MicroRNAs’ role in the environment-related non-communicable diseases and link to multidrug resistance, regulation, or alteration

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Received: 2 March 2021 / Accepted: 19 May 2021 / Published online: 27 May 2021
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Abstract
The discovery of microRNAs (miRNAs) 20 years ago has advocated a new era of “small molecular genetics.” About 2000 miRNAs are present that regulate one third of the genome. MiRNA dysregulated expression arising as a response to our environment insult or stress or changes may contribute to several diseases, namely non-communicable diseases, including tumor growth. Their presence in body fluids, reflecting level alteration in various cancers, merit circulating miRNAs as the “next-generation biomarkers” for early-stage tumor diagnosis and/or prognosis. Herein, we performed a comprehensive literature search focusing on the origin, biosynthesis, and role of miRNAs and summarized the foremost studies centering on miR value as non-invasive biomarkers in different environment-related non-communicable diseases, including various cancer types. Moreover, during chemotherapy, many miRNAs were linked to multidrug resistance, via modulating numerous, environment triggered or not, biological processes and/or pathways that will be highlighted as well.

Keywords ncRNA • miR • NCDs • lncRNA • Cancer • mTOR • ceRNA

History/background

MicroRNA: the short non-protein-coding RNAs
The human genome reveals that the protein-coding genes can be as few as 25,000 (Feinberg and Moore 2016). Despite the fact that the exact number of coding genes, within the human genome, is unknown, non-protein-coding genes make up a significant portion of the human genome (Spadafora 2015). Human cells contain several distinguishing sequences of non-coding RNA (ncRNA) that could be categorized into two major classes: long ncRNA (≥ 200 nucleotide length) and short ncRNA (< 200 nucleotides). The short ncRNA group comprises different classes such as small interfering RNAs (siRNA), small nuclear RNAs (snRNAs), small nucleolar RNAs (snoRNAs), Piwi-interacting RNAs (piRNAs), and microRNAs (miRNAs)(Wang et al. 2016a).

miRNAs are the essential gene expression environment-related regulatory molecules miRNAs regulate one third of the human genome (Hombach and Kretz 2016). These are small single-stranded 17–25 nucleotides, recently known as essential gene expression regulatory molecules (Hao et al. 2016).

The parent microRNA member is lin-4 (Horvitz and Sulston 1980) that has been discovered within a nematode called Caenorhabditis elegans. Lin-4 was found to play a pivotal role in the transition from a larval stage into another, via suppression of lin-4 gene, concerned with larval development (O’Brien et al. 2018). miRs are encoded either via separate transcription units within the pre-mRNA introns or via multi-cis-tronic clusters (Catalanotto et al. 2016). miRNAs organized in clusters within the genome and are sharing the same transcriptional regulatory elements, but are expressed individually, in the event, as if they have their own promoters (de Rie et al. 2017).

miRs direct major cellular functions such as proliferation, differentiation, maturation, and metabolism (Wang et al. 2017a). Irregular expression of miRNAs may occur in a range of distinctive pathologies, with striking modifications in tumor tissues (Wang et al. 2017a). Profiling of miRNAs has contributed to the molecular classification of tumors (Blenkiron and Miska 2007). The presence of miRNAs in
body fluids, such as the urine, serum or plasma, CSF, and tears, permitted non-invasive identification of various cancer types (Kai et al. 2018; Armand-Labit and Pradines 2017; Elkhouly et al. 2020; Condrat et al. 2020) considered as beneficial potential liquid biopsy.

Review methodology

An online search in the medical databases PUBMED and NCBI for the following terms: (“Circulating miRNA”) AND (“Health and diseases regulation of gene expression”) AND (“Role in Carcinogenesis”) AND (“Epigenetics”) AND (“Future promising biomarkers”) was done on September 2020. Priority was given to papers with higher empirical evidence methodology, including clinical guidelines, meta-analysis, randomized clinical studies, systematic review, original papers, and narrative reviews, since but not limited to 2015.

Review aims

In “Part I” section, the review aims to briefly discuss “miRs biosynthetic pathways and down-stream effects upon binding target mRNA.” In “Part II” section, the review aims to highlight “the utility of circulating miRNAs as biomarkers for environment-related non-communicable diseases (NCDs) and a brief about their role in cancer growth or resistance to treatment.”

Part I

miRNA biogeny

miRNA biogenesis include various coordinated steps and specific cellular mechanisms (de Rie et al. 2017). Biogenesis of miRNA starts with post-transcriptional or co-transcriptional preparation (Morlando et al. 2008) of RNA polymerase II–III transcripts. Around 50% of the miRNAs recently identified are intragenic and are typically regulated from introns and some protein-coding gene exons. The remaining ones are intergenic, freely transcribed and guided according to their own promoters from a host gene (Vishnoi and Rani 2017). miRNAs could be translated as a single long transcript, named clusters (Oliveto et al. 2017). Moreover, miRNA biogenesis is categorized as either canonical or non-canonical.

