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Review

MicroRNA-98 as a novel diagnostic marker and therapeutic target in cancer patients

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Abstract
The progress of cancer treatment methods in the last decade has significantly reduced mortality rate among these patients. Nevertheless, cancer is still recognized as one of the main causes of human deaths. One of the main reasons for the high death rate in cancer patients is the late diagnosis in the advanced tumor stages. Therefore, it is necessary to investigate the molecular biology of tumor progressions in order to introduce early diagnostic markers. MicroRNAs (miRNAs) have an important role in regulating cellular processes associated with tumor progression. Due to the high stability of miRNAs in body fluids, they are widely used as non-invasive markers in the early tumor diagnosis. Since, deregulation of miR-98 has been reported in a wide range of cancers, we investigated the molecular mechanisms of miR-98 during tumor progression. It has been reported that miR-98 mainly inhibits the tumor growth by the modulation of transcription factors and signaling pathways. Therefore, miR-98 can be introduced as a tumor marker and therapeutic target among cancer patients.

Keywords MicroRNA-98 · Diagnosis · Tumor suppressor · Cancer

1 Introduction

Tumor therapy improves the life expectancy among cancer patients. However, ineffectiveness of conventional therapeutic modalities highlights the importance of utilizing tumor-specific therapeutic approaches [1]. Since, most of the tumors are diagnosed in advanced tumor stages; early detection can improve the efficacy of therapeutic strategies to reduce mortality rate among cancer patients [2, 3]. MicroRNAs (miRNAs) are promising options for the early tumor detection [4, 5]. They act as tumor suppressors or oncogenes and play pivotal roles in tumor cell apoptosis, differentiation, proliferation, and stem cell differentiation [6–9]. High stability in body fluids and tissue specificity suggest the miRNAs as reliable non-invasive markers for the early tumor diagnosis and detection of metastatic tumors origin [10, 11]. MiR-98 belongs to the let-7 family of miRNAs that is aberrantly expressed in different malignancies [12–14]. It has critical roles in regulation of cell proliferation, drug resistance, differentiation, metabolism, and angiogenesis [15–18]. Therefore, we investigated the role of miR-98 during tumor progression and invasion to suggest that as a novel tumor marker and therapeutic target among cancer patients (Table 1).

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Table 1 Molecular functions and target genes of microRNA-98 during tumor progression and metastasis

Study	miR-98 target gene	Pathway	Samples	Function	Clinical application
Lung cancer					
Ni [14]	ITGB3	Structural protein	26 NT[a] H1650, HCC827, NCL-H358, SKMES-1, PC9, and A549 cell lines	Tumor suppressor	Diagnosis
Cong [37]	AKR1B10	Signaling pathway	80 NT A549, H1299, H1650, H520, SPCA-1, and SK-MES-1 cell lines	Tumor suppressor	Diagnosis and prognosis
Wang [53]	MAP4K3	Signaling pathway	90 NT A549 cell line	Tumor suppressor	Diagnosis
Wu [54]	MAPK6	Signaling pathway	A549, H1299, H460, and H1975 cell lines	Tumor suppressor	Diagnosis
Jiang [70]	TGFBR1	Signaling pathway	70 NT A549, H1299, ANIP-973, and GLC-82 cell lines	Tumor suppressor	Diagnosis and prognosis
Zhou [99]	TWIST	Transcription factor	71 NT A549 and NCI-H23 cell lines	Tumor suppressor	Diagnosis and prognosis
Qin [128]	MKP1	Structural protein	59 NT A549, H1299, Calu-3, H520, H1650, and H1730 cell lines	Tumor suppressor	Diagnosis and prognosis
Yang [116]	PAK1	Structural protein	A549 and H1299 cell lines	Tumor suppressor	Diagnosis
Ke [149]	ALG3	Metabolism	65 NT L9981, NCI-H292, NCI-H460, LTP-A2, and NCI-H522 cell lines	Tumor suppressor	Diagnosis and prognosis
Zhang [110]	TP53	Transcription factor	A549 cell line	Tumor suppressor	Diagnosis
Li [167]	IL-10	Tumor immune microenvironment	10 T 10 N KLN205 cell line	Tumor suppressor	Diagnosis and prognosis
Breast cancer					
Guo [26]	IGF1R	Signaling pathway	53 NT MDAMB-453, MDAMB-231, and MCF7 cell lines	Tumor suppressor	Diagnosis
Zhang [33]	IGF2	Signaling pathway	40 T SKBR3 and SKBR3-R cell lines	Tumor suppressor	Diagnosis and prognosis
Cai [80]	E2F5	Transcription factor	30 NT MDA-MB-231, MCF-7, MDA-MB468, and HEK293T cell lines	Tumor suppressor	Diagnosis and prognosis
Cervical cancer					
Xiao [22]	PI3K	Signaling pathway	58 NT CaSki, HT-3, C33A, and SiHa cell lines	Tumor suppressor	Diagnosis and prognosis
Oral squamous cell carcinoma					
Du [25]	IGF1R	Signaling pathway	19 NT SCC-25 and Tca-8113 cell lines	Tumor suppressor	Diagnosis and prognosis
Retinoblastoma					
Guo [27]	IGF1R	Signaling pathway	60 T 9 N WERI-Rb-1, Y79 and SO-RB50 cell lines	Tumor suppressor	Diagnosis and prognosis
Yu [130]	XIAP	Structural protein	27 T 19 N hTERT-RPE1, Y79, and WERI-RB-1 cell lines	Tumor suppressor	Diagnosis
Hepatocellular carcinoma					

Table 1 (continued)

