Molecular interactions of miR-338 during tumor progression and metastasis

Meysam Moghbeli*

Abstract

Background: Cancer, as one of the main causes of human deaths, is currently a significant global health challenge. Since the majority of cancer-related deaths are associated with late diagnosis, it is necessary to develop minimally invasive early detection markers to manage and reduce mortality rates. MicroRNAs (miRNAs), as highly conserved non-coding RNAs, target the specific mRNAs which are involved in regulation of various fundamental cellular processes such as cell proliferation, death, and signaling pathways. MiRNAs can also be regulated by long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs). They are highly stable in body fluids and have tumor-specific expression profiles, which suggest their suitability as efficient non-invasive diagnostic and prognostic tumor markers. Aberrant expression of miR-338 has been widely reported in different cancers. It regulates cell proliferation, migration, angiogenesis, and apoptosis in tumor cells.

Main body: In the present review, we have summarized all miR-338 interactions with other non-coding RNAs (ncRNAs) and associated signaling pathways to clarify the role of miR-338 during tumor progression.

Conclusions: It was concluded that miR-338 mainly functions as a tumor suppressor in different cancers. There were also significant associations between miR-338 and other ncRNAs in tumor cells. Moreover, miR-338 has a pivotal role during tumor progression using the regulation of WNT, MAPK, and PI3K/AKT signaling pathways. This review highlights miR-338 as a pivotal ncRNA in biology of tumor cells.

Keywords: Non-coding RNA, MicroRNA, MiR-338, Cancer, Biomarker

Background

Cancer is the leading cause of deaths and remains a significant challenge for human health globally. Improving the quality of life and prolonging patient survival are the main aims of cancer therapy. However, low efficiency of conventional treatments highlights the importance of effective tumor-specific therapeutic strategies [1]. Non-coding RNAs (ncRNAs) are important post-transcriptional regulators that affect cell apoptosis, proliferation, and differentiation [2–4]. MiRNAs are a group of short ncRNAs (19–24 nucleotides) that target mRNAs using binding with the 3′-untranslated region (UTR), resulting in mRNA degradation and translational suppression [5]. They are categorized based on...
their genomic origin into intergenic, intronic, and exonic. Aberrant expression of miRNAs has been reported during tumor progression [6, 7]. Based on the targeted mRNA, miRNAs can function as tumor suppressors or oncogenes [8, 9]. Clarification of miRNA mechanisms during pathogenesis of human disorders paves the way for introducing novel miRNA-based therapeutic modalities or diagnostic markers. MiRNAs are tissue specific and resistant to plasma RNAses, which suggests their use as unique non-invasive diagnostic tumor markers [10]. Since the majority of tumors are detected in advanced stages with a poor prognosis, non-invasive and sensitive markers are required for early stage tumor detection. Circulating miRNAs are highly stable in body fluids and have tumor-specific expression profiles, suggesting their suitability as efficient noninvasive diagnostic and prognostic tumor markers [11, 12]. MiR-338 is located within an intron of the AATK gene that has an essential role during neuron development [13]. In the present review, we have summarized all of the reported miR-338 targets and associated signaling pathways and other non-coding RNAs to clarify the molecular mechanisms of miR-338 during tumor progression in different cancers (Table 1).

Circular RNAs
CircRNAs are generated by back-splicing characterized by a closed loop [14]. They are involved in transcriptional regulation by microRNA sponging, which is critical in tumor cell proliferation, apoptosis, angiogenesis, and metastasis [15, 16]. Lung cancer is the second most frequent and leading cause of cancer-related deaths in the world [17, 18]. The majority of lung tumors are non-small cell lung cancer (NSCLC) cases [19]. Circ_0001649 is a circRNA transcribed from SHPRH. It was reported that there was circ_0001649 down regulation in NSCLC tissues and cell lines, which was correlated with advanced TNM stage and lymph node involvement. It inhibited cell proliferation and migration of NSCLC cells through miR-338-5p sponging [20]. Renal cell carcinoma (RCC) accounts more than 90% of renal cancers [21]. Clear cell RCC (ccRCC) is the most frequent histological type of RCC [22]. Caveolin-1 (CAV1) is a scaffold protein that interacts with G-protein and is involved in regulation of WNT and TGFβ signaling pathways [23]. It was reported that there was circAKT1 upregulation in ccRCC tissues in comparison with normal margins, which was associated with poor prognosis, TNM stage, and lymph node involvement. CircAKT1 induced cell proliferation, migration, and epithelial-mesenchymal transition (EMT) via miR-338-3p inhibition, which resulted in CAV1 upregulation [24]. Bromodomain containing 4 (BRD4) is a chromatin reader protein and transcriptional regulator that binds acetylated histones during cell proliferation [25–27]. It was reported that there was circ-007841 up-regulation in multiple myeloma (MM). It also induced cell proliferation and metastasis while suppressing apoptosis in MM cells via miR-338-3p decoy to up-regulate BRD4 [28]. TYRO3 is a tyrosine kinase significantly upregulated in various tumors, and induces cancer cell proliferation, EMT, and drug resistance [29–31]. There was an increased level of cir-cRAE1 in CRC tissues that was correlated with advanced TNM stage, tumor size, and lymph node involvement. It also promoted colorectal tumor cell migration by miR-388-3p sponging to upregulate TYRO3 [32]. RAB14 is an oncogenic GTPase involved in cell proliferation and invasion through regulation of the AKT pathway [33, 34]. There was significant circ-000326 upregulation in lung cancer tissues compared with normal
| Study    | Year | Type       | Gene          | Target       | Samples                                                                 | Function                                                   |
|----------|------|------------|---------------|--------------|--------------------------------------------------------------------------|-------------------------------------------------------------|
| Liu [20] | 2018 | Lung       | Circ-0001649  | miR-338-5p   | 53 NT A549, H358, H1299, and H1581 cell lines                            | Inhibited cell proliferation and migration                 |
| Zhu [24] | 2020 | Renal      | Circ-AKT1     | miR-338-3p   | 70 NT 768-O, A498, ACHN, Caki-1, and OS-RC-2 cell lines                 | Induced cell proliferation, migration, and EMT            |
| Wang [28]| 2020 | Myeloma    | Circ-0007841  | miR-338-3p   | 41 patients and 41 healthy controls (plasma) H929 and OPM2 cell lines   | Induced cell proliferation                                  |
| Du [32]  | 2020 | Colorectal | Circ-RAE1     | miR-338-3p   | 80 NT HCT116, SW620, HT29, and SW480 cell lines                         | Induced cell migration                                     |
| Xu [35]  | 2020 | Lung       | Circ-000326   | miR-338-3p   | 100 NT A549, SPC-A1, H1299, and H1975 cell lines                       | Induced tumor progression                                  |
| Shu [38] | 2020 | Thyroid    | Circ-HIPK3    | miR-338-3p   | 10 NT K1, CAL-62, and TPC-1 cell lines                                  | Induced progression and invasion                           |
| Liu [39] | 2020 | Liver      | Circ-104566   | miR-338-3p   | 87 NT SK-HEP-1, HLE, SNU449, Hep-3B, and HuH7 cell lines               | Induced tumor progression                                  |
| Xiong [41]| 2019 | Glioma     | Circ-SMO742   | miR-338-3p   | 10 NT A172 and U-87MG cell lines                                       | Induced cell proliferation                                 |
| Pu [43]  | 2020 | Liver      | Circ-000092   | miR-338-3p   | 40 NT Hep3B, LM3, MHCC97L, Sk-hep1, and HepG2 cell lines               | Induced tumor progression                                  |
| Qian [47]| 2020 | Cervical   | Circ-HIPK3    | miR-338-3p   | 45 NT HeLa, CaSki, SiHa, C-33A, C-4I, and SW756 cell lines             | Induced EMT                                                 |
| Jin [48] | 2020 | Gastric    | Circ-HIPK3    | miR-338-3p   | 31 NT MGC803 and BGC823 cell lines                                     | Induced cell migration                                     |
| Xiang [49]| 2020 | Osteosarcoma| Circ-CCDC66   | miR-338-3p   | 12 NT SW1353 and U2OS cell lines                                       | Induced tumor invasion                                    |
| Yang [50]| 2020 | Colorectal | Circ-0137008  | miR-338-5p   | 30 NT HT29, HCT116, HCT8, LOVO, SW480, and SW620 cell lines            | Inhibited cell proliferation and migration               |
| Yan [56]| 2017 | Esophageal | SNHG1         | miR-338-3p   | 56 NT 6 primary cell culture                                            | Induced cell proliferation                                 |
| Zhang [60]| 2019 | Neuroblastoma| SNHG1       | miR-338-3p   | 33 NT SK-N-SH and SK-N-AS cell lines                                   | Induced cell proliferation and migration                  |
### Table 1 (continued)

