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Review

Revealing the role of miRNA-489 as a new onco-suppressor factor in different cancers based on pre-clinical and clinical evidence

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ABSTRACT

Recently, microRNAs (miRNAs) have shown to be potential therapeutic, diagnostic and prognostic targets in disease therapy. These endogenous non-coding RNAs contribute to regulation of different cellular events that are necessary for maintaining physiological condition. Dysregulation of miRNAs is correlated with development of various pathological events such as neurological disorders, cardiovascular diseases, and cancer. miRNA-489 is a new emerging miRNA and studies are extensively investigating its role in pathological conditions. Herein, potential function of miRNA-489 as tumor-suppressor in various cancers is described. miRNA-489 is able to sensitize cancer cells into chemotherapy by disrupting molecular pathways involved in cancer growth such as PI3K/Akt, and induction of apoptosis. The PROX1 and SUZ12 as oncogenic pathways, are affected by miRNA-489 in suppressing metastasis of cancer cells. Wnt/β-catenin as an oncogenic factor ensuring growth and malignancy of tumors is inhibited via miRNA-489 function. For enhancing drug sensitivity of tumors, restoring miRNA-489 expression is a promising strategy. The lncRNAs can modulate miRNA-489 expression in tumors and studies about circRNA role in miRNA-489 modulation should be performed. The expression level of miRNA-489 is a

Abbreviations: Lin-4, lineage defective 4; let 7, lethal 7; ncRNAs, non-coding RNAs; miR, microRNA; circRNA, circular RNA; lncRNA, long non-coding RNA; mRNAs, messenger RNAs; RAP1B, Ras-related protein Rap-1B; AKI, acute kidney injury; I/R, ischemic/reperfusion; CKD, chronic kidney disease; HIF-1α, hypoxia inducible factor-1α; PARP1, poly(ADP-ribose) polymerase 1; cyt C, cytochrome C; NAA10, N-a-acetyltransferase 10 protein; ARD1, arrest-defetive-1; HSCs, hepatic satellite cells; ECM, extracellular matrix; TGF-β, transforming growth factor-beta; HDAC2, histone deacetylase 2; XIAP, X-linked inhibitor of Apoptosis Protein; CHRF, cardiac hypertrophy-related factor; SIX1, sine oculis homeobox 1; GSE1, Gse1 coiled-coil protein; JAG1, jagged 1; CUL4B, cullin 4B; EMT, epithelial-to-mesenchymal transition; JAG1, jagged canonical-Notch ligand 1; NF-κB, nuclear factor-kappaB; TLR4, toll like receptor 4.

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diagnostic tool for tumor detection. Besides, down-regulation of miRNA-489 in tumors provides unfavorable prognosis.

1. Introduction

The cancer is a non-communicable disease and a problem for healthcare system [1]. The emergence of COVID-19 led to some difficulties in diagnosis and treatment of cancer patients. Therefore, it is estimated that cancer incidence and death will undergo an increase in upcoming years [2]. Each cancer has a certain incidence rate and lung cancer is at the first place. The incidence rate of cancer seems to be higher in low- and middle-income countries compared to developed and wealthy countries [3]. As cancer incidence and death are going to increase in developing countries, cautions and plans should be provided to manage this condition. The cancer cells have high proliferation rate and compared to normal cells, are ignorant towards cell cycle inhibitors [4–6]. In terms of migration, they can easily spread to various tissues of body and undergo epithelial-to-mesenchymal transition (EMT) to increase their diffusion [7]. Furthermore, angiogenesis mainly helps tumor cells in migration to body tissues [8]. Although there have been efforts to develop therapies for suppressing growth and invasion of cancer cells, tumors have demonstrated resistance to therapies [9,10]. Hence, in addition to growth and invasion, capacity of cancer cells in developing therapy resistance should be considered.

It has been revealed that genetic information travels from DNA through RNA for synthesis of proteins [11]. Then, RNAs were identified as intermediators for production of proteins [12–14], until the discovery of first small temporal RNAs, lineage defective 4 (lin-4) and lethal 7 (let-7) [15,16]. These RNAs were recognized in *Caenorhabditis elegans* and it was found that in spite of lack of role in protein synthesis, a vast number of RNA molecules are required for development. This resulted in the fact that the functional products of genome are not limited to proteins and they can produce RNA molecules that play a significant role in developmental processes [17,18]. Using sequencing technologies, different ncRNAs such as microRNAs (miRNAs), circular RNAs (circRNAs), long non-coding RNAs (lncRNAs) and transcribed ultra-conserved regions were recognized. Accumulating data demonstrates that ncRNAs are able to regulate cellular mechanisms in both development and pathological conditions [19].

Based on estimates, up to 98% of human genome is comprised by non-protein coding genes [20]. Although this section of genome that non-protein coding genes occupy, was introduced as junk, it was later shown that non-protein coding part of genome has potential uses in physiological and developmental processes [21]. The non-protein coding part of genome is comprised by cis/trans-regulatory elements, introns, repeat sequences and telomerases; a part of them is transcribed into ncRNAs with functional roles. Overall, the ncRNAs can be divided based on their length or function. In terms of length, ncRNAs with more than 200 nucleotides are considered as lncRNAs, while those that have less than 200 nucleotides in length, are known as small ncRNAs. Based on function, there are regulatory RNA molecules such as miRNAs and lncRNAs, and housekeeping ncRNAs including transfer RNAs and ribosomal RNAs [22]. Recently, attention has been directed towards revealing biogenesis route and role of regulatory RNA molecules [23].