Study	miR-98 target gene	Pathway	Samples	Function	Clinical application
Shen [34]	PI3K	Signaling pathway	48 T HCCLM3 and Huh7 cell lines	Tumor suppressor	Diagnosis
Zhang [90]	EZH2	Transcription factor	33 NT HCCLM3, HepG2, SMMC7721, and Hep3 B cell lines	Tumor suppressor	Diagnosis
Li [162]	IL-10	Tumor immune microenvironment	25 NT HepG2 cell line	Tumor suppressor	Diagnosis
Zhou [101]	SALL4	Transcription factor	144 NT HepG2 and SMMC-7721 cell lines	Tumor suppressor	Diagnosis and prognosis
Wang [119]	CTHRC1	Structural protein	30 NT HepG2, HuH-7 and Hep3B cell lines	Tumor suppressor	Diagnosis
Jiang [124]	IGF2BP1	Structural protein	84 NT HepG2, Hep3B, LM3, and SMCC7721 cell lines	Tumor suppressor	Diagnosis and prognosis
Pancreatic cancer					
Fu [51]	MAP4K4	Signaling pathway	52 NT SW1990, MIAPACA-2, BXPC-3, CFPAC-1, COLO357, and PANC-1 cell lines	Tumor suppressor	Diagnosis and prognosis
Thyroid cancer					
Zhang [57]	ADAMTS8	Signaling pathway	72 NT Nthy-ori 3–1, TPC-1, K1, and BCPAP cell lines	Tumor suppressor	Diagnosis and prognosis
Ovarian cancer					
Dong [61]	STAT3	Signaling pathway	52 NT A2780, COV644, OV-90, OVCAR-3, As2O3, and SKOV3 cell lines	Tumor suppressor	Diagnosis and prognosis
Wang [136]	Dicer1	Structural protein	127 T, 45 N, and 10 borderline tissues C13*, OV2008, A2780, and A2780/DDP cell lines	Tumor suppressor	Diagnosis and prognosis
Nasopharyngeal carcinoma					
Liu [62]	STAT3	Signaling pathway	30 T 30 N CNE-1, CNE-2, and HONE-1 cell lines	Tumor suppressor	Diagnosis
Li [75]	PBX3	Transcription factor	40 NT 5–8F and SUNE1 cell lines	Tumor suppressor	Diagnosis and prognosis
Glioma					
Fan [65]	IKKε	Signaling pathway	53 T 10 N U87 and U251 cell lines	Tumor suppressor	Diagnosis
Xu [74]	PBX3	Transcription factor	24 T 8 N U87 and U251 cell lines	Tumor suppressor	Diagnosis and prognosis
Gu [121]	CPEB4	Structural protein	86 NT U87, U251, LN229, and A172 cell lines	Tumor suppressor	Diagnosis
Bladder cancer					
Luo [76]	EBF1	Transcription factor	40 NT T24, UMUC3, 5637, and J82 cell lines	Tumor suppressor	Diagnosis and prognosis

Table 1 (continued)

Study	miR-98 target gene	Pathway	Samples	Function	Clinical application
Chronic myeloid leukemia					
Huang [79]	E2F1	Transcription factor	K562 and K562/A02 cell lines	Tumor suppressor	Diagnosis
Esophageal cancer					
Huang [91]	EZH2	Transcription factor	40 NT Eca109 cell line	Tumor suppressor	Diagnosis and prognosis
Prostate cancer					
Guo [104]	HMGA2	Transcription factor	16 BPH tissues 30 NT LNCaP, PC-3, and DU-145 cell lines	Tumor suppressor	Diagnosis and prognosis
Laryngeal squamous cell carcinoma					
Zhu [105]	HMGA2	Transcription factor	10 NT Hep-2 and TU-177 cell lines	Tumor suppressor	Diagnosis
Colorectal cancer					
Zheng [113]	CLDN1	Structural protein	100 NT SW480, SW620, SW1116, HT-29, and HCT116 cell lines	Tumor suppressor	Diagnosis and prognosis
Zhu [142]	HK2	Metabolism	215 NT HIEC6, SW480, SW620, LOVO, HCT116, COLO205, and HT26 cell lines	Tumor suppressor	Diagnosis
Cholangiocarcinoma					
Wan [131]	HECTD4	Structural protein	53 NT QBC939, RBE, HuCCT1, TFK-1, and CCLP1 cell lines	Tumor suppressor	Diagnosis
Gastric cancer					
Zhan [156]	BCAT1	Metabolism	BGC-823 and SNU-16 cell lines	Tumor suppressor	Diagnosis
Wen [179]	CCND2	Tumor immune microenvironment	30 NT AGS, SNU-5, and NCI-N87 cell lines	Tumor suppressor	Diagnosis
Melanoma					
Li [168]	IL-6	Tumor immune microenvironment	48 T 48 N B16-F1 cell line	Tumor suppressor	Diagnosis and prognosis
Endometrial cancer					
Huang [173]	MRP-7	Drug resistance	30 NT RL95 and HEC-1 cell lines	Tumor suppressor	Diagnosis and prognosis