| Study | Year | Type | Gene   | Target     | Samples                                                                 | Function                                      |
|-------|------|------|--------|------------|----------------------------------------------------------------------|-----------------------------------------------|
| Li [65] | 2019 | Colorectal | SNHG15 | miR-338-3p | 203 NT HCT116, SW620, LOVO, SW480, and 293 T cell lines                | Induced cell proliferation                     |
| Zhang [66] | 2019 | Prostate | SNHG15 | miR-338-3p | LNCAP, DU145, and PC3 cell lines                                      | Induced cell proliferation and EMT             |
| Liu [69] | 2018 | Ovarian | LINC00460 | miR-338-3p | 98 NT SKOV3, A2780, OVCA1, and HO-8910 cell lines                     | Increased cell proliferation and EMT          |
| Hu [70] | 2020 | Prostate | LINC00173 | miR-338-3p | 124 NT DU145, PC3, and LNCAP cell lines                               | Induced tumor cell progression                |
| Wan [71] | 2020 | Glioma | LINC00525 | miR-338-3p | U87, MOS9K, U118, Hs683, and LN-18 cell lines                         | Regulated migration and EMT                   |
| Lu [72] | 2020 | Gastric | LINC-00689 | miR-338-3p | 40 NT HGC-27, SGC-7901, MGIC-803, and AG5 cell lines                 | Induced cell growth and EMT                   |
| Feng [74] | 2020 | Leukemia | NEAT1  | miR-338-3p | 32 patients 32 healthy controls KG-1, HL-60, THP-1, and U937 cell lines | Inhibited cell growth and migration          |
| Jing [76] | 2019 | Lung | CRNDE  | miR-338-3p | 84 NT A549, H1299, SPCA1, and H558 cell lines                         | Induced tumor progression                     |
| Song [79] | 2020 | Esophageal | BANCR  | miR-338-3p | 40 NT KYS5E450 and KYS5E10 cell lines                                 | Inhibited tumor progression                  |
| Luan [80] | 2018 | Cervical | XLOC-006390 | miR-338-3p | 20 NT SiHa, HeLa, Ca5i, C-41, and C-33A cell lines                    | Induced tumor progression                     |
| Chen [82] | 2020 | Lung | SBF2-AS1 | miR-338-3p | 56 NT A549, H1650, and H1975 cell lines                               | Induced tumor growth                          |
| Ji [83] | 2019 | Liver | DSCAM-AS1 | miR-338-3p | 48 NT HepG2, Hep3B, Huh7, and SMMC7721 cell lines                    | Induced tumor progression                     |
| Li [85] | 2019 | Oral | OIPS-AS1 | miR-338-3p | 38 NT SCC9, SCC15, Ca9-22, and HSU3 cell lines                       | Increased cell proliferation, migration, colony formation, and in vivo growth |
| Ma [89] | 2018 | Glioma | miR-338-5p | FOXD1    | 130 NT U251 cell line                                                | Inhibited cell proliferation                  |
| Hua [90] | 2017 | Cervical | miR-338-3p | MACC1    | 67 NT HeLa and Ca5i cell lines                                       | Inhibited cell proliferation                  |
| Jia [91] | 2019 | Osteosarcoma | miR-338-3p | RUNX2, CDK4 | MG-63 and U2OS cell lines                                           | Inhibited cell proliferation and migration    |
| Study          | Year | Type        | Gene          | Target | Samples                                                                 | Function                                      |
|---------------|------|-------------|---------------|--------|-------------------------------------------------------------------------|-----------------------------------------------|
| Peng [96]     | 2014 | Gastric     | miR-338-3p    | NRP1   | 41 NT SGC-7901, HGC-27, AGS, MKN-45, and N87 cell lines                 | Inhibited cell proliferation and migration   |
| Ding [98]     | 2019 | Lung        | miR-338-3p    | NRP1   | 55 NT A549, HCC2827, and H226 cell lines                                | Inhibited colony formation and cell migration |
| Liu [99]      | 2015 | Oral        | miR-338-3p    | NRP1   | 24 NT TCa-8113 and SCC-15 cell lines                                    | Inhibited cell proliferation and invasion    |
| Song [112]    | 2018 | Gastric     | miR-338-3p    | EPHA2  | AGS cell line                                                           | Inhibited proliferation and migration         |
| Niu [116]     | 2019 | Ovarian     | miR-338-3p    | WNT2B  | 54 NT SKOV3, A2780, and IOSE-80 cell lines                              | Induced cisplatin response                    |
| Xue [120]     | 2014 | Colorectal  | miR-338-3p    | SMO    | 40 NT HT29, LOVO, Caco2, and SW-620 cell lines                          | Inhibited cell migration                      |
| Huang [121]   | 2011 | Liver       | miR-338-3p    | SMO    | 36 NT Hep3B, SK-HEP-1, Huh7, Bel-7402, and SMMC-7721 cell lines         | Inhibited tumor invasion                      |
| Guo [124]     | 2014 | Gastric     | miR-338-3p    | PREX2a | 53 NT AGS and BGC-823 cell lines                                       | Inhibited tumor progression                   |
| Chen [125]    | 2013 | Neuroblastoma | miR-338-3p | PREX2a | 18 NT SH-SYSY cell line                                                 | Inhibited cell proliferation and migration    |
| Besse [128]   | 2016 | Glioblastoma | miR-338-5p   | NDFIP1, PPP2R5a | 40 NT A172, T98G, and U87MG cell lines                                | Inhibited cell proliferation                   |
| Liu [132]     | 2019 | Lung        | miR-338-3p    | AKT    | A549 cell line                                                          | Inhibited cell proliferation                  |