Canonical miRNA biogenic pathway

This is the main route by which miRNAs are developed, as shown in Fig. 1A. In this process, primary miRNAs (pri-miRNAs) are transcribed from their genes by RNA polymerase II, which is then handled by a microprocessor complex composed of DiGeorge Syndrome Critical Region 8 (DGCR8), an RNA-binding protein, and Drosha, a class 2 ribonuclease III enzyme into precursor miRNAs (pre-miRNAs) (Alarcón et al. 2015). In this process, DGCR8 identifies an N6-methyl adenylated GGAC and a different motif within the pri-miRNA (Alarcón et al. 2015), while Drosha begins processing inside the nucleus by cutting the stem-loop precursor (Kim et al. 2016).

For most of the double-stranded RNAs (dsRNAs) which are involved in small RNA production routes, pre-miRNA seems to be a signature motif. This signature is recognized by the Exportin-5 protein that facilitates the release of pre-miRNAs to the cytoplasm, through nuclear pores, depending on a GTP-GDP gradient (Kim et al. 2016). Exported pre-miRNA is transferred to another RNase-III enzyme in the cytoplasm, called Dicer. Dicer, the cytoplasmic RNase-III enzyme, cuts the pre-miRNA to a miRNA duplex, which is unwound afterwards giving the “fully developed functional miRNA” molecule.

In an ATP-dependent manner, the two strands defined from the resultant miRNA duplex might be stacked into the protein family Argonaute (AGO) known as AGO1-4 (Hansen et al. 2016). After miRNA duplex formation, one strand of the miRNA associates with an RNA-induced silencing complex (RISC) forming the “regulatory miRNA-RISC complex.” The choice of strands 5p or 3p is dependent on the thermodynamic stability at the 5’ untranslated regions (UTRs) at the 1-position of the nucleotide (Hammond 2015). The unoccupied strand known as the passenger strand is loosened by different components from the loaded strand, named the guide or leading strand, depending on complementarity (O’Brien et al. 2018).

Non-canonical miRNA biogenic pathway

Several non-canonical pathways have been illustrated to date, primarily Drosha/DGCR8-independent and Dicer-independent pathways (O’Brien et al. 2018), as illustrated in Fig. 1B.

Drosha/DGCR8-independent non-canonical miRNA pathway

This pathway joins mRNA introns and their own transients to “mirtrons transcripts.” Drosha/DGCR8 is skipped at that stage of processing and these transcripts are, again, carried by the protein Exportin-1 to the cytoplasm (Kim et al. 2016).

Dicer-independent miRNA biogenic pathway

miRNAs could be dealt by Drosha/DGCR8 to form short heterogeneous RNA (shRNA). Since these transcripts are not lengthy to serve as Dicer substrates, AGO2 protein leads in their cytoplasmic developmental steps (Seok et al. 2016), as previously mentioned.
Role of long non-coding RNAs in miRNA biogenesis

The cross talk between long non-coding RNAs (lncRNAs) and miRNAs is one of important regulators in the ncRNA world, for gene expression, mainly the epigenetic field, where lncRNAs may serve as both the source and the inhibitory regulators to miRNAs. Many intragenic miRNA sequences are embedded within lncRNA introns and to lesser extent within their exons. This genomic organization highlights the post-transcriptional regulatory role of lncRNAs in the biogenesis of miRNAs (Liu et al. 2019a; Dykes and Emanueli 2017).

miRNA target binding Via complementarity between unique sequences, which are 2–7 bases, from the 5′ end of the
miRNA and certain target mRNA sequences, recognized as “miRNA response elements” (MREs), the developed miRNA attaches to its target (Pisarello et al. 2015).

**miRNA target gene mRNA-binding types**

Ideal binding where complete complementarity occurs when miRNA binds its target ORF resulting in an “RNA decay.” On the other hand, imperfect binding results in “post-transcriptional silencing” via mRNA de-stabilization, de-capping, de-adenylation, and translational repression (O’Brien et al. 2018; Issler and Chen 2015).

It is worthy to mention the fundamental multifaced aspect of miRNAs target binding is that their suppressive role is not limited to one mRNA, highlighting the “one-mRNA paradigm” in which multiple mRNA targets can be achieved by one microRNA and multiple microRNAs can hit one mRNA (Bracken et al. 2016).

**miRNA target gene(s) mRNA silencing mode(s)** Depending on the degree of MREs complementarity, the target gene(s) mRNA silencing strategies, by miRNAs, could be attained either via target gene mRNA degradation or target gene mRNA translation repression.