[a]Tumor (T) tissues and Normal (N) margins

1.1 PI3K/AKT, MAPK, and JAK/STAT signaling pathways

PI3K/Akt and MAPK signaling pathways has critical functions in cell proliferation, death, metabolism, and neoplastic transformation [19–21]. It has been shown that miR-98 has a key role during tumor progression by modulation of PI3K/AKT and MAPK pathways (Fig. 1). MiR-98-5p repressed cervical tumor cell progression by inhibition of PI3K/Akt pathway [22]. IGF1R is a receptor tyrosine kinase (RTK) that activates MAPK and PI3K/Akt pathways to modulate neoplastic transformation, survival, and proliferation of tumor cells [23, 24]. There were remarkable miR-98 down regulations in OSCC cells and tissues. MiR-98 repressed OSCC cell migration and invasion by IGF1R targeting [25]. Inhibition of LINC01287 repressed the p-ERK1/2 and p-MEK1/2 expressions. LINC01287 exerted oncogenic functions in breast cancer via regulating the miR-98/IGF1R/MEK/ERK axis [26]. There was a relationship between reduced miR-98 expression levels and worse prognosis in retinoblastoma (RB) patients. MiR-98 suppressed RB progression and development through suppressing the IGF1R/MEK/ERK axis. It significantly reduced the levels of Bcl-2 expressions, while up regulated Bax and CASP-3. MiR-98 also decreased RB cell invasion and EMT process by CDH2, VIM, and FN1 down regulations while CDH1 up regulation.

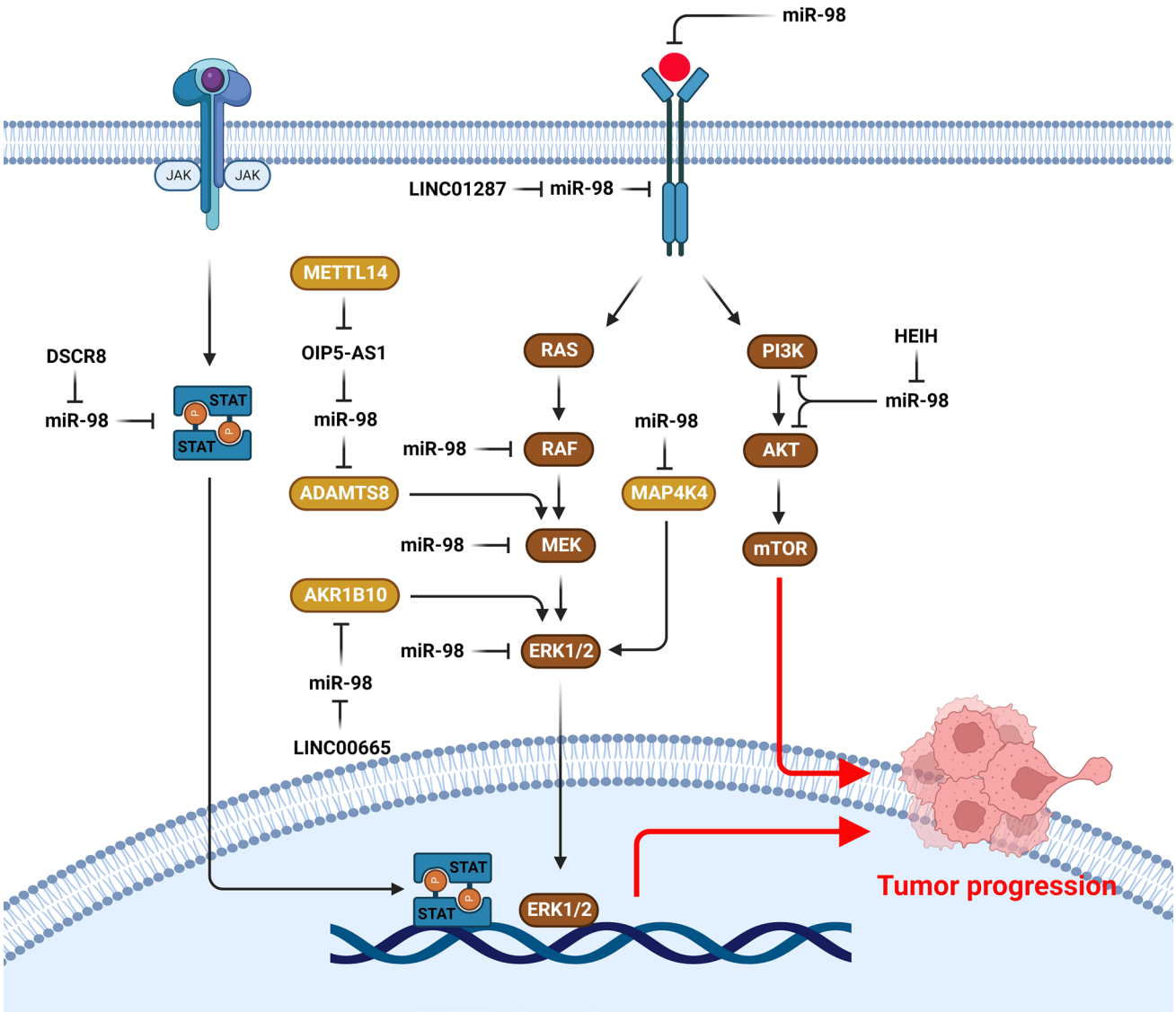

Fig. 1 Role of miR-98 during tumor progression by regulation of signaling pathways. (Created with BioRender.com)

Moreover, miR-98 decreased p-ERK1/2, p-Raf1, p-MEK1/2, and k-Ras in RB cells [27]. About 20–25% of breast cancer (BC) patients are HER2 positive [28, 29]. Herceptin as an anti-HER2 drug considerably increases survival in HER2-positive BC patients. A subset of BC patients indicates poor response to treatment, resulting in tumor recurrence. This group constitutes around 90% of BC mortalities [30]. Insulin-like growth factor 2 (IGF2) promotes PI3K/Akt and MAPK pathways to regulate tumor cell proliferation and invasion [31, 32]. There was miR-98-5p down regulation in HER2-positive BC samples that was associated with reduced overall survival. MiR-98 enhanced Herceptin sensitivity in HER2-positive BC cells by IGF2 targeting [33]. Inhibition of HEIH sensitized HCC cells to sorafenib through the modulation of miR-98-5p/PI3K/AKT axis [34].