| Sui [133]     | 2017 | Thyroid     | miR-338-3p    | AKT3   | 48 NT 8505c, TPC-1, and SW1736 cell lines                               | Inhibited cell proliferation, migration, and in vivo growth |
| Lu [137]      | 2018 | Cervical    | miR-338-3p    | ATF2   | 30 NT Siha, HeLa, C33A, and Me180 cell lines                            | Inhibited autophagy                            |
| Chu [141]     | 2019 | Colorectal  | miR-338-5p    | PIK3C3 | 66 NT SW480 and HCT166 cell lines                                       | Induced tumor invasion                         |
| Zhang [145]   | 2017 | Lung        | miR-338-3p    | IRS2   | 40 NT A549, H1299, SPCA1, and H358 cell lines                           | Inhibited cell proliferation and migration    |
| Wang [147]    | 2015 | Liver       | miR-338-3p    | FOXP4  | 30 NT HepG2 and Hep3B cell lines                                        | Inhibited cell proliferation                  |
| Tong [152]    | 2017 | Renal       | miR-338-3p    | SOX4   | 48 NT 786-O, ACHN, Caki-1, and Caki-2 cell lines                       | Inhibited colony formation and cell migration |
| Study          | Year | Type   | Gene Target | Samples                                                                 | Function                                                                 |
|----------------|------|--------|-------------|-------------------------------------------------------------------------|--------------------------------------------------------------------------|
| Jin [154]      | 2015 | Breast | miR-338-3p  | SOX4 32 NT MCF-7, MDA-MB-231, BT-549, and MDA-MB-453 cell lines         | Inhibited colony formation, in vivo growth, and cell migration            |
| Huang [155]    | 2015 | Gastric| miR-338-3p  | ZEB2 20 NT AGS, MKN-45, and NCI-N87 cell lines                         | Inhibited EMT                                                            |
| Lu [157]       | 2019 | Colorectal | miR-338-3p | MACC1 15 NT SW480 and 293 T cell lines                                 | Inhibited cell proliferation and migration                               |
| Zhang [158]    | 2019 | Melanoma| miR-338-3p | MACC1 60 NT A375 and G361 cell lines                                   | Inhibited cell proliferation and migration                               |
| Zou [159]      | 2018 | Colorectal| miR-338-3p | MACC1 98 NT SW480, SW620, HT29, HCT116, and SW1116 cell lines          | Inhibited tumor progression                                              |
| Zhang [160]    | 2019 | Ovarian | miR-338-3p  | MACC1 105 NT                                                             | Inhibited cell proliferation and migration                               |
| Shang [161]    | 2016 | Glioma | miR-338-3p  | MACC1 39 T and 17 N U251 and U87 cell lines                            | Induced cisplatin sensitivity                                            |
| He [166]       | 2020 | Breast | miR-338-3p  | ZEB1 148 NT MCF7 and HCC1937 cell lines                                | Inhibited cell proliferation and migration                               |
| Shan [167]     | 2015 | Nasopharyngeal | miR-338-3p | HIF1A 5 NT CNE-1, CNE-2, S-8F, and 6-10B cell lines                    | Inhibited cell migration and proliferation                               |
| Xu [168]       | 2014 | Liver  | miR-338-3p  | HIF1A 15 NT HepG2, SMMC-7721, BK-7402, Hep3B, and Huh7 cell lines      | Induced sorafenib response                                               |
| He [170]       | 2020 | Lung   | miR-338-3p  | NFATc1 20 NT A549, H1650, SPCA-1, H460, H226, and H1299 cell lines     | Inhibited cell proliferation                                             |
| Zhang [174]    | 2019 | Bladder| miR-338-3p  | ETS1 39 NT J82, 5637, and T24 cell lines                               | Inhibited cell proliferation and migration                               |
| Li [176]       | 2018 | Glioma | miR-338-5p  | TSHZ3 35 NT U87 and U251 cell lines                                    | Increased invasiveness                                                   |
| Wen [178]      | 2015 | Ovarian| miR-338-3p  | RUNX2 54 NT SKOV3, OVCAR3, and A2780 cell lines                       | Inhibited cell proliferation, migration, and in vivo growth              |
| Duan [181]     | 2019 | Breast | miR-338-3p  | MORC4 30 NT MCF7 and MDA-MB-231 cell lines                             | Inhibited cell migration                                                 |
It regulated lung tumor cell proliferation and migration via RAB14 upregulation following miR338-3p sponging. There were also associations between circ-0000326 upregulation, T stage, N stage, and tumor grade of differentiation [35]. RAB23 belongs to the Rab GTPase family involved in vesicular transportation and endocytosis. It functions as an oncogene in many solid tumors such as bladder (BCa) and prostate (PCa) cancers. RAB23 induced BCa cell proliferation via the NF-κB and integrin β1/Rac1 axis, and induced cisplatin resistance by the Shh-Gli-ABCG2 axis [36, 37]. It was reported that circHIPK3 silencing significantly reduced thyroid cancer (TC) cell proliferation and migration. It upregulated RAB23 via miR-338-3p sponging in TC cells [38]. FOXP1 is a developmental transcription factor involved in embryogenesis and tumorigenesis. There was circ_104566 upregulation in high-grade compared with low-grade hepatocellular