It is completely troublesome to observe the function of ncRNAs in isolation. This is due to the fact that a number of ncRNAs such as miRNAs are able to affect different messenger RNAs (mRNAs), and one mRNA could be affected by different miRNAs [20]. So, ncRNAs form a signaling network in which each component has a critical role, necessary for proper function of entire network [24,25]. Another topic that adds more complexity to miRNAs is that they can affect their stability by interacting with other ncRNAs such as lncRNAs and circRNAs. Besides, lncRNAs and circRNAs can function as upstream mediators and control the abundance of miRNAs via sequestration. This complicated nature of interactions and regulations confirm the role of miRNAs in controlling vital cellular events. It is obvious that any disturbance in this network can lead to alterations in cell fate, cellular programs and generation of pathological events, particularly cancer [26].

The present review focuses on function of a new emerging miRNA in cancers, known as miRNA-489. This mechanistic review aims to reveal regulation of growth and metastasis of tumors by miRNA-489. Then, miRNA-489 impact on therapy response in cancers is discussed to provide directions for its targeting in future experiments for sensitizing tumors to therapy. Next, interaction of miRNA-489 with other molecular pathways is described. Finally, role of miRNA-489 as diagnostic and prognostic factor for clinical application is provided.

2. miRNAs as key players in cancer

With 19-24 nucleotides in length, miRNAs are capable of regulating various biological mechanisms including cell proliferation, apoptosis, differentiation, migration, angiogenesis, etc. There are two major kinds of miRNAs including tumor-suppressor and tumor-promoting miRNAs in cancers. The cell homeostasis and biological processes are modulated by miRNAs, and aberrant expression of miRNAs leads to initiation of diseases that cancer is among them [27,28]. Restoring expression of tumor-suppressor miRNAs can result in cancer suppression. Investigating the role of miRNAs in cancer therapy also reveals that complicated signaling networks are involved in this case. Each miRNA affects certain targets, and different molecular pathways and mechanisms can be targeted by various miRNAs. For instance, autophagy is a catabolic process accounting for toxic and aged macromolecule and organelle decomposition [29]. Autophagy may contribute to tumor growth and drug resistance [30]. Various studies have been performed to reveal the relationship between miRNAs and autophagy in cancer therapy. It has been demonstrated that miRNAs such as miRNA-205, -20a, -221 and -138-5p suppress autophagy to impair tumor proliferation, and sensitize to chemotherapy and radiotherapy [31–34].

Both onco-suppressor and oncogene miRNAs have been extensively examined in cancer cells. miRNAs can be considered as major upstream modulators of molecular pathways in cancer cells. Finding the relationship between miRNAs and their down-stream targets is associated with improving our knowledge and accelerating the pace of providing of an effective cancer treatment. For instance, miRNA-206 dually suppresses metastasis and growth of thyroid tumor by reducing Ras-related protein Rap-1B (RAP1B) expression [35]. In contrast to onco-suppressor miRNAs, oncogene miRNAs are capable of promoting malignant behavior of cancer cells. This is due to the fact that oncogene miRNAs direct conditions towards enhancing metastasis and growth of cancer cells. For example, angiogenesis is a positive factor for embryogenesis and processes such as wound healing, but its induction during cancer is a negative factor for prognosis [36]. Stimulation of angiogenesis by miRNA-9-5p elevates growth and invasion of tumors [37]. Hence, oncogene and onco-suppressor miRNAs exert different effects on their down-stream targets, and a unique axis is followed in each case [38,39].

In ensuring survival and triggering chemo- and radio-resistance, cancer cells switch among signaling pathways to inhibit apoptosis. It has been demonstrated that miRNAs are able to influence apoptosis in cancer cells. miRNA-4500 activates caspase-3 to induce apoptotic cell death [40]. miRNA-16 and miRNA-34a trigger cell cycle arrest to disrupt tumor progression [41]. The impact of miRNAs on apoptotic factors has resulted in their role in inhibiting chemoresistance. For instance, miRNA-7 suppresses breast tumor resistance to paclitaxel and carboplatin by decreasing Bcl-2 expression level [42]. The molecular pathways responsible for growth inhibition of cancer cells undergo down-

regulation by oncogenic miRNAs. PTEN suppresses PI3K/Akt axis to impair tumor progression and diminish growth rate [43]. A recently published study demonstrates that miRNA-552 decreases PTEN expression to promote ovarumo tumor progression [44]. These are just a few descriptions in respect to the role of miRNAs in cancer therapy. Using genetic manipulation, aforementioned miRNAs and other ones can be targeted to suppress survival of cancer cells (upregulation of onco-suppressor miRNAs, and down-regulation of oncogenic ones). Besides, anti-tumor drugs modulate miRNA expression. Using anti-tumor drugs can be a considerable advancement in cancer therapy by targeting onco-suppressor and oncogene miRNAs [45].