ERK pathway has a key function in promoting tumor cell invasion by facilitating the degradation of the extracellular matrix through the activation of MMPs [35, 36]. There was a significant linc00665 up regulation in lung adenocarcinoma (LUAD) tissues that was associated with shorter recurrence-free survival. Linc00665 enhanced LUAD cell invasion via miR-98 sponging that resulted in AKR1B10/ERK activation [37]. MAP4K4 is a ser/thr kinase that is involved in cytoskeleton rearrangement, cell motility, and cell proliferation [38–40]. MAP4K4 overexpression has been found as a prognostic biomarker in multiple cancers [41–45]. Inhibition of MAP4K4 was also observed to promote cell cycle arrest and apoptosis while suppressing cell growth, invasion and migration in various cancer cells [43, 46–48]. Moreover, MAP4K4 induced tumor growth by activation of Notch, JAK-STAT, MAPK, and NF-κB pathways [40, 43, 47, 48]. MAPK/ERK pathway has been implicated in PDAC progression and development [49, 50]. There was miR-98-5p down regulation in PDAC tissues that was correlated with tumor size, TNM stage, and lymph node invasion. MiR-98-5p reduced PDAC cell invasion through MAP4K4 targeting and subsequent MAPK/ERK inhibition [51]. MAP4K3 can be activated by TNF-α and ultraviolet radiation [52]. MiR-98-5p inhibited mTOR signaling via MAP4K3 suppression in NSCLC cells [53]. NEAT1 promoted NSCLC cell invasion by modulating the miR-98-5p/MAPK6 axis [54]. N6-methyladenosine (m6 A) methylation is essential for maintaining tumor cell properties. M6 A is a dynamic modification process initiated by methyltransferase-like 14 (METTL14) and METTL3 that can also be reversed by ALKBH5, FTO, and RNA demethylases [55]. ADAMTS protein family consists of metalloproteinases and disintegrins with thrombospondin motifs that participate in cell migration, apoptosis, extracellular matrix degradation, and angiogenesis. ADAMTS8 serves as an anti-angiogenic mediator in a variety of cancers [56]. There was significant OIP5-AS1 up regulation in papillary thyroid cancer (PTC) tissues in comparison with controls, which was correlated with tumor malignancy. OIP5-AS1 promoted PTC cell invasion and proliferation through regulation of miR-98/ADAMTS8 axis and subsequent activation of MEK/ERK pathway. METTL14 also suppressed PTC progression by inhibiting the OIP5-AS1 and subsequent MEK/ERK pathway [57].

JAK/STAT signaling is a key regulator of cell proliferation and apoptosis that can be regulated by miR-98 during tumor progression (Fig. 1). STAT3 activation is correlated with malignant nasopharyngeal carcinoma features such as EMT, metastasis, invasion, migration, proliferation, and drug resistance [58, 59]. STAT3 is an important component of JAK/STAT pathways that activates HIF-1α to regulate tumor progression during hypoxia [60]. There was DSCR8 up regulation in ovarian cancer (OC) tissues that was contributed with poor prognosis. DSCR8 promoted EMT process and OC progression via miR-98-5p/STAT3/HIF1a axis [61]. MiR-98 inhibited nasopharyngeal tumor cell migration while promoted apoptosis via STAT3 targeting [62]. NF-κB signaling has important roles in inflammation and tumor progression. NF-κB is composed of two subunits, commonly known as p50 and p65 that are typically confined to the cytoplasm due to the presence of IᵒB inhibitors. IKK kinases phosphorylate IκB in response to biological stimuli, resulting in ubiquitin-mediated degradation. NF-κB is then released to the nucleus, where it stimulates target genes that increase cell invasion and proliferation while inhibiting apoptosis [63]. IKKε is implicated in LPS- and TNFα-induced MMP-13 and MMP-3 gene expressions through c-JUN activation and phosphorylation [64]. MiR-98 suppressed cell invasion in glioma cells via IKKε targeting. MiR-98 modulated glioma cell invasion and migration by suppressing IKKε/NF-κB signaling and acting as a tumor suppressor by directly inhibiting NF-κB nuclear translocation [65]. TGF-β pathway has key roles in cell proliferation, migration, and apoptosis. TGFBR1 is involved in modulation of apoptosis, cell adhesion, differentiation, and proliferation [66–69]. It has been demonstrated that miR-98-5p decreased NSCLC metastasis and EMT process through TGFBR1 targeting. There was also miR-98-5p down regulation in NSCLC samples compared with controls that was associated with advanced tumor stage [70].