Table 1 (continued)

| Study      | Year | Type      | Gene         | Target | Samples                                                                 | Function                                                                                           |
|------------|------|-----------|--------------|--------|------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|
| Li [185]   | 2013 | Gastric   | miR-338-3p   | SSX2IP | 66 NT SGC-7901, NCI-N87, BGC-823, AGS, KATO-III, SNU-1, MKN-28, and MKN-45 cell lines | Inhibited cell proliferation and in vivo growth                                                      |
| Lei [191]  | 2017 | Glioblastoma | miR-338-5p   | EFEMP1 | 15 NT U251, A172, U-118, and U87 cell lines                            | Inhibited cell proliferation and migration                                                          |
| Chen [197] | 2016 | Lung      | miR-338-3p   | ITGB3  | 115 NT AS49, NCI-H292, NCI-H460, NCI-H446, and NCI-H1299 cell lines     | Inhibited tumor invasion                                                                           |
| Li [200]   | 2018 | Renal     | miR-338-3p   | KIFC1  | 58 NT 786-O, 769-P, and OS-RC-2 cell lines                             | Inhibited cell proliferation and migration                                                          |
| Cao [202]  | 2018 | Osteosarcoma | miR-338-3p   | AHSA1  | 20 NT MG-63, Saos2, and HOS cell lines                                 | Inhibited EMT and invasion                                                                           |
| Xiao [207] | 2018 | Liver     | miR-338-3p   | SPHK2  | 39T and 21N HepG2, SMMC-7721, and BEL7402 cell lines                  | Inhibited cell proliferation                                                                         |
| Zhang [209]| 2017 | Lung      | miR-338-3p   | SPHK2  | 34 NT H460, H1299, AS49, SPC-A-1, and Calu-3 cell lines               | Inhibited cell proliferation                                                                         |
| Han [216]  | 2017 | Glioblastoma | miR-338-3p   | PKM2   | U87, LN229, and SNB19 cell lines                                      | Inhibited cell proliferation                                                                         |
| Zhang [217]| 2016 | Ovarian   | miR-338-3p   | PKM2   | HO-890, A2780, CoC1, CoC2, SKOV3, and Caov-3 cell lines               | Inhibited cell proliferation                                                                         |
| Sun [220]  | 2018 | Gastric   | miR-338-3p   | PTP1B  | 12 NT MKN-45 and MGC-803 cell lines                                   | Inhibited cell proliferation                                                                         |

*Normal and Tumor tissues*
carcinoma (HCC) tumors, introducing a direct association between circ_104566 and TNM stage. Circ_104566 upregulation was also correlated with shorter overall survival that referred to the prognostic role of this marker in HCC. Circ_104566 silencing reduced HCC tumor cell progression, whereas it increased apoptosis through the miR-338-3p/FOXP1 axis [39]. Smoothened (SMO) is a G protein coupled receptor of the hedgehog signaling pathway that activates GLI1 to promote cell cycle progression and migration [40]. It was shown that there was circSMO742 upregulation in glioma cells in comparison with normal cells, which induced cell proliferation and inhibited apoptosis via miR-338-3p sponging and SMO upregulation [41]. HN1 is a negative regulator of AKT-mediated GSK3B signaling. It promotes CTNNB1 phosphorylation and degradation via GSK3B activation, resulting in APC/CTNNB1/GSK3B complex inhibition. It also suppresses the AR-signaling pathway by receptor degradation [42]. Circ_0000092 silencing reduced the levels of HN1 expression by miR-338-3p upregulation, which resulted in reduced HCC tumor progression. There was also circ_0000092 upregulation while there was miR-338-3p downregulation in HCC samples [43]. Hypoxia upregulates HIFs by stabilization of HIF1A subunits, which has critical functions during tumor angiogenesis and chemo-radio resistance [44, 45]. HIF1A and hypoxia-related miRNAs are involved in clinical outcomes of cancer patients [46]. There was circ-HIPK3 upregulation in cervical cancer (CC) cells and tissues. Circ-HIPK3 upregulated HIF1A by miR-338-3p sponging in CC [47]. It was observed that circ-HIPK3 upregulation by HIF-2α increased GC cell migration and invasion through the miR-338-3p/miR-653-5p/NPR1 axis. There was also circ-HIPK3 upregulation in gastric cancer (GC) tissues in comparison with normal margins [48]. Tyrosine phosphatase functions as a regulator of protein folding in endoplasmic reticulum. It was observed that there was circCCDC66 upregulation in osteosarcoma (OS) tissues compared with normal tissues, which was associated with relapse and metastasis. CircCCDC66 silencing also suppressed OS cell proliferation and metastasis via the miR-338-3p/PTP1B axis [49]. CDH1 is a Ca2+-dependent cell adhesion factor participating in cell motility and proliferation. Significant circ-0137008 downregulation was observed in colorectal cancer (CRC) tissues and cell lines. It sponged the miR-338-5p to inhibit colorectal tumor cell proliferation and migration through CDH1 upregulation [50].

**Long non-coding RNA**

LncRNAs are a type of ncRNAs longer than 200 nucleotides that have pivotal regulatory roles in cell proliferation, apoptosis, and angiogenesis [51, 52]. LncRNAs mainly function as competing endogenous RNAs (ceRNAs) to regulate mRNA through miRNAs sponging [53]. Cystatins are considered as inhibitors of C1 cysteine proteases in various cellular processes and disorders [54]. Cystatin C (CysC) triggers caspase-mediated apoptosis by cathepsin targeting [55]. It was reported that there was miR-338 downregulation in 30% of a sample of esophageal squamous cell carcinoma (ESCC) tissues in comparison with normal margins. Significant CysC protein upregulation was also observed in ESCC tissues that induced tumor cell growth, while inhibiting apoptosis. Moreover, there was significant SNHG1 upregulation in ESCC tissues compared with normal margins that inhibited cell apoptosis and induced proliferation through miR-338-3p sponging [56]. Polo-like kinases (PLKs) are important regulators of various cellular
processes such as the cell cycle, centrosome duplication, and cell motility [57, 58]. Polo-like kinase 4 (PLK4) is involved in centriole duplication and cell cycle progression [59]. SNHG1 induced neuroblastoma cell proliferation and migration by miR-338-3p sponging resulting in PLK4 upregulation [60]. SNHG16 upregulation is also associated with drug resistance and tumor progression in various cancers [61–63]. It was reported that there was significant SNHG16 upregulation in cisplatin-resistant NB cells and tissues. SNHG16 upregulated PLK4 through miR-338-3p sponging in cisplatin-resistant NB cells. The SNHG16/PLK4/miR-338-3p axis also activated the PI3K/AKT signaling pathway in NB cells [64]. RAB14 is a member of the GTPases that has a pivotal role in intracellular membrane trafficking between Golgi and endosomes. FOS is a leucine zipper DNA binding protein that forms a heterodimer transcriptional complex with the JUN family to regulate cell proliferation, apoptosis, and differentiation. SNHG15 upregulation was observed in CRC tissues compared with normal margins that were associated with poor prognosis. It promoted CRC cell proliferation while suppressing apoptosis by miR-338-3p sponging, which resulted in FOS and RAB14 upregulation [65]. As a critical regulator of TGFβ signaling, FKBP1A prevents TGFβ receptor activation in ligand absence. There were increased levels of SNHG15 expression in PCa cells. SNHG15 silencing reduced PCa cell proliferation and the EMT process. It seems that SNHG15 has oncogenic roles by regulation of the FKBP1A/miR338-3p axis in PCa cells [66].

