), regulation of phosphatidylinositol 3-kinase signaling (hsa-miR-126-3p, hsa-miR-20a-5p, hsa-miR-21-5p), and positive regulation of cell migration (hsa-miR-1290, hsa-miR-181b-5p, hsa-miR-21-5p, hsa-miR-29b-3p) (Table 4S). Therefore, they can also be implicated in the positive effects observed after the injection of human AT-MSC-EVs in animal model of osteoarthritis [66], and in osteoarthritis chondrocytes [66] and osteoblasts [78] in vitro.

Regarding the use of AT-MSC-EVs for cardiology and vascular diseases, the rationale may be the role of the detected miRNAs in negative regulation of heart rate (hsa-miR-26a-5p), regulation of heart contraction (hsa-miR-92a-3p), positive regulation of cardiac muscle cell proliferation (hsa-miR-199b-3p, hsa-miR-19b-3p, hsa-miR-204-5p, hsa-miR-222-3p, hsa-miR-23b-3p), negative regulation of cardiac muscle cell apoptotic process (hsa-miR-145-5p, hsa-miR-199b-3p, hsa-miR-19b-3p, hsa-miR-21-5p, hsa-miR-30e-5p), regulation of cardiac muscle hypertrophy (hsa-miR-20a-5p), cell differentiation (hsa-miR-155-5p) and proliferation (hsa-miR-199a-5p), and regulation of cardiac conduction (hsa-miR-19a-3p), among others (Table 4S). AT-MSC-EV proteins are also involved in some of these biological processes. Therefore, both types of molecules, proteins and miRNAs, may present a synergistic action, supporting the cardioprotection observed in an in vivo model of myocardial infarction after the administration of AT-MSC-EVs [79].
and apoptosis (Tables 2S and 4S), it should be noted that each miRNA targets more than one mRNA. Therefore, each one can show effects on numerous proteins.

**tRNA, mRNA, rRNA, snRNA, snoRNA and scRNA**

According to Kaur et al. [53], the detected tRNA in AT-MSC-EVs represents 47% of all small RNAs observed. Although this percentage is slightly higher than that of miRNA, the available information about the presence of this type of RNA [11, 53, 54] is significantly less. The main tRNAs, in order of quantity detected in AT-MSC-EVs, are tRNA GCC (Gly), tRNA CTC (Glu) and tRNA TTC (Glu). Surprisingly, in AT-MSC the tRNA CTC (Glu) is the most abundant, while tRNA GCC (Gly) makes up a significantly lower percentage than in AT-MSC-EVs [11]. Other tRNAs present in lesser amounts in AT-MSC-EVs are tRNA GTC (Asp), tRNA CCC (Gly), tRNA GTG (His), tRNA CTT (Lys), tRNA AAC (Val) and tRNA CAC (Val) [11].

84 different mRNAs were detected in the AT-MSC-EVs. Their corresponding gene symbols, in order of quantity detected, are FN1, COL4A3, PGF, MMP2, PLG, HGF, IGF1, TEK, FGFR2, HIF1A, VEGFA, EDN1, PF4, CXCL9, FGFI, TGBB2, ITGAV, PROK2, EGF, FLT1, IL8, IFNG, IGF1A, SERPINE1, FIGF, TIMP3, JAG1, CXCL10 ANGPT1, TIMP2, IL6, TIMP1, SERPINF2, AKT1, ANPEP, EFNB2, CXCL6, HPSE, THBS1, EPHB4, NRPI, THBS2, CCL11, TGFA, TIE1, TGBF1, COL18A1, PDGFA, KDR, TGFBR1, BAI1, NRP2, ANGPT2, MMP9, CXCL1 ANGPTL4, ANG, ENG, PTGS1, CCL2, VEGFC, EFNA1, TNF, CTGF, NOS3, VEGFB, CXCL5, LECT1, CDH5, LEP, ITGFI, MMP14, IL1B, SPHK1, PLAU, FGFR3, ID1, SIPRI, ERBB2, PECAM1, NOTCH4, TYMP and MDK [52].
Other types of small RNA, such as rRNA [54], snRNA, snoRNA [53, 54] and scRNA [53], are present in AT-MSC-EVs, but the available information about these is even less than that of tRNA.