1.2 Transcription factors

MiR-98 has a pivotal role during tumor progression by modulation of transcription factors (Fig. 2). PBX3 belongs to the homeobox (HOX) transcription factors that is involved in regulation of tumor cell invasion and migration [71–73]. PBX3 regulates tumor cell invasion by activation of MAPK/ERK signaling [71]. There was a significant miR-98 down regulation

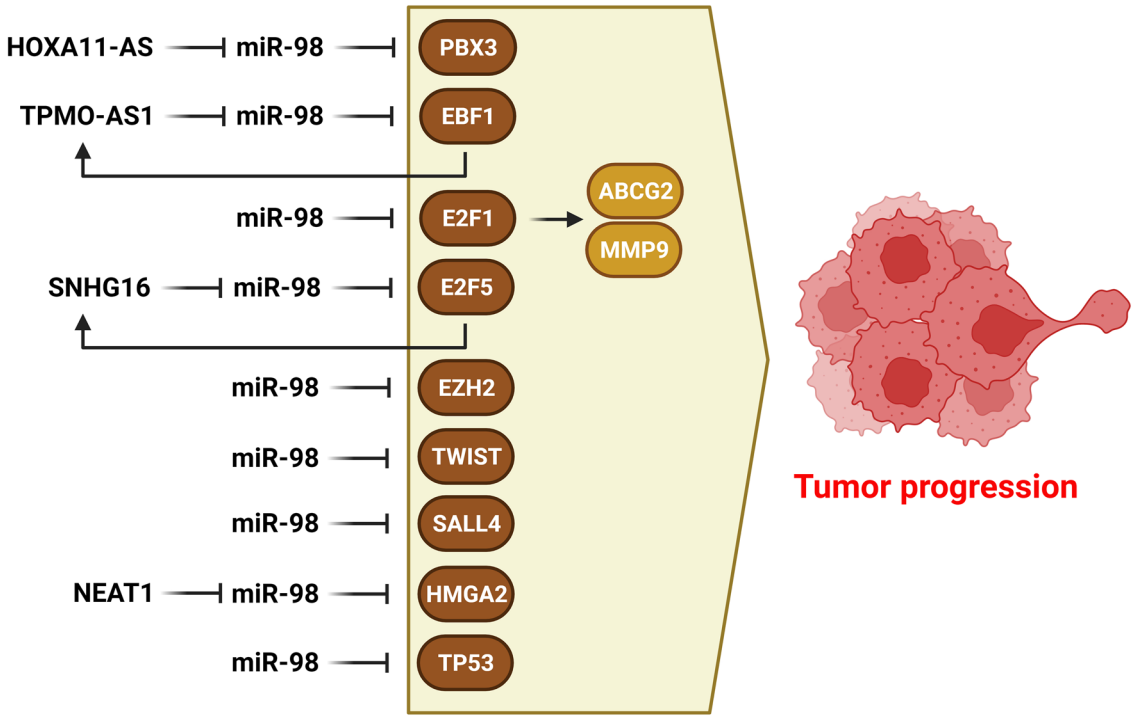

Fig. 2 Role of miR-98 during tumor progression by regulation of transcription factors. (Created with BioRender.com)

in glioma samples that was contributed with high-grade tumors and PBX3 up regulation. MiR-98 reduced glioma cell migration and invasion through PBX3 targeting [74]. Inhibition of HOXA11-AS increased cisplatin sensitivity of nasopharyngeal tumor cells via miR-98/PBX3 axis [75]. EBF1 transcription factor could activate TMPO-AS1 transcription, which subsequently up regulated EBF1 via miR-98-5p sponging in a positive feedback loop. There was TMPO-AS1 up regulation in bladder tumor cells and tissues that was associated with poor prognosis. TMPO-AS1 promoted bladder tumor cell migration, while inhibited apoptosis via miR-98-5p/EBF1 axis [76].

E2F transcription factors have essential roles in cell cycle progression [77]. E2F1 enhances chemo resistance by ABCG2 up regulation [78]. There was miR-98 down regulation in Adriamycin resistant leukemia cells. MiR-98 enhanced Adriamycin response by E2F1 targeting that resulted in ABCG2 and MMP9 down regulations while BAX and p21 up regulations [79]. There were SNHG16 up regulations in breast cancer (BC) tissues in comparison with normal specimens, which were correlated with increased mobility and worse prognosis. MiR-98 inhibited BC cell migration through E2F5 targeting. E2F5 up regulated SNHG16 to regulate miR-98/ E2F5 axis in a positive feedback loop [80]. Enhancer of zeste homolog 2 (EZH2) is a member of Polycomb protein family and contains a SET domain that regulates transcription at the epigenetic level through affecting DNA methylation and histone modification [81]. EZH2 up regulation is significantly associated with tumor cell invasion and poor prognosis in various malignancies [82–89]. MiR-98 suppressed HCC cell proliferation through the inhibition of EZH2 mediated Wnt/b-catenin signaling [90]. There were remarkable miR-98 down regulations in ESCC tissues that were contributed with higher grade, stage, and lymph node metastasis. Inhibition of miR-98 promoted ESCC metastasis by EZH2 up regulation [91].

Epithelial-mesenchymal transition (EMT) has a pivotal function in tumor invasion in which an epithelial cell acquires mesenchymal cell phenotype by loss of E-cadherin while Vimentin and N-cadherin up regulations [92–94]. TWIST is a transcription factor that is widely recognized for its function in EMT, angiogenesis, drug resistance, and metastasis [95–98]. There was a positive relationship between the miR-98 expression levels and overall survival in NSCLC patients. TWIST-activated Akt was implicated in survival, proliferation, and self-renewal characteristics. MiR-98 inhibited NSCLC progression via regulating TWIST/AKT axis [99]. SALL4 is a zinc finger transcription factor that has crucial roles in maintaining the self-renewal ability of embryonic stem cells [100]. There was miR-98 down regulation in HCC tissues in comparison with normal margins that was correlated with tumor size and poor overall survival. MiR-98 significantly reduced HCC cell invasion through SALL4 targeting. Moreover, it significantly reduced EMT process through CDH2, VIM, and FN1 down regulations, while CDH1 over expression [101].