Epithelial ovarian cancer (EOC) represents about 90% of all ovarian cancers (OC) [67]. Conventional therapeutic methods such as surgery and chemotherapy have been improved during recent years; however, there is still a poor prognosis in OC patients because of tumor metastasis and chemoresistance [68]. It was observed that there was LINC00460 upregulation in EOC tissues and cell lines that was correlated with FIGO stage, lower survival, and lymph node involvement. LINC00460 increased EOC cell proliferation and the EMT process partially through miR-338-3p regulation [69]. As a member of RAS GTPases, RAB25 is involved in intracellular membrane traffic and cell survival. It has a dual function and can play an oncogenic or tumor suppressor role based on cell context. LINC00173 increased PCa progression through RAB25 upregulation following miR-338-3p sponging [70]. It was reported that there was LINC00525 upregulation in glioma cell lines that regulated the tumor growth, migration, and EMT process through miR-338-3p sponging [71]. Homeobox proteins are developmental transcription factors with pivotal roles during morphogenesis and differentiation. LINC00689 upregulation was observed in GC tissues and cell lines. LINC00689 promoted GC cell growth and the EMT process by miR-338-3p targeting that resulted in HOXA3 overexpression [72]. CREB3 is a leucine zipper DNA binding protein that regulates cell proliferation by binding with cAMP-response element. CREB3 functions as a tumor suppressor of glioblastoma via inhibition of hypoxia-induced autophagy [73]. NEAT1 upregulated CREBRF via miR-338-3p sponging to suppress AML cell growth and migration, while induction of apoptosis [74]. CRNDE is an oncogenic IncRNA involved in tumor cell proliferation and migration [75]. There was significant CRNDE upregulation in NSCLC tissues and cell lines, which was directly correlated with lymph node involvement, advanced stage, and shorter overall survival. CRNDE silencing also inhibited tumor growth in nude mice. It induced NSCLC progression via miR-338-3p sponging [76]. IGF1R/IGF interaction
activates Raf/MEK/ERK and PI3K/AKT/mTOR signaling pathways, which are critical processes during tumor progression [77, 78]. There was BANCR upregulation in ESCC cells and tissues. BANCR silencing reduced in vivo tumor growth, migration, and EMT via miR-338-3p sponging, which resulted in inhibition of the IGF1R/Raf/MEK/ERK pathway in ESCC cells [79]. It was reported that XLOC_006390 inhibition significantly upregulated miR-338-3p, which resulted in PKM2 and EYA2 targeting in cervical tumors [80]. ADAM metallopeptidase domain 17 (ADAM17) is a metalloprotease that has pivotal roles in activation of TGFβ, MAPK, and NOTCH signaling pathways [81]. There was significant SBF2-AS1 upregulation in NSCLC tissues and cell lines, which was correlated with distant metastasis, poor prognosis, and advanced stage. SBF2-AS1 increased NSCLC tumor growth probably through ADAM17 upregulation following miR-338-3p sponging [82]. There was DSCAM-AS1 upregulation in HCC cell lines and tissues, which was correlated with poor prognosis. DSCAM-AS1 silencing reduced HCC cell proliferation, migration, and in vivo tumor growth. DSCAM-AS1 upregulated CCND1 and SOD via miR-338-3p sponging [83]. NRPI is a co-receptor of VEGF functioning as an onco-gene in different tumors [84]. It was reported that there was OIP5-AS1 upregulation in oral squamous cell carcinoma (OSCC) tissue and cell lines in comparison with normal margins and cells. OIP5-AS1 significantly increased OSCC cell proliferation, migration, colony formation, and in vivo growth by regulation of the miR-338-3p/NRP1 axis [85].

MAPK and EGFR signaling pathways

Mitogen-activated protein kinase (MAPK) is a critical signaling pathway involved in regulation of cell proliferation, migration, differentiation, and apoptosis in response to extracellular signals [86]. Glioma tumors originate from glial progenitor or glial cells in the spine or brain [87]. FOXD1 is considered as a developmental transcription factor [88]. It was found that miR-338-5p suppressed MAPK signaling by FOXD1 downregulation to inhibit glioma cell proliferation and induce apoptosis [89]. MET transcriptional regulator (MACC1) is a transcription factor involved in tumor metastasis through the HGF/c-MET/MAPK axis. There was significant miR-338-3p downregulation in cervical cancer tissues that was associated with lymph node involvement, FIGO stage, and depth of invasion. MiR-338-3p inhibited MAPK signaling by p38 and ERK1/2 downregulation in cervical tumor cells. Generally, miR-338-3p reduced cervical tumor cell proliferation through MACC1 targeting [90]. There were lower levels of miR-338-3p expressions in OS cell lines in comparison with normal cells. MiR-338-3p also decreased OS cell proliferation and migration, while it induced apoptosis via RUNX2 and CDK4 targeting and MAPK signaling pathway regulation [91]. EGFR belongs to the tyrosine kinase receptors, which are activated EGF ligands. Deregulation of EGFR signaling has been reported in tumor progression in different cancers [92]. MiRNAs are associated with drug resistance to anti-EGFR agents [93]. Neuropilin 1 (NRPI) as a coreceptor of growth factors is involved in tumor progression that affects tumor cell viability through EGFR and ErbB2 signaling pathways [94, 95]. NRPI is widely upregulated in different solid tumors such as GC [96] and esophageal cancer [97]. It was observed that EGFR-TKI-mediated chemosensitivity was associated with the regulatory role of miR-338-3p on NRPI in lung cancer. MiR-338-3p suppressed NSCLC colony formation and migration via NRPI targeting [98]. It was reported that there was miR-338-3p downregulation in oral squamous cell
carcinoma (OSCC) tissues. MiR-338-3p suppressed OSCC cell proliferation and invasion via NRP1 targeting [99]. NRP1 induces angiogenesis by p38 MAPK and ERK signaling pathways [100]. MiR-338-3p suppresses GC cell migration and proliferation, while it induces apoptosis through NRP1 targeting [96].

**WNT and hedgehog signaling pathways**

WNT signaling is a pivotal pathway that regulates various cellular processes during embryogenesis and tumorigenesis. Regarding the post-transcriptional regulatory roles of miRNAs, they can be suggested as modulators of protein components in the WNT pathway [101–103]. Gastric cancer (GC) is the most frequent gastrointestinal malignancy and the leading cause of cancer-related mortality in developing countries [104]. Despite recent progress in surgical and chemotherapeutic methods, there is still a low rate of 5-year survival due to advanced stage diagnosis [105]. SOX5 is a developmental transcription factor [106]. Significant miR-338-3p downregulation was observed in GC tissues and cell lines, which was associated with lymph node metastasis and advanced TNM stage. There was also cross-talk between WNT and hypoxia signaling, in which hypoxia promoted WNT signaling by the HIF-a/miR-338-3p/SOX5 axis. MiR-338-3p was downregulated by HIF1A [107]. EMT is critical process during tumor progression and metastasis in which epithelial cells gain mesenchymal features to have better abilities for invasion. This process is characterized by E-cadherin downregulation and vimentin upregulation [108–110]. The WNT signaling pathway regulates cell proliferation, polarity and death during embryogenesis [111]. It affects cell adhesion by E-cadherin downregulation that induces cell migration and EMT. It was reported that miR-338-3p inhibited GC proliferation and migration via EPHA2 targeting [112]. MACC1 regulates Met expression, which is a pivotal factor of HGF/Met and master regulator of EMT [113]. HGF/MET signaling promotes migration and angiogenesis in ovarian cancer (OC) [114]. It was reported that miR-338-3p reduced OC cell proliferation and migration by MACC1 or MET regulation. MiR-338-3p also downregulated MMP2/9, VIM, CTNNB1, and N-cadherin, while it upregulated E-cadherin, which resulted in inhibition of WNT and MEK/ERK signaling pathways [115]. WNT2B is a ligand for the frizzled family receptors that triggers the canonical WNT signaling pathway as an important regulatory pathway involved in cell proliferation and EMT. There was a correlation between cisplatin resistance and levels of miR-338-3p expression in OC patients. MiR-338-3p increased cisplatin sensitivity through WNT2B targeting in ovarian tumor cells [116].