**Lipids**

The third type of molecule transported by EVs is lipids [3, 4]. The lipid composition of EVs has been less studied than that of proteins or miRNAs [8]. Thus, the number of lipid entries (639) in the Vesiclepedia database [41] is notably lower than the number of protein and miRNA entries (349,988 and 10,520, respectively). None of these lipid entries are related to AT-MSC-EVs or any other MSC-EVs. The total lipid content of AT-MSC-EVs has been analysed by Bari et al. [58], using the Nile Red assay. However, to our knowledge, there is no detailed information about the different types of lipids present in AT-MSC-EVs.

**Modification of Cargo Components to Improve their Potential Effects**

Different cell culture conditions and pre-treatments have been used to modify the profile of human AT-MSC-EV cargo, with the aim to improve its effects in skin flap survival [59, 86], angiogenesis [60, 61, 64, 80], immune response [71, 87], bone regeneration [77] and cancer [118, 119]. To this purpose, human AT-MSCs have been exposed to oxidative stress [59, 86], hypoxic [61, 80] or inflammatory culture conditions [71, 87], stimulation with platelet-derived growth factor (PDGF) [60, 65] and basic fibroblast growth factor (bFGF)
and transfected with lentiviral particles with different miRNAs [77, 118, 119].

Under oxidative stress conditions (50 μM H₂O₂), AT-MSC-EVs showed an enhanced effect on skin flap survival after ischemic injury in vivo models [59, 86]. This improvement was associated with a promotion of angiogenesis, reduction of inflammation and apoptosis [86]. The proteomic analysis of these EVs showed an increase (>2-fold) of histone H4, beta ig-h3, ITI-HC2, FLG-2, periostin, thrombospondin-1, pentraxin-related protein PTX3 and annexin A5; and a decrease (>2-fold) of plakophilin-1, VDB, Apo B-100, lactotransferrin, serotransferrin, alpha-fetoprotein, fatty acid-binding protein 5, dermcidin, and hornerin [59]. The RNA sequencing analysis showed that hsa-miR-10,395-5p and hsa-miR-10,395-3p were increased in H₂O₂ AT-MSC-EVs, while hsa-miR-24-3p, hsa-miR-93-5p, hsa-miR-134-5p, hsa-miR-221-3p, hsa-miR-222-3p were decreased [59]. Finally, the peak size of EV from H₂O₂-stimulated AT-MSC was larger than that of unstimulated cells [59].

Hypoxic culture conditions also induce the release of larger EVs according to Han et al. [61], although other authors claim that there are no significant differences in size [80]. The EVs collected from AT-MSC cultured under hypoxic conditions (5% O₂) seemed to enhance angiogenic properties in cultured human umbilical vein endothelial cells and in an in vivo model of fat grafting [61, 80]. The results of these studies showed that the amount of the surface marker CD44 was significantly lower in hypoxic EVs [80], while VEGF-A, EGF, FGF-4, VEGFR-2, VEGFR-3, C-C motif chemokine 8 and 13 were increased under these culture conditions [61].

EVs contents are also different after AT-MSC exposure to inflammatory cytokines. In EVs secreted by INF-γ-stimulated AT-MSC, indoleamine 2,3-dioxygenase mRNA was detected, although its presence did not significantly improve their potential to control activated T cell proliferation, in comparison with those derived from unstimulated AT-MSC [87]. However, when AT-MSCs were pretreated with both INF-γ and TNF-α, the enriched EVs induced the polarization of macrophages to the M2 phenotype [71]. Under this proinflammatory culture condition, AT-MSC-EVs cause differences in the expression of 81 different miRNAs [71] (Table 3).

Other methods used to alter the expression of cargo components are stimulation with PDGF [60, 65], with bFGF [64], and lentiviral transfection with the miRNA of interest [77, 118, 119]. In the former case, PDGF stimulation increased release of smaller AT-MSC-EVs, and improved their angiogenic potential, both in cultured human microvascular endothelial cells and in an in vivo model of severe combined immunodeficiency [60]. This stimulation also improved the AT-MSC-EVs anti-inflammatory and immunomodulatory potential both in vitro and in vivo in peripheral blood mononuclear cell and in a murine model of hindlimb ischemia, respectively [65]. Regarding protein composition, these EVs contained several proteins not observed in unstimulated AT-MSC-EVs: C-C motif chemokine 21, IL-17RD, IL-20RA, inhibin A, tyrosine-protein kinase Lck, LIF, SL-2, SL-3, MMP-14,
Table 3 miRNA detected in EVs derived from human AT-MSC treated with IFN-γ and TNFα, PDGF and bFGF (Modified tables from Domenis et al., 2018 [71], Lopatina et al., 2014 and 2018, [64, 65])