3. An overview of miRNA-489 in non-cancerous diseases

miRNA-489 is located on chromosome 7q21.3. Recently, the role of this miRNA has been examined in different disorders, particularly cancer. Regardless of onco-suppressor role of miRNA-489, this miRNA plays significant role in diseases and affecting their progression and development. To date, various experiments have evaluated the involvement and role of miRNA-489 in disorders that we briefly describe them in this section. The acute kidney injury (AKI) results from renal ischemic/reperfusion (I/R) injury. AKI has high mortality around the world and it can result in development and generation of chronic kidney diseases (CKD) [46]. HIF-1α promotes miRNA-489 to inhibit apoptosis in renal tubular cells and suppress poly(ADP-ribose) polymerase 1 (PARP1) [47]. Although previous study demonstrated that miRNA-489 is a protective factor during I/R injury, another study provides conflicting data. SPIN1 is a key member of Spin/Ssty family and a meiotic spindle protein [48]. SPIN1 is an oncogenic factor in different cancers [49]. The story is a little different in myocardial I/R injury. miRNA-489 exacerbates conditions in myocardial I/R injury via reducing MDA levels, and enhancing SOG and GSH activities. miRNA-489 upregulation triggers apoptosis in myocardial cells, and inhibits their proliferation. It seems that miRNA-489 induces mitochondrial-mediated apoptotic cell death via reducing Bcl-2 expression, releasing cytochrome C (cyt C) and activating caspase cascade. These adverse effects of miRNA-489 are mediated via down-regulation of SPIN1 [50]. These two studies provide controversial data about miRNA-489 in I/R injury, and more studies are needed to clarify its role.

NAA10, the paralog of the yeast gene arrest-defective-1 (ARD1) possesses biological functions including cell growth, metastasis, apoptosis and autophagy [51,52]. miRNA-489-3p exerts negative effects on the survival and growth of neuronal cells. The miRNA-489-3p inhibits NAA10 to impair neuronal cell growth. Besides, miRNA-489-3p induces apoptosis in neuronal cells, showing potential function of miRNA-489-3p in neurological disorders [53]. In addition to neurological disorders, miRNA-489 involves in liver diseases. The liver fibrosis is an increasing challenge for physicians and activation of hepatic satellite cells (HSCs) by pro-inflammatory factors can lead to liver fibrosis. Stimulated HSCs produce high amounts of extracellular matrix (ECM) that disrupts normal structure of liver, leading to liver fibrosis [54,55]. Notch signaling pathway participates in generation of liver fibrosis via myofibroblast differentiation and induction of EMT [56,57]. JAG1 is a ligand of Notch pathway that mediates fibrosis [58–60]. miRNA-489-3p is able to inhibit liver fibrosis by suppressing HSCs via down-regulation of JAG1/Notch axis [61].

In addition to liver fibrosis, miRNA-489 can regulate pulmonary fibrosis. It has been shown that transforming growth factor-beta (TGF-β) contributes to development of fibrosis and its inhibition is of importance in fibrosis alleviation [62]. TGF-β/Smad signaling pathways can result in formation of pulmonary fibrosis [63]. TGF-β activates Smad3 to form Smad3/Smad4 complex. This complex translocates into nucleus where it induces fibrosis formation [64]. It is worth mentioning that miRNA-489 diminishes N-cadherin and vimentin levels, while it enhances E-cadherin levels, leading to an amelioration in pulmonary fibrosis [65]. Interestingly, miRNA-489 and its role in cardiac fibrosis has also been investigated. Histone deacetylase 2 (HDAC2) belongs to HDAC class II that is involved in different disorders such as cancer and cardiovascular diseases [66]. Accumulating data demonstrates that inhibition of HDAC2 paves the way into fibrosis amelioration [67,68]. A same story is followed by miRNA-489 in improving cardiac fibrosis. miRNA-489 down-regulates expression of HDAC2 to suppress cardiac fibrosis [69].

Restoring expression level of miRNA-489 can be beneficial in ameliorating liver fibrosis. A recent experiment has revealed that miRNA-489-3p demonstrates a decrease in expression, while expression level of jagged canonical Notch ligand 1 (JAG1) increases. The miRNA-489-3p binds to 3′-UTR of JAG1 to reduce its expression, leading to a significant reduction in levels of profibrotic markers and alleviating liver fibrosis [70]. The anti-inflammatory agents modulate miRNA-489 expression. For this purpose, shikonin increases miRNA-489-3p expression to down-regulate MAP2K1, resulting in decreased lipopolysaccharide (LPS)-mediated cell damage [71]. The nuclear factor-kappaB (NF-κB) is considered as an inflammatory factor [23]. In order to diminish inflammation in psoriasis, miRNA-489-3p suppresses NF-κB signaling via down-regulating toll like receptor-4 (TLR4) [72]. The overexpressed miRNA-489 is able to induce adipocyte differentiation and adipogenesis metabolism via affecting *Postn* gene [73]. However, enhancing miRNA-489 expression is not always beneficial and it may result in unexpected and adverse impacts. For instance, a recent experiment has revealed that down-regulation of miRNA-489-3p prevents apoptosis, neuronal cell death and improves viability [74]. Hence, various physiological mechanisms are regulated by miRNA-489 and modulating its expression can be considered as a promising therapeutic strategy [75–77]. Besides, miRNA-489 expression can be regulated by upstream mediators in non-cancerous disease. The lncRNA CHRF elevates cardiac hypertrophy by sponging miRNA-489 and increasing Myd88 expression [78].

Taking everything into account, experiments show that miRNA-489 has different roles in various pathological events. Identification of its roles during pathological conditions can provide a therapeutic target [76,78–81]. At the next sections, we specifically focus on the role of miRNA-489 in different cancers to show the effect of this miRNA on cancer cells based on pre-clinical and clinical studies.