HMGA2 is a transcription factor that is involved in cell aging, differentiation, growth, and apoptosis [102]. MiR-98-5p down regulation was reported in papillary thyroid carcinoma (PTC) specimens that was contributed with poor prognosis. MiR-98-5p suppressed PTC cell migration and growth while inducing apoptosis via regulating the HMGA2/Bax/CASP3 axis [103]. Inhibition of NEAT1 suppressed prostate tumor cell invasion and proliferation through miR-98-5p/HMGA2 axis. There was also significant NEAT1 up regulation in prostate cancer tissues that was associated with advanced TNM stage and higher Gleason score [104]. MiR-98 down regulation was reported in laryngeal squamous cell carcinoma (LSCC) cells and tissues. MiR-98 reduced LSCC cell invasion and EMT by HMGA2 targeting and subsequent POSTN up regulation [105]. TP53 as a transcription factor promotes the expression of genes implicated in cell death or cell growth arrest in response to genotoxic stress [106]. It functions as a checkpoint control to determine cellular fate in response to DNA damages [107, 108]. TP53 can also promote apoptosis as a response to DNA damage, particularly when the damage is extensive and out of the function of DNA repair systems [108, 109]. It has been investigated that inhibition of miR-98 promoted cisplatin-induced A549 cell apoptosis through up regulating TP53 pathway [110].

1.3 Structural proteins

Structural proteins have also key roles in tumor cell migration, proliferation, and apoptosis that can be regulated by miR-98 during tumor progression (Fig. 3). Claudin-1 (CLDN1) is the main component of the tight junction that regulates intercellular junctions [111, 112]. MiR-98 inhibited colorectal carcinoma (CRC) cell proliferation while promoting apoptosis through CLDN1 targeting. It also down regulated PCNA, C-myc, and Bcl-2, while up regulated RUNX3 and Bax in CRC cells [113]. P21-activated protein kinase 1 (PAK1) is a major effector of the small Rho GTPases that are involved in actin dynamics and cell migration. PAKs as the serine/threonine kinases regulate actin polymerization and cytoskeletal dynamics through modulating ADF and cofilin [114, 115]. MiR-98 inhibited NSCLC cell apoptosis, invasion, and proliferation through PAK1 targeting [116]. Integrins are a type of trans-membrane receptors that plays critical functions in signal transduction and tumor progression [117]. MiR-98 repressed lung tumor cell migration and invasion through ITGB3 targeting [14]. Collagen triple helix repeat containing 1 (CTHRC1) is a glycoprotein with a small collagen-like motif that is involved in cell adhesion and migration [118]. There were remarkable miR-98 down modulations in HCC cells and tissues. MiR-98 repressed HCC cell invasion through CTHRC1 targeting [119].

Cytoplasmic polyadenylation element binding (CPEB4) belongs to the RNA binding family proteins that are involved in tumor growth, invasion, and vascularization [120]. Inhibition of FOXD2-AS1 decreased glioma cell invasion, EMT, and drug resistance while promoting apoptosis via regulation of miR-98-5p/CPEB4 axis. FOXD2-AS1 inhibition repressed EMT via VIM and CDH2 up regulations, while CDH1 down regulation [121]. IGF2BP1 is also a RNA-binding protein that functions by attaching to the mRNAs of β-actin and IGF2 to regulate the translation of these genes, which in turn affects cell survival and proliferation [122, 123]. MiR-98-5p down regulation was correlated with poor prognosis in liver tumor tissues. It inhibited HCC cell growth while promoting apoptosis via IGF2BP1 targeting [124].

MKP1 is a threonine-tyrosine phosphatase that is involved in regulation of apoptosis and cell proliferation during tumor progression [125]. It regulates dephosphorylation and subsequent deactivation of JNK and various other kinases associated with apoptosis, resulting in a decrease in apoptosis [126, 127]. It has been demonstrated that there were circ_0006349 up regulations in NSCLC patients that were associated with poor prognosis. CircRNA_0006349 enhanced development and glycolysis of NSCLC cells through miR-98/MKP1 axis [128]. X-linked inhibitor of apoptosis protein (XIAP) belongs to the IAPs protein family, which inhibits apoptosis by suppressing caspase function [129]. There was significant circ_0000527 up regulation in retinoblastoma (RB) specimens. Circ_0000527 induced RB progression through regulating the miR-98-5p/XIAP axis [130]. HECTD4 is an E3 ubiquitin-protein ligase that is involved in glucose homeostasis. HEIH induced cell invasion, proliferation, and migration in cholangiocarcinoma through miR-98-5p/HECTD4 axis [131].

Functional mature miRNAs are formed through multiple post-transcriptional processes, which involve the actions of Drosha/DGCR8 in the nucleus to form pre-miRNA, then being transported to the cytoplasm, and finally being cleaved by the Dicer [132–134]. Dicer down regulation have been correlated with poor clinical outcomes and advanced tumor stage in epithelial ovarian cancer (EOC) patients [135]. MiR-98-5p down regulation was correlated with poor prognosis in EOC patients. MiR-98-5p induced CDDP resistance of EOC cells through Dicer1 targeting that resulted in miR-152 down regulation. MiR-152 also increased DNA repair defects and induced CDDP sensitivity in EOC cells via RAD51 targeting [136].