The hedgehog (Hh) signaling pathway is a conserved evolutionary embryonic signal transduction pathway from extracellular signals by specific receptors such as SMO and PTCH to the nucleus where it activates Gli transcription factors. Aberrant Hh signaling is associated with tumor progression [117]. Therefore, miRNAs have critical functions in regulation of Hh signaling during tumorigenesis. Activated SMO triggers a cytoplasmic cascade to activate GLI transcription factor that regulates cell proliferation, adhesion, and differentiation [118, 119]. MiR-338-3p downregulation has been reported in CRC tissues, which was correlated with TNM stage and invasion. Advanced stage tumors had lower levels of miR-338-3p expression compared with primary stage tumors. MiR-338-3p inhibited CRC invasion and migration via SMO targeting [120]. It was reported that there was miR-338-3p downregulation in liver tumor cells. MiR-338-3p reduced
liver tumor cell migration via SMO targeting. SMO and MMP9 levels of expressions were also correlated with advanced stages in HCC tissues. Therefore, miR-338-3p inhibited HCC invasiveness by downregulation of SMO-mediated MMP9 expression [121].

**PI3K/AKT signaling**

Phosphatidylinositol 3-kinase (PI3K) is a pivotal coordinator between extracellular signals and intracellular signaling which is activated by tyrosine kinase or G-protein coupled receptors. AKT is the main effector of PI3K that is negatively regulated by PTEN [122]. PREX2a belongs to the PIP3-dependent Rac exchanger (PREX) family of proteins associated with aggressive tumors [123]. It can directly suppress the lipid phosphatase activity of PTEN, resulting in PIP3 accumulation and increased AKT phosphorylation that induces cell cycle progression and growth during tumorigenesis. There was PREX2a upregulation in GC in comparison with normal margins. MiR-338-3p targeted PREX2a, resulting in PTEN activation and reduced AKT phosphorylation. MiR-338-3p also regulated BCL-2 and BAX through induction of the PI3K/AKT signaling pathway [124]. MiR-338-3p reduced neuroblastoma tumor cell proliferation and migration via PREX2a targeting and PTEN/AKT regulation [125]. NDFIP1 is a ubiquitin E3 ligase that regulates PTEN stability and nuclear translocation along with RAB5. PTEN has a regulatory effect on the PI3K/Akt pathway, and also on E2F1 and RAD51 transcriptional functions. Moreover, PTEN is involved in double-strand break DNA repair [126, 127]. Significant miR-338-5p and 3p downregulation was reported in glioblastoma multiforme (GBM) patients in comparison with normal controls. MiR-338-5p significantly reduced GBM cell proliferation, while promoting apoptosis through NDFIP1 and PPP2R5a targeting [128]. AKT is a serine-threonine kinase that promotes tumor cell proliferation, inhibits apoptosis, and improves hypoxia resistance [129, 130]. It is involved in CREB1 phosphorylation, which has a critical role in BCL2 and MCL1 upregulation [131]. It was found that miR-338-3p reduced lung tumor cell proliferation by inhibition of the AKT/β-catenin pathway [132]. There was significant miR-338-3p downregulation in TC tissues compared with normal margins, which was inversely associated with stage and lymph node involvement. MiR-338-3p also significantly inhibited TC cell proliferation, motility, and in vivo growth via AKT3 targeting [133]. It was reported that there was miR-338-5p upregulation in melanoma tissues that was conversely associated with CD82 expression levels. MiR-338-5p induced melanoma cells proliferation and metastasis via CD82 targeting and p-AKT upregulation [134]. Autophagy is promoted by many factors, including growth factors and DNA damage, and it regulates many pathways [135]. As a double-edged sword autophagy can suppress tumor progression in the early stages. Increased autophagy stress of tumor cells is observed following anticancer therapy, which suggests that autophagy is a cellular protection mechanism [136]. MiR-338-3p suppresses autophagy in cervical tumor cells by ATF2 regulation via the PI3K/AKT/mTOR signaling pathway [137]. PIK3C3 induces autophagy nucleation and inhibits EMT by degrading SNAIL and TWIST transcription factors in BC cells, leading to decreased cell migration and metastasis [138–140]. It was reported that miR-338-5p promoted CRC invasion by PIK3C3 targeting. It also repressed autophagy and inhibited degradation of snail and twist to induce tumor progression via EMT. Moreover, there was a direct association between levels of miR-338-5p expressions and clinicopathological
tumor features including advanced stages and poor survival among CRC patients [141]. IRS2 is an adaptor protein for surface receptors such as IGF-1R that activates PI3K/AKT signaling to promote cell proliferation [142–144]. It was reported that there was miR-338-3p downregulation in NSCLC tissues and cell lines in comparison with normal margins and cells, which was inversely correlated with advanced stage tumors with lymph node involvement. MiR-338-3p also reduced NSCLC cell proliferation and migration, while it increased apoptosis via IRS2 targeting [145].

Transcription factors and regulators

The forkhead box proteins are a family of transcription factors which are involved in regulation of cell cycle progression, cell migration, and angiogenesis. There is a complex association between miRNAs and function of forkhead box transcription factors [146]. FOXP4 is a member of the forkhead box (FOX) transcription factors with critical roles during embryogenesis and tumor progression. There was significant miR-338-3p downregulation in HCC tissues compared with normal margins. It also inhibited HCC cell proliferation via FOXP4 targeting [147]. SOX4 is a developmental transcription factor and critical regulator of EMT that is overexpressed in a variety of tumors [148, 149]. It regulates the miRNA machinery and various signaling pathways such as NOTCH, TGF-β, WNT, and hedgehog [150, 151]. There was miR-338-3p downregulation in renal cell carcinoma (RCC) tissues that was correlated with lymph node involvement and TNM stage. MiR-338-3p also suppressed colony formation and migration of RCC through SOX4 targeting [152]. EMT can be promoted by SOX4 through EZH2 as a polycomb epigenetic regulator [153]. MiR-338-3p was downregulated in BC tissues, which was correlated with advanced TNM stage and lymph node involvement. MiR-338-3p suppressed breast tumor cell colony formation, in vivo growth, and migration, while promoting apoptosis via SOX4 targeting [154].