**Stimulation with IFN-γ and TNFα**

| miRNA over-expressed                                                                 | miRNA under-expressed                                                                 |
|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|
| has-let-7a-5p                                                                        | has-miR-125a-5p                                                                        |
| has-miR-10a-5p                                                                       | has-miR-125b-5p                                                                        |
| hsa-miR-16-5p                                                                        | hsa-miR-125b-5p                                                                        |
| hsa-miR-23a-3p                                                                       | hsa-miR-125b-5p                                                                        |
| hsa-miR-92a-3p                                                                       | hsa-miR-92b-3p                                                                          |
| miRNA over-expressed                                                                 | miRNA under-expressed                                                                 |
| has-let-7c-5p                                                                        | has-miR-125b-5p                                                                        |
| hsa-miR-10b-5p                                                                       | hsa-miR-125b-5p                                                                        |
| hsa-miR-191-5p                                                                       | hsa-miR-125b-5p                                                                        |
| hsa-miR-28-3p                                                                        | hsa-miR-125b-5p                                                                        |
| hsa-miR-941                                                                          | hsa-miR-99b-5p                                                                          |

**Lost miRNA**

| miRNA lost                                                                            | miRNA over-expressed                                                                 |
|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|
| hsa-let-7c-5p                                                                        | hsa-miR-125b-5p                                                                        |
| hsa-miR-150-5p                                                                       | hsa-miR-125b-5p                                                                        |
| hsa-miR-193b-3p                                                                      | hsa-miR-125b-5p                                                                        |
| hsa-miR-27b-3p                                                                       | hsa-miR-125b-5p                                                                        |
| hsa-miR-409-3p                                                                       | hsa-miR-125b-5p                                                                        |
| hsa-miR-671-3p                                                                       | hsa-miR-7706                                                                            |

**Gained miRNA**

| miRNA gained                                                                          | miRNA over-expressed                                                                 |
|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|
| hsa-miR-100-3p                                                                       | hsa-miR-125b-5p                                                                        |
| hsa-miR-155-3p                                                                       | hsa-miR-125b-5p                                                                        |

**Stimulation with PDGF**

| miRNA under-expressed                                                                 | miRNA over-expressed                                                                 |
|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|
| hsa-miR-1225-3p                                                                      | hsa-miR-1226-5p                                                                        |
| hsa-miR-125b                                                                         | hsa-miR-1226-5p                                                                        |

**miRNA over-expressed only in stimulated**

| miRNA over-expressed only in stimulated                                              | miRNA over-expressed                                                                 |
|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|
| has-let-7e                                                                           | hsa-miR-125b-5p                                                                        |
| has-miR-129                                                                          | hsa-miR-125b-5p                                                                        |
| has-miR-186                                                                          | hsa-miR-125b-5p                                                                        |
| has-miR-221                                                                          | hsa-miR-125b-5p                                                                        |
| has-miR-373                                                                          | hsa-miR-125b-5p                                                                        |
| has-miR-511                                                                          | hsa-miR-125b-5p                                                                        |
| has-miR-550                                                                          | hsa-miR-125b-5p                                                                        |
| has-miR-579                                                                          | hsa-miR-125b-5p                                                                        |
| has-miR-621                                                                          | hsa-miR-125b-5p                                                                        |
| has-miR-872                                                                          | hsa-miR-125b-5p                                                                        |

**Stimulation with bFGF**

| miRNA under-expressed                                                                 | miRNA over-expressed                                                                 |
|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|
| has-let-7a                                                                           | hsa-miR-125b-5p                                                                        |
| hsa-miR-100                                                                          | hsa-miR-125b-5p                                                                        |
| hsa-miR-10b                                                                          | hsa-miR-125b-5p                                                                        |
| hsa-miR-138                                                                          | hsa-miR-125b-5p                                                                        |
| hsa-miR-185                                                                          | hsa-miR-125b-5p                                                                        |
| hsa-miR-199a                                                                         | hsa-miR-125b-5p                                                                        |
| hsa-miR-210                                                                          | hsa-miR-125b-5p                                                                        |
OSM, kit ligand, IL-6RB (soluble form), TGF-beta 5 (not found in UniProtKB), thrombopoietin, metalloproteinase inhibitor 1, and TNF receptor superfamily member 10D [60]. In addition, 65 proteins were up-regulated and 15 proteins were down-regulated (Table 4). The miRNA composition of stimulated AT-MSC-EVs also showed variations in the expression of 55 different miRNAs [65] (Table 3).