**Target mRNA decay** MiRNA-induced silencing complex (miRISC) AGO proteins bind to the GW182 (a protein-containing glycine–tryptophan repeat) to enroll the “deadenylase complex” and promote de-adenylation of the target gene mRNA poly(A) tail. With the aid of the catalytic de-capping protein-2 (DCP2), after de-adenylation, and in the presence of an additional de-capping activators, miRISC de-caps the de-adenylated gene mRNAs. In the presence of an enhancer of de-capping 4 (EDC4), DCP1 and additional de-capping cofactors, the decay of the target mRNA is aided by the cytoplasmic 5’ to 3’ exonuclease1 (Xrn1p) (Iwakawa and Tomari 2015)

**Target mRNA translation repression** miRNA-mediated target mRNA translational repression can occur before and after translational initiation step, through several mechanisms.

miRISC ties to the target mRNA (Wightman et al. 1993) at that point AGO protein interacts with the GW182. This interaction promotes the relocation of poly(A) binding protein from the 3’ poly(A)-tail and blocks its binding to the eukaryotic initiation factor 4 complex (eIF4G), interfering with the “translation-initiation step.”

Repressing cap-structure recognition by eIF4F complex where the AGO protein separates the eIF4A from the 5’ cap binding complex of the target mRNA, and therefore, the ribosomal subunit will not be recruited or attached to the mRNA for translation initiation (Khan et al. 2019).

Also, miRNA can repress protein synthesis after target mRNA translation initiation. Additionally, miRISC could interfere with the targeted mRNA elongation components (Wightman et al. 1993). Finally, to ensure no escape from miR silencing effect, if the target mRNA was translated,

| Table 1 miRNA list in relation to glucose homeostasis, adipogenesis, metabolic syndrome, and type 2 DM |
|---------------------------------------------------------------|---------------------------------------------------------------|
| **Metabolic disease** | **miRNAs effect** | **miRNA list** |
| **Obesity and metabolic syndrome** | Adipogenesis promoting | miR-26b (Li et al. 2017a), miR-103 (Li et al. 2015a), miR-146b, miR-148a (Shi et al. 2015), miR-199a, miR-181, miR-320 (Iacomino and Siani 2017) |
| | Anti-adipogenic | miR-33b, miR-93 (Cioffi et al. 2015), miR-125a, miR-193a/b (Belarbi et al. 2015), miR-194, miR-363, miR-709 (Amer and Kulyte 2015) |
| **Type 2 DM** | β-cell development | miR-197-3p, miR-9-5p, miR-9-3p, miR-99a-3p, miR-124a, miR-135a, miR-138, miR-149, miR-342-3p, miR-375, miR-100b, miR-222 (Tattikota et al. 2015; Coskun et al. 2018; Samandari et al. 2017; LaPierre and Stoffel 2017; Sebastiani et al. 2017; Bai et al. 2017; Engelmann et al. 2017) |
| | Insulin sensitivity/resistance | miR-31, miR-127, miR-302c-3p, miR-373, miR-518b, miR-520c-3p, miR-200, miR-7 (Vienberg et al. 2017; Greco et al. 2017; Sims et al. 2017; Anuradha et al. 2014; Sebastiani et al. 2017) |
| | Insulin production/secretion | miR-29, miR-221, miR-222, miR-103, miR-107, miR-223 (Hubal et al. 2017), miR-320, miR-126, miR-103, miR-107 (Vivacqua et al. 2017; He et al. 2017), Let-7 family (Martinez-Sanchez et al. 2015), miR-375, miR-9, miR-7, miR-124a, miR-96, miR-124, miR-184, miR-29a (Tattikota et al. 2015; Sebastiani et al. 2017) |
| | Insulin signaling | miR-7, miR-1, miR-133a/b, miR-206, miR-128a, miR-330, miR-223 (Wu et al. 2017a; Gu et al. 2017; Lima et al. 2017), miR-144 |
miRISC could recruit proteases resulting in degradation of the nascent polypeptide chains (Khan et al. 2019).

miRNA target gene(s) activation mode Activated targeted mRNA expression could be triggered by miRNAs (O’Brien et al. 2018), via AGO2 protein and fragile-x-mental retardation related protein-1, rather than GW182. This is achieved via miR attachment on the target promoter, to induce RNA polymerase II recruitment followed by transcription activation (Mohammadi et al. 2016).

Either “miR-target gene(s) binding” results in an expression silencing or activation; these effects have been witnessed and recorded by researchers to be associated with various disease(s), which will be discussed in the current review part II.