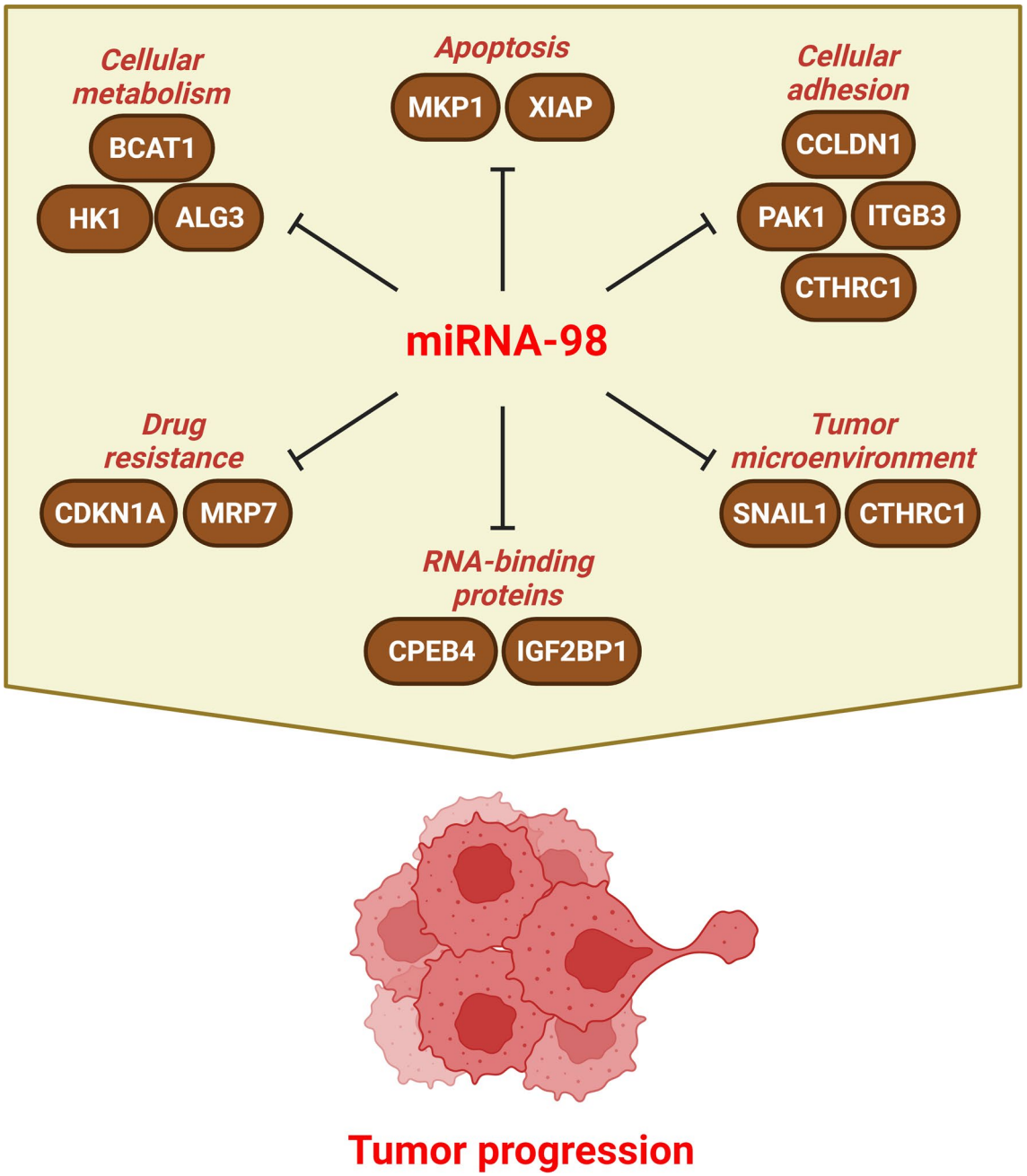

Fig. 3 Role of miR-98 during tumor progression by regulation of apoptosis, cellular adhesion, metabolism, tumor microenvironment, drug resistance, and RNA-binding proteins. (Created with BioRender.com)

1.4 Cellular metabolism

Tumor cell metabolism is developed to maintain the tumor cells in hypoxic and nutrient deprivation conditions. It has been shown that miR-98 has a key role in regulation of cellular metabolism during tumor progression (Fig. 3). The aerobic glycolysis is a well-recognized characteristic of tumor cells [137]. During this metabolic process, tumor cells undergo glycolysis despite sufficient oxygen levels that reduces ATP production and impaired glucose utilization [138]. Hexokinase 2 (HK2) is an important enzyme that modulates the irreversible glucose to glucose-6-phosphate conversion. HK2 expression has been investigated to be up regulated in various malignancies [139–141]. There was a significant decrease in miR-98 levels in colon cancer cells and tissues. MiR-98 inhibited Warburg effect in colon cancer

cells via HK2 targeting, resulting in reduced proliferation, glucose uptake, lactate production, and cellular ATP levels [142]. Glycosylation plays a crucial role in various pathophysiological conditions, such as tumor metastasis and growth [143, 144]. For instance, colorectal and breast cancer patients exhibit elevated levels of mannose glycan expression [145, 146]. The expression patterns of tumor cell glycosyltransferases, tumor-related glycans, and their target proteins are utilized as diagnostic tumor markers [143]. ALG3 encodes an alpha-1, 3-mannosyltransferase that functions in the endoplasmic reticulum to synthesize mannose-type glycans. Abnormal glycosylations of N-cadherin and E-cadherin are involved in EMT and tumor metastasis [147, 148]. There was significant ALG3 up regulation in non-small cell lung cancer (NSCLC) tissues that was associated with poor prognosis. MiR-98-5p suppressed EMT process via ALG3 targeting in NSCLC cells [149]. Gastric cancer stem cells (GCSCs) are involved in gastric tumor progression, metastasis, and chemo resistance [150]. CD44 as a trans-membrane glycoprotein is involved in the induction of tumor growth [151, 152]. Branched-chain aminotransferase 1 (BCAT1) is a catabolic enzyme that is involved in tumor progression [153–155]. There was miR-98 down regulation in CD44 + GCSCs which was associated with the maintenance of cancer stemness cell properties. It reduced GC stemness characteristics while enhanced chemo sensitivity to cisplatin and paclitaxel through BCAT1 targeting. MiR-98 influenced the stemness of GCSCs through NANOG, OCT4, and SOX2 down regulations. MiR-98 significantly reduced the ABCG2 expression levels that decreased drug resistance in GCSCs. Moreover, miR-98 inhibited EMT of CD44 + GCSCs through CDH1 up regulation while VIM down regulation [156].