### Table 3 (continued)

| miRNA-expressed only in stimulated |
|-----------------------------------|
| hsa-miR-27b                        |
| hsa-let-7c                         |
| hsa-miR-199b                       |
| hsa-miR-340                        |
| hsa-miR-545                        |

| miRNA-expressed only in control |
|---------------------------------|
| hsa-miR-130b                    |
| hsa-miR-223                     |
| hsa-miR-381                     |
| hsa-miR-579                     |

### Table 4  
Protein detected in EVs derived from human AT-MSC treated with PDGF (Modified table from Lopatina et al., 2018, [65])

| Stimulation with PDGF |
|------------------------|
| Proteins up-regulated |
| Adenomatous polyposis coli protein* |
| Calsyntenin-1 |
| C-C motif chemokine 1* |
| Coagulation factor XIII B chain |
| C-X-C motif chemokine 11* |
| Insulin-degrading enzyme* |
| Interleukin-23 subunit alpha* |
| Lymphotoxin beta |
| Matrix metalloproteinase-9* |
| Neurogenic differentiation factor 1* |
| Platelet-derived growth factor D* |
| Secreted frizzled-related protein 1* |
| Toll-like receptor 2* |
| Transforming growth factor beta-1 |
| Tumor necrosis factor ligand superfamily member 15* |
| Vascular endothelial growth factor A* |
| Vascular endothelial growth factor receptor 2* |

| Proteins down-regulated |
|-------------------------|
| Activin receptor type-1* |
| SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily E member 1* |
| Calbindin |
| Receptor-interacting serine/threonine-protein kinase 1* |

*The referred article used alternative or short names

* Springer
The stimulation with bFGF did not affect the number or size of released AT-MSC-EVs but it reduced their antigenic properties, stimulating the stabilization of vessel growth, both in cultured human microvascular endothelial cells and in an in vivo model of severe combined immunodeficiency [64]. The analysis of these EVs showed that angiogenic and antiangiogenic proteins such as tumor necrosis factor ligand superfamily member 13, artemin, lactadherin, MMP-20, angiopoietin-related protein 7, thrombospondin, angiotatin and endostatin were lost, while new angiogenesis modulatory proteins, such as tumor necrosis factor ligand superfamily member 11 and matrilysin were gained. Regarding miRNA profile, differences in the expression of 55 different miRNAs were observed [64] (Table 3).

Finally, AT-MSC-EVs have been transfected with lentiviral particles to produce EVs enriched in miRNA 375 [77], miRNA-125b [119] and miRNA 101 [118]. The miRNA-375-enriched EVs promoted bone regeneration in an in vivo model of calvarial defects. AT-MSC-EVs enriched in miRNA-125b [119] and miRNA 101 [118] induced a reduction in cell proliferation of hepatocellular carcinoma cells and inhibited osteosarcoma cell invasion and migration in vitro, respectively. In addition, miRNA-101-enriched EVs also induced inhibition of osteosarcoma metastasis in a lung metastasis model in vivo [118].

Conclusions

There is an increasing interest in the study of EVs as new therapeutic options in several research fields, due to their role in different biological processes, including cell proliferation, apoptosis, angiogenesis, inflammation and immune response, among others. Their potential is based upon the molecules transported inside these particles. Therefore, both molecule identification and an understanding of the molecular functions and biological processes in which they are involved are essential to advance this area of research. To the best of our knowledge, the presence of 591 proteins and 604 miRNAs in human AT-MSC-EVs has been described. The most important molecular function enabled by them is the binding function, which supports their role in cell communication. Regarding the biological processes, the proteins detected are mainly involved in signal transduction, while most miRNAs take part in negative regulation of gene expression. The involvement of both molecules in essential biological processes such as inflammation, angiogenesis, cell proliferation, apoptosis and migration, supports the beneficial effects of human AT-MSC-EVs observed in both in vitro and in vivo studies, in diseases of the musculoskeletal and cardiovascular systems, kidney, and skin.