Table 2 miRNA lists associated with different cardiovascular diseases

| Cardiovascular disease(s) | miRNA list |
|---------------------------|------------|
| Acute myocardial infarction | miR-208a/b, miR-1, miR-133a/b, miR-499 (Liu et al. 2015), miR-328, miR-134, miR-1291, miR-663b, miR-22 (Wang et al. 2019b), miR-126 (Potosi et al. 2015) |
| Heart failure | miR-423-5p, miR-22, miR-320a, miR-92b (Schulte et al. 2017), miR-21 (Li et al. 2018) |
| Atrial fibrillation | miR-133b, miR-328 (Seok et al. 2016), miR-499 (da Silva et al. 2018), miR-126 (Shen et al. 2020) |
| Hypertension | miR-34a, miR-21 (Hijmans et al. 2018), miR-23b, miR-191, miR-451, miR-126-3p, miR-26a-5p, miR-107 (Yang et al. 2018a) |

Table 3 miRNA list in some cerebrovascular diseases

| Cerebrovascular disease(s) | miRNA regulatory effect | miRNA list |
|---------------------------|-------------------------|------------|
| Stroke Upregulation | miR-125b-2, miR-422a, miR-488, miR-627 (Dewdney et al. 2018), miR-290 (Li et al. 2013b), miR-124, miR-27a, miR-10a, miR-182, miR-200b (Stary et al. 2015), miR-298, miR-106b-5P, miR-4306 (Kim et al. 2015) |
| Downregulation | let-7i, miR-126, miR-1259, miR-142-3p, miR-15b, miR-186, miR-519e, miR-768-5p (Völgyi et al. 2015), miR-320e, miR-320d (Völgyi et al. 2015) |
| Alzheimer’s Upregulation | miR-146a (Dong et al. 2015), miR-361-5p, miR-30e-5p, miR-93-5p, miR-15a-5p, miR-143-3p, miR-106b-5p, miR-101-3p, miR-424-5p, miR-106a-5p, miR-18b-5p, miR-3065-5p, miR-20a-5p, miR-582-5p (Cheng et al. 2015) |
| Downregulation | miR-31, miR-93, miR-143, miR-146a (Dong et al. 2015), miR-1306-5p, miR-342-3p, miR-15b-3p (Cheng et al. 2015) |
| Parkinson’s Upregulation | miR-331-5p (Ding et al. 2016), miR-137-3p, miR-124-3p (Li et al. 2017b), miR-30a/b-5p (Schwienbacher et al. 2017) |
| Multiple sclerosis | Upregulation, miR-18 and IL-17A (Mohamed et al. 2019) |
an effect on glucose homeostasis and adipogenesis increment, characterized by the final upregulation of adipogenic markers (Hamam et al. 2015). On the other hand, miRNAs would repress adipogenic differentiation via adipogenic factor downregulation, together with a decreased triacylglycerol level (Das et al. 2020).

### miRNA relation to type 2 diabetes mellitus

As listed in Table 1, many miRNAs are linked to β-cell growth, insulin resistance or sensitivity, insulin production/secretion, and insulin signaling, which can influence the obesity or gene-based T2DM disease course (He et al. 2017). Therefore, diabetes-related nephropathy or retinopathy is