4. miRNA-489 and cancer cells

4.1. miRNA-489 and chemotherapy

Cancer arises from mutations in different genes, providing conditions for uncontrolled tumor progression [82]. To date, various therapeutics have been introduced for tumor treatment with satisfactory results [83]. However, drug resistance is an emerging and challenging phenomenon for scientists [84]. Drug resistance is one of the main causes of failure of most therapeutics in treatment of cancer. In fact, cancer cells use resistance as a shield against therapeutics such as chemotherapy, radiotherapy, and immunotherapy. Increasing evidence demonstrates that different factors are involved in development of drug resistance, and genetic and epigenetic modifications play a significant role in this case. MiRNAs are considered as key players in drug resistance/sensitivity [85,86]. miRNA-489 is one of them that its role in cancer chemotherapy has been examined. Akt3 is positioned on chromosome 1q44 and a key member of Akt serine/threonine proteins. Akt3 has a number of functions including cell growth, apoptosis, differentiation and tumorigenesis [87,88]. Akt3 is a tumor-promoting factor that enhances proliferation and invasion [89]. miRNAs affect Akt3 expression in various tumors [90]. Notably, Akt3 is a down-stream target of miRNA-489 in ovarian cancer cells. The most common way that chemotherapeutic agents follow in decreasing survival of cancer cells is apoptosis induction. However, ovarian cancer cells acquire resistance to cisplatin chemotherapy via reducing apoptotic cell death. Enhancing expression of miRNA-489 sensitizes ovarian cancer cells to cisplatin chemotherapy and restricts their proliferation and growth via down-regulation of Akt3

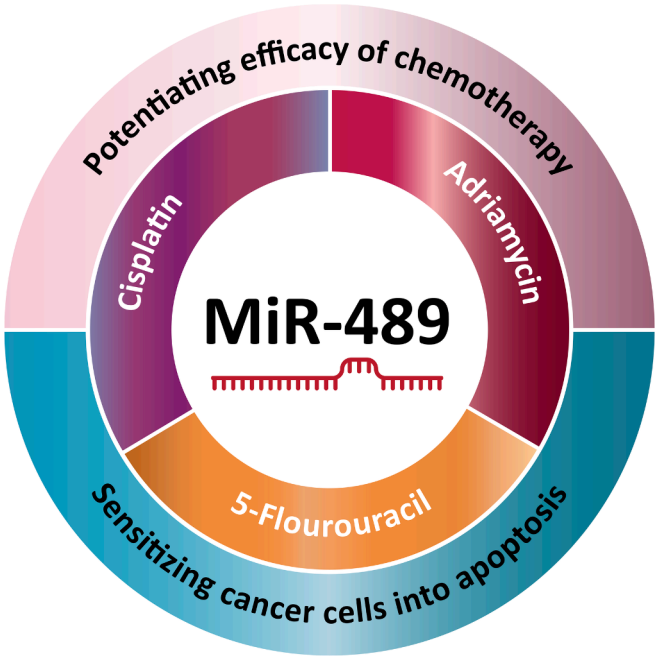

Fig. 1. miRNA-489 as a chemosensitizer. Upregulation of miRNA-489 sensitizes cancer cells to chemotherapy with cisplatin, Adriamycin and fluorouracil-5.

[91].

As it was mentioned previous sections, TGF-β is one of the downstream targets of miRNA-489 in disease therapy. TGF-β activates Smad3 to provide its nuclear translocation, leading to stimulation of target genes [92]. EMT mechanism can be induced by TGF-β that subsequently, mediates the migration and invasion of cancer cells [93,94]. Accumulating data demonstrates that EMT induction can lead to resistance of cancer cells to chemotherapy [95,96]. Inhibitory effect of miRNA-489 on chemoresistance is mediated by suppressing EMT. It seems that upregulation of miRNA-489 expression inhibits TGF-β/Smad3 axis that in turn, suppresses EMT, resulting in Adriamycin sensitivity [97].

As an anti-apoptotic factor, XIAP regulates the function of caspases and Smad/DIABLO. It has been reported that XIAP suppresses apoptosis via interacting with apoptotic inducers [98]. Overexpression of XIAP is correlated with cancer migration and proliferation, and XIAP induces chemoresistance [99,100]. miRNA-489 targets XIAP in sensitizing breast cancer cells to 5-fluorouracil chemotherapy. It appears that miRNA-489 elevates cytotoxicity of 5-fluorouracil chemotherapy and sensitizes cancer cells to its apoptotic effect via inhibition of XIAP [101]. In previous sections, we provided a brief discussion of SPIN1 in diseases. SPIN1 overexpression is in favor of tumor progression and it is regulated by miRNAs [102]. Upregulation of SPIN1 is associated with induction of chemoresistance and much effort has been made in inhibition of its expression [103]. The miRNA-489 affects SPIN1 in sensitizing cancer cells to chemotherapy. Normally, SPIN1 stimulates PI3K/Akt axis to promote growth and malignancy of breast tumor and prevents apoptosis. Overexpression of miRNA-489 suppresses SPIN1/PI3K/Akt axis to enhance breast tumor chemosensitivity [104]. Overall, miRNA-489 is a potential tumor-suppressor increasing sensitivity of cancer cells to chemotherapy (Fig. 1) [105].