1.5 Tumor immune microenvironment and drug resistance

Tumor microenvironment (TME) consists of cancer tissue and adjacent stromal cells, allowing for reciprocal interactions between cancer cells, inflammatory cells, and microcapillary vessels [157]. MiR-98 has an important role in regulation of TME during tumor progression (Fig. 3). Macrophages are highly plastic cells that can be polarized in response to microenvironmental stimuli and acquire a range of functional phenotypes [158]. M1 macrophages have been shown to increase cell recruitment to the inflammatory site via secreting IL-12, IL-1β, TNF-α, and NO, whereas M2 macrophages release TGF, IL-4, IL-10, FN1, and MMPs [159]. Tumor-associated macrophages (TAMs), which have a predominantly M2-like phenotype [160], are critical regulators of the TME that affect the neoplastic cell proliferation, extracellular matrix remodeling, and angiogenesis [161]. MiR-98 suppressed the inducing effects of TAMs on invasion of HCC cells through IL-10 targeting [162]. Tumor tolerance refers to the immune system ability to disregard the growth of tumors within the body, enabling their uncontrolled progression. During this process, tumors evade immune surveillance through mechanisms that are not fully understood [163]. Immune tolerant cells encompass a variety of cells that synthesize TGF-β and IL-10 [164]. Following appropriate stimulation, immune regulatory B or T cells release IL-10 to suppress immune reactions by inhibiting the functions of other immune effector cells [165]. B10 cells possess the ability to diminish the anti-cancer capacity of the body by suppressing the activities of other immune effector cells through the IL-10 production [166]. There was a negative contribution between the levels of miR-98 and IL-10 expressions in peripheral B cells of lung cancer patients compared with normal individuals that were correlated with tumor size. MiR-98 inhibited lung tumor growth through the IL-10 targeting in peripheral B lymphocytes [167]. MiR-98 down regulation was correlated with increased melanoma metastasis and stage. MiR-98 inhibited melanoma cell invasion through IL-6 targeting [168].

Cisplatin (CDDP) is commonly prescribed as an antineoplastic agent for ovarian cancer. However, CDDP resistance is a common therapeutic challenge in cancer patients [169]. Autophagy, cancer stem cell-like properties, ABC transporters-induced drug efflux, EMT, and accelerated DNA repair are the main reasons of multidrug resistance (MDR) in tumor cells [170, 171]. It has been shown that miR-98 has a pivotal role in chemo resistance via modulation of cell cycle progression, drug efflux, and DNA repair (Fig. 3). MDR is a main cause of chemotherapy failure in endometrial cancer (EC) patients [172]. NEAT1 promoted paclitaxel resistance through the regulation of miR-98/MRP7 pathway in EC cells [173]. Cancer-associated fibroblasts (CAFs) are common types of stromal cells found in different tumor types [174], have been linked to poor prognosis of OC [175]. They have the ability to release exosomes to regulate tumor progression and drug resistance [176]. Cyclin-dependent kinase inhibitor 1A (CDKN1A) belongs to the Cip/Kip family of CDK inhibitors that is recognized as a target for antineoplastic medications [177]. CAF-exosomal miR-98-5p enhanced CDDP resistance in ovarian tumod cells by CDKN1A targeting [178]. There was significant TTTY15 up regulation in GC cells and tissues. Suppression of TTTY15 reduced GC progression by miR-98-5p sponging that resulted in CCND2 down regulation [179]. The efficiency of platinum drugs for postoperative gastric cancer (GC) patients has been severely restricted due to chemo-resistance [180]. Platinum resistance is associated with enhanced detoxification by metallothionein and glutathione systems [181], impaired cellular uptake of platinum drugs [181, 182], increased tolerance to DNA damage [183], and increased DNA repair [182, 184]. A significant PITPNA-AS1 up regulation was reported in GC patients that were correlated with poor

prognosis. PITPNA-AS1 promoted GC progression via adversely regulating the expression levels of miR-98-5p. Lobaplatin (LBP) and CDDP could inhibit expression of PITPNA-AS1 and promote miR-98-5p expression in GC cells [185].

2 Conclusions

In this review, we assessed the role of miR-98 during tumor progression and invasion. It was shown that miR-98 mainly exerts its tumor suppressor function by the modulation of transcription factors, tumor microenvironment, and signaling pathways. This review can be of great value in introducing miR-98 as an efficient diagnostic/prognostic tumor marker. In addition, due to the tumor suppressor function, miR-98 can be introduced as a novel therapeutic target through miR-98 mimics strategy. However, the clinical application of miR-98 in cancer diagnosis and treatment requires more in-vivo studies and clinical trials. It is also required to assess the levels of miR-98 expressions in serum samples and other biological fluids of cancer patients to suggest that as a non-invasive tumor marker in clinics.

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