| Cancer type      | miRNA role       | miRNA list                                                                 |
|------------------|------------------|-----------------------------------------------------------------------------|
| Leukemia         | Oncogenic        | miR-128a, miR-128b, miR-150, miR-155, miR-181b-5p, miR-423-3p, miR-486-5p, miR-92b-3p (Wallaert et al. 2017) |
|                  | Tumor suppressor | miR-15a, miR-16-1 (Pekarsky and Croce 2015), miR-495                        |
| Breast           | Oncogenic        | miR-128b/Hiromaka-Mitsuhashi et al. 2020, miR-10b, miR-373 (Youness and Gad 2019), miR-520c, miR-21, miR-155 |
|                  | Tumor suppressor | miR-125a/b, miR-142 (Jin et al. 2018), miR-124-3p (Wang et al. 2016c), miR-101, miR-204-5p (Hong et al. 2019), miR-491-5p (Hui et al. 2015), miR-491-5p (Hui et al. 2015), miR-206 (Yin et al. 2016), miR-152 (Ge et al. 2017), miR-142-3p (Mansoori et al. 2019) |
| Gastric          | Oncogenic        | miR-23a (Hu et al. 2017), miR-27a (Zhou et al. 2016), miR-223 (Wang et al. 2020), miR-106a (Hou et al. 2015), miR-106b-5-25 cluster, miR-107 (Wang et al. 2016b) |
|                  | Tumor suppressor | miR-145, miR-143 (Lei et al. 2017), miR-9 (Fan et al. 2019), miR-34b (Jafari and Abediankenari 2017), miR-124a, miR-335, miR-218, miR-484 (Zare et al. 2018) |
| HCC              | Oncogenic        | miR-182-5p (Cao et al. 2018), miR-106b-3p, miR-101-3p, miR-1246 (Moshiri et al. 2018), miR-221, miR-224 |
|                  | Tumor suppressor | miR-34a, miR-199a (Lou et al. 2018), miR-200a                                |
| Prostate         | Oncogenic        | miR-141 and miR-21 (Sharma and Baruah 2019), miR-125b (Yin et al. 2015)     |
|                  | Tumor suppressor | miR-145, miR-143 (Ma et al. 2017)                                           |
| Pancreatic       | Oncogenic        | miR-132, miR-212, miR-122-5p, miR-125b-5p, miR-192-5p, miR-193b-3p, miR-221-3p, miR-27b-3p (Zhou et al. 2018), miR-222 (Li et al. 2018), miR-181a/bd (Pop-Bica et al. 2018), miR-155, miR-103, miR-107 |
|                  | Tumor suppressor | miR-125b-5p (Zhou et al. 2018), miR-34a, miR-96, miR-221                    |
| Ovarian          | Oncogenic        | miR-16, miR-939 (Ying et al. 2015), miR-21, miR-27a, miR-26a/b, miR-103, miR-182, miR-223, miR-205 (He et al. 2019), miR-195, miR-10b, miR-7, miR-429 (Meng et al. 2015) |
|                  | Tumor suppressor | miR-145, miR-125b, miR-211 (Xia et al. 2015a), miR-25, miR-93, miR-377, miR-432, miR-124a, miR-436, miR-302a (Guo et al. 2015) |
| Uterine leiomyoma | Oncogenic        | miR-15b (Kim et al. 2018)                                                   |
|                  | Tumor suppressor | miR-29a/b/c, miR-197, miR-200c (Kim et al. 2018)                            |
| Thyroid          | Oncogenic        | miR-129-1, miR-146b, miR-183, miR-197 (Sheikhholeslami et al. 2020), miR-146b (Ramirez-Moya et al. 2018) |
|                  | Tumor suppressor | miR-338-3p (Sui et al. 2017), miR-497 (Wang et al. 2017b)                   |
| Colorectal       | Oncogenic        | miR-1246, miR-1308, miR135b-5p, miR-183-5p, miR-18a-5p, miR18b-5p, hsa-miR-21-5p, miR-223-3p, miR-224-5p, miR-503-5p (Falzone et al. 2018) |
|                  | Tumor suppressor | miR-1-3p, miR-133b, miR-143-3p, miR-145-5p, miR-150-5p, miR-195-5p, miR215-5p, miR-375, miR-378-3p, miR497-5p (Falzone et al. 2018) |
| Melanoma         | Oncogenic        | miR-195 (Cirilo et al. 2017), miR-210 (Šapková et al. 2020)                  |
|                  | Tumor suppressor | miR-193a, miR-33a (Zhou et al. 2015), miR-let-7b/c                          |
| Pituitary adenoma| Oncogenic        | miR-128a, miR-155, miR-516a-3p, miR-372, miR-181b-5p, miR-181d, miR-191-3p, miR-598 (Wu et al. 2017b) |
|                  | Tumor suppressor | miR-34a (Yang et al. 2018b), miR-3676-5p, miR-383 (Wu et al. 2017b)         |
| Osteosarcoma     | Oncogenic        | miR-504 (Cai et al. 2017), miR-149 (Xie et al. 2018b)                       |
| Neuroblastoma    | Oncogenic        | miR-181a/b (Liu et al. 2018), miR-1208, miR-1303 (Li et al. 2016c), miR-1308, miR-1908, miR-198, miR-513b-5p, miR-548b, miR-580 |
|                  | Tumor suppressor | miR-513, miR-548a/b-5p, miR-323-5p, miR-342 (Soriano et al. 2019), miR-639, miR-640, miR-641, miR-662, miR-34a (Cheng et al. 2019), miR-16, miR-15a/b (Chava et al. 2020) |
| Lung non-small cell| Oncogenic        | miR-25 (Ding et al. 2018), miR-7, miR-34a, miR-328-3p (Ma et al. 2016), miR-499a (Wu et al. 2019) |
|                  | Tumor suppressor | miR-451 (Liu et al. 2019b), miR-214                                        |
| Bladder          | Oncogenic        | miR-222, miR-452, miR-6724-5p, miR-1185-1-3p, miR-6831-5p (Usuba et al. 2019) |
|                  | Tumor suppressor | miR-143, miR-99a-5p (Tsai et al. 2018), miR-6087, miR-3960, miR-1343-5p (Usuba et al. 2019) |
| Cervical         | Oncogenic        | miR-31 (Zheng et al. 2015), miR-19a/b, miR-145 (Ma and Li 2019), miR-155 (Li et al. 2019), miR-125a (Xue et al. 2015) |
|                  | Tumor suppressor | miR-34a (Geng et al. 2015), miR-886-5p (Xiang et al. 2019)                  |
also affected by an altered microRNA expression (Barutta et al. 2018).