4.2. *LncRNA-mediated regulation of miRNA-489*

Similar to miRNAs, lncRNAs belong to ncRNAs and have more than 200 nucleotides in length [106,107]. They are able to exert regulatory impact at various stages such as transcription, post-transcription, and translation. The lncRNAs and their expression levels are of importance in pathological and physiological events such as embryonic development, cell growth and tumorigenesis [108]. The lncRNAs can modulate miRNA expression in various tumors [109,110]. LncRNA LINC00460 is a tumor-promoting factor increasing tumor growth and metastasis. This lncRNA prevents apoptotic cell death for enhancing cancer proliferation

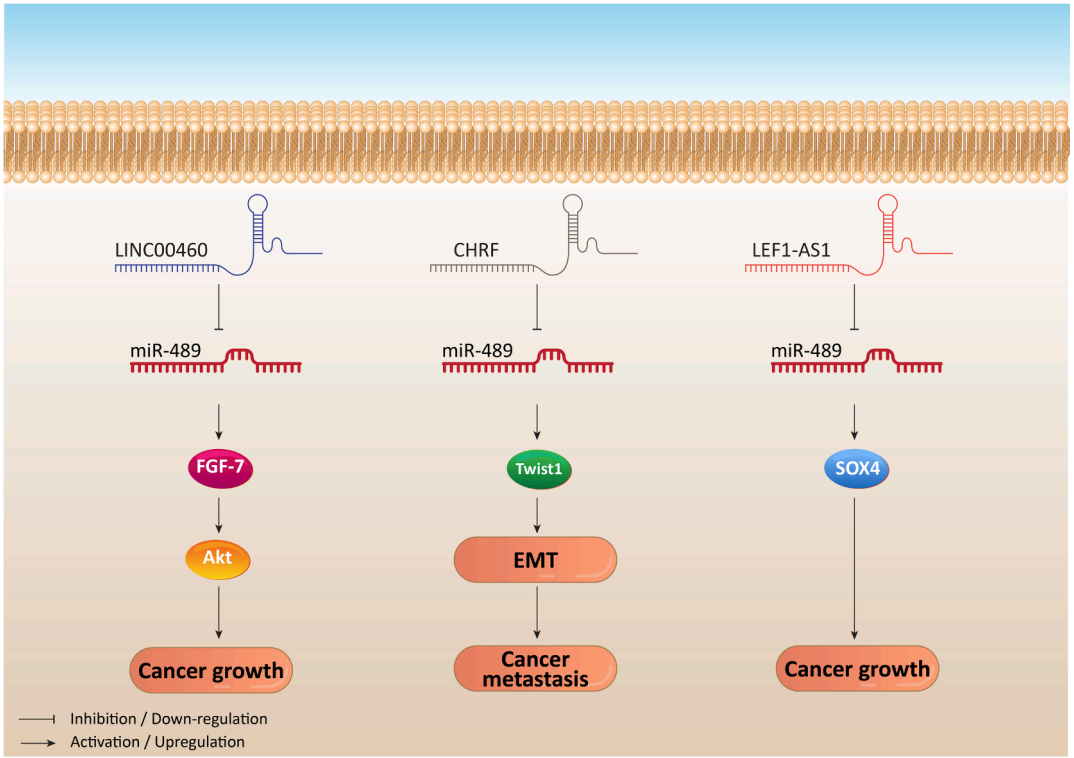

Fig. 2. Regulation of miRNA-489 by lncRNAs in cancer.

[111,112]. LncRNA LINC00460 functions as an endogenous competitor of miRNA-489. By sponging miRNA-489, lncRNA LINC00460 activates FGF-7, resulting in stimulation of Akt and enhanced proliferation of breast cancer cells [113]. LINC00460/miRNA-489/FGF-7/Akt axis can be targeted in further studies to suppress breast cancer malignancy.

One of the therapeutic strategies is enhancing expression of miRNA-489. As it was mentioned, EMT induction is in favor of tumor metastasis. Twist1 is able to regulate EMT in cancer. Twist 1 enhances levels of vimentin to induce EMT [115]. The positive relationship between Twist1 and EMT emanates from the fact that Twsit1 degradation results in EMT inhibition and decreased tumor metastasis [116]. LncRNA cardiac hypertrophy-related factor (CHRF) increases metastatic capability of colorectal tumor by decreasing miRNA-489 expression. As a consequence, an increase occurs in Twist1 level to activate EMT mechanism, resulting in invasion of colorectal tumor [117]. The miRNA-489 overexpression disrupts Twist1/EMT axis to inhibit metastasis of colorectal cancer cells.

The SOX4 function as oncogene has been examined in various tumors during recent years. SOX4 inhibition by lncRNA LINC01133 suppresses migration of cancer cells [118]. Besides, SOX4 can function as upstream mediator in elevating tumor progression. For instance, SOX4 is able to affect Wnt5a and RB1 in elevating growth and invasion of tumors [119,120]. Normally, miRNA-489 inhibits SOX4 to restrict growth and invasion of lung tumor. LncRNA LEF1-AS1 induces SOX4 expression via miRNA-489 down-regulation to provide condition for growth and malignancy of lung cancer cells [121]. Hence, lncRNA and miRNA-489 interaction is a determinant factor for growth and metastasis of tumor cells (Fig. 2) [122,123].