MACC1 is an important transcription factor involved in EMT that promotes tumor cell migration and distant metastasis [155]. It also regulates the basolateral polarity of epithelial cells and angiogenesis [156]. There was significant downregulation of miR-338-3p in CRC tissues. MiR-338-3p functions as a tumor suppressor through MACC1 inhibition in CRC [157]. It was observed that there was miR-338-3p downregulation in malignant melanoma (MM) tissues that was correlated with advanced TNM stages and lymph node involvement. MiR-338-3p reduced MM cell proliferation and migration through MACC1 targeting, resulting in E-cadherin upregulation and vimentin downregulation [158]. MiR-338-3p was downregulated in CRC cell lines and tissues compared with normal cells and margins, which was correlated with differentiation, TNM stage, and overall survival. It inhibited CRC progression by MACC1 targeting [159]. Another study reported that there were significant miR-338-3p downregulation and MACC1 upregulation in EOC tissues compared with normal tissues, which were associated with advanced stage, high grade, recurrence, and metastatic lymph nodes. EOC patients with low levels of miR-338-3p expression also had significantly shorter overall survival [160]. MiR-338-3p downregulation was observed in glioma tissues, which was inversely associated with histological grades. MiR-338-3p also inhibited cell proliferation, while it induced apoptosis and cisplatin sensitivity by MACC1 targeting [161].
Tumor hypoxia is one of the main reasons for chemoradiotherapeutic resistance, which affects tumor invasiveness and poor prognosis [162]. *HIF1A* is a transcription factor with critical functions in the hypoxia response by induction of metastasis and angiogenesis [163–165]. It was reported that there was miR-338-3p downregulation in BC tissue and cells. MiR-338-3p suppressed breast tumor cell proliferation and EMT through *ZEB2* targeting. *HIF1A* also reduced the levels of miR-338-3p expression [166]. It was found that miR-338-3p inhibited cell migration and proliferation by *HIF1A* targeting in nasopharyngeal carcinoma (NPC) cells. There was also miR-338-3p downregulation in NPC tissues [167]. Another study showed that there was significant miR-338-3p downregulation in HCC tissues compared with normal tissues. MiR-338-3p inhibited HCC cell viability, while it increased the sorafenib response and apoptosis rate through *HIF1A* targeting [168].

*NFATc1* is a DNA binding transcription complex with critical roles in stimulation of production of cytokines such as IL-2 and IL-4 in T-cells. It can also regulate activation and apoptosis of T-cells, lymphoid, and non-lymphoid cells [169]. It was reported that there was significant *NFATc1* upregulation in NSCLC tissues. *NFATc1* silencing increased the levels of *CCND1* and *CDK4* expression, whereas it downregulated *p27*. Moreover, *NFATc1* silencing upregulated *CDH1* and downregulated *CDH2* and vimentin. MiR-338 reduced cell proliferation and EMT via *NFATc1* targeting in NSCLC cells [170]. *ZEB1* is a zinc finger E-box-binding transcription factor that functions as a transcriptional suppressor in various genes such as *IL-2* and *CDH1*. It recruits the SMARCA4/BRG1 complex to represses *CDH1* during EMT [171, 172]. There was miR-338-3p downregulation in advanced GC tumors. MiR-338-3p reduced GC cell migration and EMT through *ZEB2* targeting and MACC1/MET/AKT axis inhibition. MiR-338-3p was inversely associated with *CDH2*, *MACC1*, and *ZEB2*, while directly associated with *CDH1* expression in GC samples [155]. *ETS1* is a transcription factor involved in tumor metastasis [173]. There was miR-338-3p downregulation in bladder cancer (BCa), which was correlated with TNM stage and lymph node involvement. MiR-338-3p reduced BCa cell proliferation and EMT via *ETS1* inhibition [174]. *TSHZ3* is a critical developmental transcription factor during muscle cell differentiation [175]. An inverse association was found between levels of miR-338-5p and *TSHZ3* expression in high-grade astrocytic gliomas. MiR-338-5p increased glioma invasiveness by *TSHZ3* targeting [176]. *RUNX2* is a developmental transcription factor involved in normal bone development [177]. There was significant miR-338-3p downregulation in EOC tissues compared with normal margins that was inversely correlated with lymph node metastasis, advanced FIGO stage, and grade. MiR-338-3p significantly reduced EOC cell proliferation, in vivo tumor growth, and migration through *RUNX2* targeting and inhibition of the PI3K/AKT pathway [178]. Baicalin is an anti-proliferative and anti-inflammatory alkaloid used in treatment of cancers or disorders [179]. *MORC4* functions in generation of nuclear bodies and is involved in cell cycle progression. It is also involved in chemoresistance by activation of the transcription factor *STAT3* [180]. Baicalin reduced the levels of *MORC4* following miR-338-3p upregulation, which resulted in increased apoptosis and reduced migration in BC cells [181]. Methylation is an important epigenetic mechanism during tumor progression that promotes tumor growth via hypermethylation and hypomethylation of the CpG island promoter sequences in tumor suppressors and oncogenes,
respectively [182]. MECP2 is a key member of the DNA methylation machinery involved in neural development [183]. There was also MECP2 upregulation in GC which promoted cell proliferation in vitro/vivo. MECP2 reduced the levels of miR-338 expression by binding with methylated CpG islands in the promoter sequence. Significant miR-338-5p downregulation was observed in GC tissues that inhibited cell growth through BMI1 targeting as a proto-oncogene involved in transcriptional regulation [184].