miRNA lists in cardiovascular diseases

miRNAs regulate the cardiac progenitor cell differentiation and proliferation, controlling cardiac myocytes, endothelial cells, pacemaker cells, and smooth muscle cell’s function. Table 2 shows miRNA lists dysregulated in various CVDs (Schulte et al. 2017). For example, miR-208a and miR-208b, encoded within alpha and beta-cardiac muscle myosin heavy chain genes, respectively, were found to be elevated in patients with acute myocardial infarction (AMI). Liu et al. (2015) demonstrated a significant predictive value for miR-208, miR-1, and miR-499 in AMI, higher than the traditional cardiac biomarkers, namely, TnT and CPK-MB.

miRNA list in cerebrovascular diseases

miRNAs are essential to the nervous system’s improvement, with few miRNAs having function in developing ischemic cerebrovascular disorders incapacity (Volný et al. 2015). Many miRNAs have been associated with post-stroke brain edema and post-stroke cell death, namely, apoptosis; a protective facility against environmental toxicants as inflammation or stressors and heat, etc., (Vasudeva and Munshi 2020) as listed in Table 3.

miRNAs in the oncology field

Onco-miR or tumor suppressor miR: a coin with two faces

Being a multifactorial player, miRNA in the oncology field represents a coin with two faces, either oncogenic or tumor suppressor (Youness and Gad 2019), as listed in Table 4. miRNA that can hit/suppress various mediators of the oncogenic signaling pathways is known as a tumor suppressor mediator (Ahmed Youness et al. 2020; Shaalan et al. 2018; Rahmoon et al. 2017). On the contrary, the miRNA that aims the cell cycle checkpoint proteins or the fundamental tumor suppressor proteins is nominated the oncogenic miRNA or an onco-miR (Frixa et al. 2015).

Again, the cross talk is between miRNAs and IncRNAs in the oncology field. IncRNAs are evolving as miRNA sponges, with critical functions in cancer biology and growth. Several bioinformatic techniques for analyzing the competitive relations between IncRNAs and miRNA to target mRNAs.
Table 5 miRNA list targeting various mTOR pathway signals

| miRNA list | Targeted gene(s) | Cancer type | Effect |
|------------|------------------|-------------|--------|
| miR-7 (Glover et al. 2015) | AKT, PI3K | HCC, Adrenocortical | Proliferation, Invasion |
| miR-99 family (Yu et al. 2015a; Li et al. 2015c; Zhao et al. 2016a; Li et al. 2016b) | mTOR, AKT | Endometrial, NSCLC, Cervical, Breast, Pancreatic, HCC, Esophageal, Bladder | Proliferation, Invasion, Apoptosis, Cell cycle, Autophagy, Tumor formation |
| miR-101 (Zhang et al. 2017) | EZH2, mTOR | HCC, Osteosarcoma | Proliferation, Invasion, Cell cycle |
| miR-122 (Yang et al. 2015) | PI3K | Breast | Proliferation |
| miR-149 (Zhang et al. 2017) | mTOR | Cervical | Proliferation |
| miR-193a-3p/5p (Jian et al. 2016; Shen et al. 2015; Yu et al. 2015b) | mTOR, PI3K | NSCLC | Proliferation, Migration, Epithelial–mesenchymal transition (EMT) |
| miR-204 (Xia et al. 2015b) | mTOR | NSCLC | Metastasis |
| miR-155 (Zhang et al. 2017) | AKT, S6K1, Rictor | Cervical, Nasopharyngeal, Breast | Proliferation, Autophagy |
| miR-214 (Yu et al. 2015c; Das et al. 2016) | mTOR | Renal | Proliferation |
| miR-218 (Lu et al. 2015; Zhang et al. 2015a, b; Tian et al. 2015) | PI3K, mTOR | Colorectal, OSCC, Cervical | Tumorigenesis Progression, Invasion, Migration |
| miR-125a (Chen et al. 2019) | mTOR | HCC | Metastasis |
| miR-199a (Callegari et al. 2018) | mTOR | Glioma, Endometrial, HCC | Proliferation |
| miR-22 (Meng et al. 2020) | mTOR | Suprarenal epithelioma | Metastasis |
| miR-93 (Chen et al. 2015b; Ohta et al. 2015; Jiang et al. 2015; Kawano et al. 2015) | PTEN | Osteosarcomas, Ovarian | Proliferation, Migration, Invasion, Inhibiting apoptosis |
| miR-532-5p (Wang et al. 2019a) | mTOR | Gastric | Proliferation, Metastasis |
| miR-451 (Du et al. 2015) | mTOR, AMPK | Colon | Proliferation, Migration |
| miR-205 (Zhuo and Yu 2017) | PTEN | NSCLC | Proliferation, Angiogenesis |
| miR-96 (Zhang et al. 2015a, b; Leung et al. 2015; Chong 2016) | mTOR, PRAS40 | Prostatic, Breast | Proliferation, Metastasis |
| miR-634 (Cong et al. 2016) | mTOR | Prostatic, Pancreatic, Cervical | Proliferation, Metastasis, Apoptosis |
| miR-21 (Shi 2016; Fragni et al. 2016; Li et al. 2016; Kalorigiou et al. 2016; Chen et al. 2015a; Yu et al. 2016) | TSC, PTEN, PI3K, PDCD4 | Gastric, Lymphadenoma, NSCLC, HCC, Breast, Pancreatic, Renal | Proliferation, Proapoptosis, Cell cycle |
| miR-1271 (Xie et al. 2018a) | mTOR | Gastric | Proliferation, Apoptosis |
| miR-125b (Vilquin et al. 2015) | mTOR | Sarcoma, Small cell osteosarcoma | Proliferation, Metastasis, Cell cycle, apoptosis |
have been suggested based on the hypothesis of competing endogenous RNAs (ceRNAs). For instance, lncRNA–CDC6 functions as ceRNA to regulate CDC6 by sponging miRNA-215 (Kong et al. 2019) and lncRNA PICSAR sponges miRNA-4701-5p (Xuan et al. 2019).