4.3. miRNA-489 and cancer growth

Cancer cells demonstrate high rate of aerobic glycolysis to meet their needs for energy. Shifting from oxidative phosphorylation into glycolysis is known as Warbrug effect [124–126]. The miRNAs can affect glycolysis in tumor cells. A newly published study has examined effect of miRNA-489 on glucose metabolism in melanoma cells. It has been shown that miRNA-489 suppresses growth of melanoma via disrupting glycolysis [127]. In regulation of glycolysis in melanoma cells, miRNA-489 affects sine oculis homeobox 1 (SIX1). SIX1 is considered as an enhancer of glycolysis in different cancer cells [128]. miRNA-489 down-regulates expression of SIX1 to interfere with glycolysis metabolism, inhibiting tumor growth [128].

HDAC7 is an inducer of tumor growth and metastasis confirmed by multiple experiments [129,130]. Inhibition of HDAC7 via acetylation paves the way into suppressing growth and cancer stem cell phenotype [130]. In colorectal cancer cells, miRNA-489 affects HDAC7 to suppress their proliferation. miRNA-489 binds to 3′-UTR of HDA7 that in turn, reduces its expression, disrupting growth of cancer cells [131]. In order to suppress cancer proliferation, miRNA-489 targets a variety of molecular signaling pathways. These pleiotropic effects of miRNA-489 have made it a suitable option in cancer therapy. Gse1 coiled-coil protein (GSE1) is proline rich protein with molecular weight of 136 kDa [132]. GSE1 is considered as an oncogenic factor mediating undesirable prognosis of cancer patients [133]. The GSE1 down-regulation by miRNA-489 is in favor of decreasing breast tumor growth [134].

Notch signaling pathway is involved in regulation of embryogenesis, nervous system development, endocrine development and cardiovascular development [135–137]. Increasing evidence demonstrates that abnormal expression of Notch signaling pathway increases tumor growth and anti-tumor agents inhibit its expression to interfere with growth of cancer cells [138–140]. The miRNA-489 and Notch signaling demonstrate interactions in bladder tumor. It has been shown that miRNA-489 binds to 3′-UTR of jagged 1 (JAG1), as a ligand of Notch signaling pathway to inhibit its activation, reducing bladder tumor proliferation [141].

4.4. miRNA-489 and cancer metastasis

In addition to uncontrolled proliferation, cancer cells demonstrate metastasis into neighboring and distant sites. Different molecular pathways and mechanisms are responsible for migration of cancer cells. Stimulation of EMT, induction of angiogenesis, overexpression of MMPs, and TGF-β and ZEB participate in metastasis of cancer cells [142–145]. The miRNA-489 and cancer migration has been examined, but the number of experiments is limited and requires more clarification and attempt to reveal miRNA-489 function in regulating tumor migration. Clinical trials have also confirmed the relationship between miRNA-489 and cancer metastasis. In an experiment, the relationship between miRNA-489 expression and melanoma metastasis was investigated. The low expression of miRNA-489 provides condition for migration of melanoma cells [146] and enhancing its expression can be considered as promising candidate in suppressing metastasis of melanoma.

4.5. miRNA-489 and PI3K/Akt signaling pathway

PI3K/Akt induces angiogenesis and growth of tumors and its expression profile is negatively affected by PTEN to impair tumor progression [147]. Different molecular pathways act as upstream mediators of PI3K/Akt and miRNAs are among them [148,149]. Increasing evidence demonstrates that miRNA-489 affects PI3K/Akt signaling pathway to exert tumor-suppressor function. Expression of miRNA-489 undergoes down-regulation in gastric cancer, and is associated with poor prognosis. Enhancing expression of miRNA-489 remarkably reduces viability of gastric cancer cells and induces apoptotic cell death. The miRNA-489 diminishes HDAC7 level to suppress PI3K/Akt axis, reducing growth and migration of gastric tumor [150]. In fact, PI3K/Akt pathway acts as an inducer of gastric tumor progression and miRNA-489 disrupts PI3K/Akt signaling to suppress gastric cancer growth. The PI3K/Akt axis modulation by miRNA-489 is also of interest in mediating tumor chemosensitivity.

SPIN1 is a member of SPIN/SSTY family that was first discovered in ovarian cancer and was suggested to be a carcinogenic factor [151]. More studies were conducted about role of SPIN1 in cellular events and it was found that this factor involves in cell cycle, senescence, apoptosis, cell growth and cell transformation [48,152–154]. SPIN1 could be regulated by miRNAs to affect efficacy of chemotherapy and inhibit progression of cancer cells [155,156]. By decreasing SPIN1 expression, miRNA-489 impairs breast tumor progression and suppresses PI3K/Akt axis There is a reverse relationship between miRNA-489 and SPIN1 in breast tumor. Overexpression of miRNA-489 inhibits SPIN1. This suppresses PI3K/Akt signaling pathway that in turn, interferes with growth and survival of breast tumor, leading to drug sensitivity [104].

For apoptosis induction, miRNA-489 target Akt signaling pathway. Increasing evidence demonstrates that Akt3 overexpression is correlated with tumor progression [87,157]. In pancreatic cancer cells, expression of miRNA-489 undergoes down-regulation that ensures viability and uncontrolled growth of cancer cells. Enhancing expression of miRNA-489 provides desirable prognosis and considerably decreases pancreatic tumor growth. The miRNA-489 is able to down-regulate Akt3 that in turn, suppresses proliferation of pancreatic cancer cells [158]. Taking everything into account, miRNA-489 is a potential inhibitor of PI3K/Akt axis in cancer therapy, and mediates reduction in tumor growth and metastasis [159].