**Structural and adhesion factors**

SSX2IP is a member of the adhesion system that is involved in cell–cell adherens junctions through alpha-actinin. It also regulates cell motility in response to PDGF by activation of Rac signaling. It was found that there was miR-338-3p downregulation in GC tissues in comparison with normal margins. MiR-338-3p reduced GC cell proliferation and in vivo growth, while it induced apoptosis through SSX2IP targeting. MiR-338-3p downregulation was correlated with metastatic lymph nodes, larger tumor size, and advanced tumor stage [185]. EGF containing fibulin extracellular matrix protein 1 (EFEMP1) belongs to the fibulin family of extracellular matrix (ECM) glycoproteins that regulate cell adhesion, growth, and movement [186]. It also maintains tissue hemostasis by regulation of the tissue inhibitors of matrix metalloproteinase (TIMMPs) and MMPs [187, 188]. EFEMP1 exerts its tumor suppressor activity by suppression of tumor angiogenesis and inhibition of the EGFR/AKT signaling pathway [189, 190]. It was reported that miR-338-5p was downregulated in GBM tissues. MiR-338-5p also reduced GBM cell proliferation and migration, while it significantly induced apoptosis through EFEMP1 inhibition [191]. ITGB3 is a receptor of various ECM proteins including fibronectin, laminin, MMP-2, and thrombospondin [192]. It regulates several signaling pathways, such as NRG1-ERBB, FGF1, and IGF1 signaling [193–195]. Therefore, it can be introduced as a pivotal regulator of angiogenesis, adhesion, and metastasis [196]. There was an inverse association between levels of miR-338 and ITGB3 expression in lung tumor tissues [197]. KIFC1 is a kinesin motor protein involved in clustering of extra centrosomes in tumor cells [198]. It is required for tumor cell survival and invasion by regulation of excess centrosomes to generate progeny cells and maintenance toward apoptosis-mediated aneuploidy [199]. KIFC1 silencing reduces RCC cell proliferation, migration, and in vivo growth by inhibition of PI3K/AKT signaling and downregulation of MMP-2 and VEGF. MiR-338-3p reduced cell migration and proliferation by KIFC1 targeting. Also KIFC1 upregulation was significantly correlated with advanced pT and pTNM stage and larger tumor size in RCC tissues [200]. AHSA1 is a chaperone involved in maturation, degradation, and stabilization of oncogenes [201]. There was miR-338-3p downregulation in osteosarcoma (OS) cell lines and tissues. MiR-338-3p suppressed viability, EMT, and invasion of OS cells through AHSA1 targeting [202]. RAB14 belongs to the RAS family of GTPases involved in intracellular membrane traffic during embryogenesis. MiR-338-3p downregulation was observed in NSCLC tissues compared with normal margins, which was directly correlated with differentiation, and conversely associated with stage and lymph node involvement. MiR-338-3p inhibited NSCLC cell proliferation, while it promoted apoptosis through RAB14 targeting [203].
Kinases and phosphatases

Sphingolipids are a group of hydrophobic molecules including sphingoid-base phosphates and sphingoid bases that are associated with cell proliferation and apoptosis [204, 205]. Sphingosine kinase 2 (SphK2) is involved in formation of sphingosine-1-phosphate (SPP) as a lipid mediator in cellular functions. It also participates in transcriptional regulation by HDAC1 and HDAC2 suppression and histone acetylation [206]. It regulates ATP and ROS levels in dopaminergic neurons. Significant miR-338-3p downregulation was observed in liver tumor tissues in comparison with normal margins. MiR-338-3p exerts its tumor suppressor role by SPHK2 targeting in liver tumor cells [207]. MiR-338-3p downregulation was reported in colorectal and gastric cancers [155, 203, 208]. There was miR-338-3p downregulation in NSCLC tissues that was significantly associated with stage. MiR-338-3p also reduced NSCLC cell proliferation and promoted apoptosis via SPHK2 targeting [209]. Pyruvate kinase M2 (PKM2) is responsible for ATP production via regulation of aerobic glycolysis [210, 211]. Despite the metabolic functions, PKM2 inhibits mTOR-mediated tumor progression, and also it is involved in cell cycle regulation and drug resistance [212, 213]. PKM2 regulates the WNT pathway by regulation of CTNNB1 transcriptional activity and also functions as a transcriptional regulator by phosphorylation of histone H3 [214, 215]. It was reported that there was a rising trend of PKM2 expression levels with glioma grade in which PKM2-overexpressed glioblastoma tumors had worse outcomes. PKM2 ectopic expression promoted glioma cell proliferation and metabolism. MiR-338-3p suppressed glioma cell proliferation by PKM2 targeting [216]. There was miR338-3p downregulation in OC tissues in comparison with normal margins. MiR-338-3p also suppressed cell proliferation and ATP production in OC cells through PKM2 targeting [217]. Protein-tyrosine phosphatase 1B (PTP1B) is a tyrosine phosphatase involved in regulation of leptin and insulin signaling pathways [218]. It also functions as a tumor suppressor by dephosphorylation and inactivation of oncogenic kinases. MiR-338-3p is a brain-specific miRNA participating in regulation of axonal respiration [156, 219]. There was an inverse association between levels of miR-338-3p and PTP1B expression in GC tissues. MiR-338-3p exerted its tumor suppressor role through PTP1B targeting in GC. PTP1B upregulation also significantly increased the levels of pAKT and p-ERK1/2 expression in GC tumor cells [220].

Conclusions

Since the mammalian miRNAs and their target mRNA sequences are not perfectly complementary, various mRNAs can be targeted by a specific miRNA. Therefore, there is a great challenge to clarify the precise molecular mechanisms of specific miRNAs. Understanding the molecular mechanism of miRNAs is important to introduce novel therapeutic strategies for human disorders and malignancies. However, there are contradictory reports about the role of miRNAs in different malignancies, which may be related to the use of computational and predictive methods instead of experimental verification. Moreover, the protein levels do not always exactly reflect the levels of mRNA expression. Therefore, miRNA studies should always be accompanied by protein assessments [221]. In the present review, we have summarized miR-338 target genes and associated signaling pathways to clarify the molecular mechanisms of miR-338 during tumor
progression. It was observed that miR-338 mainly functions as a tumor suppressor in different cancers. There were also significant associations between miR-338 and other non-coding RNAs including circular and long non-coding RNAs in tumor cells.

Abbreviations
miRNAs: MicroRNAs; ncRNAs: Non-coding RNAs; IncRNAs: Long non-coding RNAs; miRNAs: MicroRNAs; circRNAs: Circular RNAs; RISC: RNA induced silencing complex; EMT: Epithelial mesenchymal transition; NSCLC: Non-small cell lung cancer; RCC: Renal cell carcinoma; ccRCC: Clear cell RCC; CAV1: Caveolin-1; BRD4: Bromodomain containing 4; MM: Multiple myeloma; TC: Thyroid cancer; HCC: Hepatocellular carcinoma; SMO: Smoothened; C: Cervical cancer; CRC: Colorectal cancer; PLKs: Polo-like kinases; PLK4: Polo like kinase 4; PCa: Prostate cancer; EOC: Ovarian cancer; ADAM17: ADAM metallopeptidase domain 17; VEGF: Vascular endothelial growth factor; EGFR: Epidermal growth factor receptor; NRP1: Neuritin 1; GC: Gastric cancer; OC: Ovarian cancer; Hh: Hedgehog; P38K: Phosphatidylinositol 3-kinase; PREX: PI3-dependent Rac exchanger; FOX: Forkhead box; MM: Malignant melanoma; NPC: Nasopharyngeal carcinoma; ECM: Extracellular matrix; TIMPs: Tissue inhibitors of matrix metalloproteinase; OS: Osteosarcoma; SpH2: Sphingosine kinase 2; SPP: Sphingosine-1-phosphate; PKM2: Pyruvate kinase M2; PTP1B: Protein-tyrosine phosphatase; CysC: Cystatin C; CysC: Oral squamous cell carcinoma; CysC: Osteosarcoma; GC: Gastric cancer; MACC1: MET transcriptional regulator; EFEMP1: EGF containing fibulin extracellular matrix protein 1.

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