**miRNA involvement in carcinogenesis via mTOR signaling**

In different types of cancer, the mechanistic target of rapamycin (mTOR), a conserved serine/threonine kinase enzyme involved in cell metabolism, tied to environmental cues including nutrient levels and growth factors, could be subsequently hyperactive, leading to an abnormal cell proliferation and eventually cancer (Katayama et al. 2007). An association was observed between miRNA(s) and the mTOR pathway during cancer growth (Kovalchuk et al. 2008; Zhang et al. 2017).

Targeted Raptor mutation, a fundamental component of mTORC1 type, may affect increments in miRNA biogenesis (Ye et al. 2015). On the other hand, Mdm2-dependent ubiquitination of Drosha, an RNase, is assigned to pri-miRNA formation to give pre-miRNA; therefore, mTOR activation widely suppresses miRNA biogenesis (Katayama et al. 2007). Few specific miRNA(s) related to cancer are known to be regulated by mTOR signaling, as sketched in Fig. 2.

**miRNAs and multidrug resistance in cancer therapy**

Over decades, the significant clinical obstacle to successful cancer treatment is multidrug resistance (MDR), arising from ATP binding cassette (ABC) drug transporter(s) dysregulation, apoptosis or autophagy machinery surrender, redox homeostasis imbalance, drug-dysregulated metabolism, and drug target alterations (An et al. 2017). Several manuscripts addressed miRNAs role in MDR (Kovalchuk et al. 2008; Geretto et al. 2017; Bach et al. 2017; Si

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**Table 6** miRNA list involved in multidrug resistance highlighting their regulatory function(s) and the MDR targets

| Regulation of | Target | miRNA list |
|--------------|--------|------------|
| MDR transporters | ABCB1/MDR1 | miR-302c, miR-3664 (Ghanbarian et al. 2018), miR-873 (Wu et al. 2016), miR-381, miR-495, miR-223, miR-203a, miR-200c (Armada et al. 2019), miR-508-5p (Shang et al. 2016), miR-451 (Kovalchuk et al. 2008) |
|               | ABCG2/BCRP | miR-328, miR-519, miR-520, miR-181a, miR-487a, miR-519c, miR-212 (To et al. 2015) |
|               | ABCC1/MRP1 | miR-326, miR-1291, miR-508-5p (Pei et al. 2016) |
|               | p53 | miR-125a/b, miR-140 (Liang et al. 2016), miR-122, miR-34 |
|               | CDK6 | miR-34a, miR-139-5p (Li et al. 2016a), miR-143 (Zhuang et al. 2015), miR-503, miR-1271 |
|               | BCL2 | miR-15b, miR-16, miR-21, miR-497, miR-200bc/429, miR-1915, miR-214, miR-195 (Qu et al. 2015), miR-205 |
|               | BCL-XL | miR-574-3p |
|               | MCL-1 | miR-101 (He et al. 2016) |
|               | BIM | miR-494 |
|               | BAX | miR-365 |
|               | Caspase-3 | miR-30 b/c, miR-21 |
|               | PTEN | miR-21, miR-22, miR-221, miR-214, miR-19a/b, miRNA-17-5p, miR-222 (Zeng et al. 2016) |
| Autophagy induction | Beclin-1 and ATG5 | miR-30a, miR-30d/c, miR-155, miR-15a (Huang et al. 2015), miR-16 (Chatterjee et al. 2015), miR-200b (Pei et al. 2016), miR-181a (Zhao et al. 2016b) |
| Anti-cancer drug metabolism modulation | CYP1B1 | miR-27b (Mu et al. 2015) |
|               | CYP1A1 | miR-892a, miR-130b (Rieger et al. 2015) |
|               | CYP2J2 | let-7b (An et al. 2017) |
| Drug target modulation (An et al. 2017) | TS enzyme | miR-148a, miR-27b |
|               | DPD enzyme | miR-192, miR-215 |
|               | RRMI2 | miR-27a, miR-27b, miR-134, miR-582-5p |
|               | MMR proteins | miR-21, miR-155 |
|               | BRCA1 | miR-182, miR-9, miR-218 (He et al. 2015), miR-638 (Strumiało et al. 2017) |
| GSH and GSH-dependent enzymes | GSH | miRNA-27a (An et al. 2017) |
|               | GST | miR-513a-3p, miR-133b (Chen et al. 2015c) |
et al. 2019). Therefore, miRNAs might be potential targets for preventing chemotherapy MDR.