4.6. miRNA-489 and Wnt/β-catenin signaling pathway

The uncontrolled and abnormal growth of cells can be observed in tumors. It is obvious that this high growth is due to impairment in molecular pathways regulating important biological mechanisms such as cell proliferation and apoptosis [160–162]. Wnt/β-catenin is one of the main signaling pathways that its abnormal expression (upregulation/down-regulation) occurs in cancer cells [163–165]. Wnt signaling

Table 1
The onco-suppressor role of miRNA-489 in different cancers.

Cancer type	Signaling network	Major outcomes	Refs
Breast cancer	miRNA-489/ ULK1/autophagy	Sensitizing cancer cells into doxorubicin chemotherapy Down-regulation of ULK1 Inhibition of autophagy	[105]
Breast cancer	LINC00460/ miRNA-489/ FGF7/Akt	Repressing miRNA-489 expression Activation of FGF7/Akt by LINC00460 Enhancing cancer progression	[113]
Breast cancer	miRNA-489/ Smad3/EMT	Inhibiting nuclear translocation of Smad3 Suppressing EMT Enhancing chemosensitivity	[97]
Breast cancer	miRNA-489/ GSE1	Exerting a reduction in GSE1 expression Interfering with proliferation and viability of cancer cells	[134]
Breast cancer	miRNA-489/ HER2	Suppressing tumor growth and aggressive behavior Down-regulation of HER2	[182]
Breast cancer	miRNA-489/ SPIN1/PI3K/Akt	Suppressing SPIN1/PI3K/Akt axis Enhancing chemosensitivity	[104]
Breast cancer	miRNA-489/XIAP	Stimulation of apoptosis Sensitizing into 5-fluoro-uracil chemotherapy Inhibition of XIAP expression	[101]
Breast cancer	–	Association of miRNA-489 with better 3-survival	[181]
Cervical cancer	miRNA-489/ PI3K/Akt	Down-regulation of PI3K/ Akt Stimulation of apoptosis Association with desirable prognosis	[180]
Colorectal cancer	LINC00115/ miRNA-489-3p/ PI3K/Akt/mTOR	Apoptosis inhibition by LINC00115 Enhanced colorectal cancer proliferation and invasion upon LINC00115 overexpression Reducing miRNA-489-3p expression Inducing PI3K/Akt/mTOR signaling	[183]
Colorectal cancer	miRNA-489/ HDAC7	Interfering with proliferation and metastasis of cancer cells Down-regulation of HDAC1	[184]
Colorectal cancer	LEF1-AS1/ miRNA-489/ DIAPH1	Sponging miRNA-489 and reducing its expression Enhancing DIAPH1 expression Developing colorectal cancer	[123]
Colorectal cancer	CHRF/miRNA-489/Twist1/EMT	Down-regulation of miRNA-489 by lncRNA CHRF Subsequent activation of Twist1 and EMT Enhancing metastasis of cancer cells	[117]
Bladder cancer	miRNA-489/ JAG1	Suppressing growth of cancer cells Binding into 3′-UTR of JAG1 and repressing its expression	[141]
Bladder cancer	miRNA-489-3p/ HDAC2	Reduced expression level of miRNA-489-3p in bladder cancer compared to normal tissues Impairing growth of xenograft model The miRNA-489-3p decreases HDAC2 expression to suppress growth and metastasis of cancer cells	[185]
Pancreatic cancer	KRAS/NF-κB/ YY1/miRNA-489	Activation of NF-κB/YY1 axis by KRAS Subsequent inhibition of miRNA-489 Promoting metastasis via MMP-7 and ADAM9 upregulation	[186]
Pancreatic cancer	miRNA-489/Akt3	Down-regulation of Akt3 Suppressing growth of cancer cells	[158]
Pancreatic cancer	Circ-0071036/ miRNA-489	Reverse association between circRNA and miRNA-489 Unfavorable prognosis of pancreatic cancer patients upon circRNA upregulation Increasing growth and metastasis Apoptosis inhibition	[187]
Gastric cancer	miRNA-489/ PI3K/Akt	Down-regulation of PI3K/ Akt Disrupting proliferation of cancer cells	[150]
Gastric cancer	miRNA-489/ PROX1	Inhibiting aggressive behavior and growth of cancer cells Reducing expression of PROX1	[188]
Gastric cancer	miRNA-489/ Wnt/β-catenin	Inactivating Wnt signaling pathway Suppressing metastasis and proliferation	[170]
Gastric cancer	miRNA-489-3p/ SLC7A11	The levobupivacaine induces ferroptosis in cancer cells Impairing tumor growth in vivo Enhancing iron and lipid ROS levels Enhancing miRNA-489-3p expression to reduce SLC7A11 expression by binding to 3′-UTR	[189]
Melanoma	–	Overexpression of miRNA-489 inhibits cancer cell metastasis	[146]
Melanoma	miRNA-489/SIX1	Inhibiting glycolysis Down-regulation of SIX1	[127]
Lung cancer	LEF1-AS1/ miRNA-489/ SOX4	Down-regulation of miRNA-489 Enhancing expression of SOX4 Inducing carcinogenesis	[121]
Lung cancer	MIR503HG/ miRNA-489	Down-regulation of miRNA-489 Decreasing apoptotic cell death Inhibiting EMT Enhancing E-cadherin levels Reducing N-cadherin levels	[190]
Lung cancer	miRNA-489/ SUZ12	Down-regulation of SUZ12 Suppressing proliferation of cancer cells	
Ovarian cancer	miRNA-489/Akt3	Sensitizing cancer cells into cisplatin chemotherapy Inhibiting expression of Akt3	[191]
Ovarian cancer	miRNA-489/ PI3K/Akt	Inhibiting PI3K/Akt axis Suppressing proliferation	[159]