Interestingly, the contents of AT-MSC-EVs can be modified by cell stimulation and different cell culture conditions, such as oxidative stress or hypoxia, to engineer a cargo selection with improved antigenic, anti-inflammatory or immunosuppressive effects. Moreover, it is also possible to enrich specific miRNAs in the cargo via transfection of AT-MSC with lentiviral particles. These modifications have enhanced the positive effects in skin flap survival, immune response, bone regeneration and cancer treatment. This phenomenon opens new avenues to examine the therapeutic potential of AT-MSC-EVs.

Abbreviations

Apo B-100, apolipoprotein B-100; AT, adipose tissue; AT-MSC-EVs, adipose mesenchymal cell-derived extracellular vesicles; Beta ig-h3, transforming growth factor-beta-induced protein ig-h3; bFGF, basic fibroblast growth factor; BMP-1, bone morphogenetic protein 1; BMPR-1A, bone morphogenetic protein receptor type-1A; BMPR-2, bone morphogenetic protein receptor type-2; BM, bone marrow; BM-MSC, bone marrow mesenchymal stem cells; EF-1-alpha-1, elongation factor 1-alpha 1; EF-2, elongation factor 2; EQF, epidermal growth factor; EMBL-EBI, the European Bioinformatics Institute; EV, extracellular vesicle; FGF-4, fibroblast growth factor 4; FGF-R-1, fibroblast growth factor receptor 1; FGF-R-4, fibroblast growth factor receptor 4; FLG-2, filaggrin-2; G alpha-13, guanine nucleotide-binding protein subunit alpha-13; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; GO, gene ontology; IBP-7, insulin-like growth factor-binding protein 7; IL-1 alpha, interleukin-1 alpha; IL-4, interleukin-4; IL-6, interleukin-6; IL-6RB, interleukin-6 receptor subunit beta; IL-10, interleukin-10; IL-17RD, interleukin-17 receptor D; IL-20RA, interleukin-20 receptor subunit alpha; ISEV, International Society for Extracellular Vesicles; ITI-HC2, inter-alpha-trypsin inhibitor heavy chain H2; LIF, leukemia inhibitory factor; LTBP-1, latent-transforming growth factor-beta-binding protein 1; MAP kinase 1, mitogen-activated protein kinase 1; MAP kinase 3, mitogen-activated protein kinase 3; miRNA, microRNA; MMP-9, matrix metalloproteinase-9; MMP-14, matrix metalloproteinase-14; MMP-20, matrix metalloproteinase-20; mRNA, messenger RNA; MSC, mesenchymal stem cells; OSM, oncostatin-M; PDGF, platelet-derived growth factor; PDGF-R alpha, platelet-derived growth factor receptor alpha.; PDGF-R beta, platelet-derived growth factor receptor beta; rRNA, small ribosomal RNA; SCFR, mast/stem cell growth factor receptor Kit; scRNA, small cytoplasmic RNA; SL-2, stromelysin-2; SL-3, stromelysin-3; snRNA, small nuclear RNA; snoRNA, small nucleolar RNA; TGFR-2, TGF-beta receptor type-2; IRNA, transfer RNA; UniProtKB, Universal Protein Knowledgebase; VDB, vitamin D binding protein; VEGF-A, vascular endothelial growth factor A; VEGF-R-2, vascular endothelial growth factor receptor 2; VEGF-R-3, vascular endothelial growth factor receptor

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1007/s12155-021-10155-5. Acknowledgements

The authors acknowledge Dr. Teresa Nieto-Miguel and Dr. Sara Galindo for critical reading of the manuscript. English grammar and spelling of this manuscript have been professionally revised and corrected by Proof-Reading-Service (Hertfordshire, United Kingdom).

Availability of Data and Materials

The data used to support the findings of this review are available from the corresponding author upon request.

Author’s Contributions

All authors contributed to the study conception and design. Literature search and data analysis were performed by MLAA. The first draft of the manuscript was written by MLAA and MLAA, LGP and YD commented on previous versions of the manuscript. MLAA, LGP and YD read and approved the final manuscript.
**Funding** This work was supported by Ministerio de Ciencia, Innovación y Universidades (MCIU), Agencia Estatal de Investigación (AEI) and Fondo Europeo de Desarrollo Regional (FEDER), Grant number RTI2018–094071–B-C21.

**Declarations**

**Ethical Approval** Not applicable.

**Consent to Participate** Not applicable.

**Consent to Publish** Not applicable.

**Competing Interests** The authors declare that they have no conflict of interest.

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