Differences in miRNA expression pattern in drug-resistant cancer cells relative to drug-sensitive cells (An et al. 2017) have been reported. A list of miRNAs regulating MDR by stressing on a specific cellular-signaling pathway or transporters is summarized in Table 6.

**Conclusion**

One abundant class of ncRNAs is miRs. MiRs are involved in the pathogenesis as well as detection of various environment-related NCDs, including different cancer types. Moreover, miRNAs are linked to mTOR signaling pathway, a fundamental pathway of MDR and/or carcinogenesis. Current evidence indicates that in most diseases, including the NCDs, miRNAs and mTOR binding do happen.

**Prospects** Being ideal biomarkers for predicting chemotherapy response, miRs would be possible goals for future drug design to solve MDR (1). Additionally, (2) combining miRNAs detection together with the mTOR signaling route components, being related to SNPs, would draw the complete picture concerning miRNAs as viable targets for evaluating and prognosticating NCDs.

**Author contribution** Mahmoud MM: data curation, original draft preparation, and rewriting; Sanad EF: editing, rewriting, and reviewing; Hamdy NM: conceptualization, supervision, editing, rewriting, and reviewing from submission till acceptance.

**Availability of data and materials** Not applicable.

**Declarations**

**Conflict of interest** The authors declare no competing interests.

**Abbreviations** ABCB1, ATP Binding Cassette Subfamily B Member 1; ABCC1, ATP Binding Cassette Subfamily C Member 1; ABCG, ATP binding cassette super-family G member; AGO, Argonaute; AMI, Acute myocardial infarction; AMPK, Adenosine 5-monophosphate-activated protein kinase; ATG5, Autophagy related 5; BCL-XL, B-cell lymphoma-extra large; BCL2, B-cell lymphoma 2; BCRP, Breast cancer resistant protein; CDK6, Cyclin-dependent kinase 6; CeRNA, Competitive endogenous non-coding RNA; CRC, Colorectal cancer; CYP, Cytochrome P450; CVD, Cardiovascular diseases; DCP, De-capping protein; DGCR8, Drosophila-DiGeorge syndrome-critical region gene 8; DPD, Dihydroorotidine dehydrogenase; dsRNA, Double stranded RNAs; EDC4, Enhancer of de-capping 4; eIF4G, Eukaryotic initiation factor 4; ERK, Extracellular signal-regulated kinase; GSH, Glutathione; GST, Glutathione S-transferases; HCC, Hepatocellular carcinoma; LncRNA, Long non-coding RNA; MAPK, Mitogen-activated protein kinase; MDR, Multidrug resistance; miRNA, MicroRNA; MRE, MiRNA response elements; MRP1, Multidrug resistance-associated protein 1; mTOR, Mechanistic target of rapamycin; NCDs, Non communicable diseases; ncRNA, Noncoding RNAs; NSCLC, Non small-cell lung carcinoma; ORF, Open reading frame; Onco miR, Oncogenic miRNA; PD, Parkinson’s Disease; PDCD4, Proapoptotic factors programmed cell death 4; PI3K, Phosphoinositide 3- kinase; piRNA, Piwi-interacting RNAs; PPARY, Peroxisome Proliferator-activated Receptor y; Pre-miRNAs, Precursor-miRNAs; Pri-miRNAs, Primary miRNAs; PTEN, Phosphatase and tensin homolog; Rictor, Rapamycin-insensitive companion of mTOR; RISCs, RNA-induced silencing complex; S6K1, Ribosomal protein S6 kinase beta 1; shRNAs, Short heterogenous RNAs; siRNA, Small interfering RNA; snoRNAs, Small nucleolar RNAs; snRNAs, Small nuclear RNAs; TS, Thymidylate synthase; UTR, Untranslated Region;

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