(continued on next page)

Table 1 (*continued*)

Cancer type	Signaling network	Major outcomes	Refs
		and migration Inhibition of EMT	
Glioma	ENST01108/ miRNA-489/SIK1	Enhancing SIK1 expression via miRNA-489 sponging Promoting proliferation and invasion	[122]
Glioma	LEF1-AS1/ miRNA-489-3p/ HIGD1A	Increasing carcinogenesis in vitro and in vivo LEF1-AS1 knock-down induces apoptosis in glioma cells Reducing miRNA-489-3p expression to upregulate HIGD1A	[192]
Glioblastoma	miRNA-489-3p/ BDNF/PI3K/Akt	Acting as tumor-suppressor factor and reducing growth and invasion of cancer cells The miRNA-489-3p binds to BDNF and reduces its expression Decreasing protein levels of Akt and PI3K	[193]
Glioblastoma	miRNA-489/ TWIST1	Decreased expression level of miRNA-489 in glioblastoma Reducing TWIST1 expression by miRNA-489 Elevating caspase-3 and -8 expressions Inducing apoptosis Suppressing migration and invasion of cancer cells	[194]
Hypopharyngeal squamous cell carcinoma	miRNA-489/ PTPN11	Reducing PTPN11 expression Disrupting growth and migration	[195]
Hypopharyngeal squamous cell carcinoma	Circ-0003214/ miRNA-489-3p/ ADAM10	The metformin administration diminishes viability and colony formation capacity of cancer cells Metformin induces apoptosis and cell cycle arrest Reducing circ-0003214 expression to enhance miRNA-489-3p expression, resulting in ADAM10 down-regulation	[196]
Multiple myeloma	miRNA-489/ LDHA	Decreasing proliferation rate of cancer cells via down-regulating LDHA expression Inhibiting aerobic glycolysis	[197]
Renal cancer	DHX33/miRNA-489-3p/MEK1	Increasing tumor growth in vivo Positive association with invasion of cancer cells and advanced TNM stage The circRNA DHX33 reduces miRNA-489-3p expression via sponging to enhance MEK1 expression	[198]
Acute myeloid leukemia	SNHG1/miRNA-489-3p/SOX12/ Wnt/β-catenin	The lncRNA SNHG1 functions as tumor-promoting factor SNHG1 decreases miRNA-489-3p expression to enhance SOX12 expression, resulting in Wnt signaling activation	[199]
Acute myeloid leukemia	SNHG5/miRNA-489-3p/SOX4	Overexpression of lncRNA SNHG5 in cancer cells Apoptosis induction and growth inhibition upon SNHG5 knock-down Reduced expression of miRNA-489-3p by SNHG5 to enhance SOX4 expression	[200]
Hepatocellular carcinoma	miRNA-489/ SOX4	Apoptosis induction Decreasing growth and metastasis of cancer cells Preventing hepatocellular carcinoma development Reducing SOX4 expression	[201]

can enhance metastasis and proliferation of tumors and notably, it is under regulation by miRNAs in cancer [166–168]. Targeting Wnt signaling pathway is a promising way in restricting invasion and growth of tumors [169]. Notably, miRNA-489 is capable of targeting Wnt/β-catenin signaling pathway. In inhibiting gastric tumor progression, miRNA-489 down-regulates Wnt expression [170]. On the other hand, cullin 4B (CUL4B) is a scaffold protein participating in ubiquitin-mediated proteolysis and has shown oncogenic role in cancer cells [171–173]. miRNA-489 inhibits Wnt signaling pathway by CUL4B down-regulation, reducing gastric tumor growth and metastasis [170]. Since miRNA-489 is a new emerging miRNA, just one study has investigated its effect on Wnt signaling pathway and more studies will be performed in near future to elucidate relationship between miRNA-489 and Wnt/β-catenin signaling pathway in cancer cells.

4.7. miRNA-489 as diagnostic and prognostic factor

The miRNAs are promising candidates in clinical course due to their prognostic and diagnostic potentials [174,175]. In respect to increased incidence rate and survivors of cancer [176,177], using miRNAs for diagnosis and predicting overall survival of patients with cancer is of importance. To date, three studies have demonstrated potential of miRNA-489 as prognostic and diagnostic factors that we include here. Cervical cancer causes high mortality and morbidity worldwide and is considered as a common gynecologic malignancy [178,179]. miRNA-489 acts as tumor-suppressor in cervical and its expression level determines prognosis of cervical cancer patients. The expression of miRNA-489 significantly diminishes in cervical tumor and its upregulation is correlated with desirable prognosis. The positive relationship between miRNA-489 and favorable prognosis of cervical cancer is due to growth and viability suppression by miRNA-489. Enhancing expression of miRNA-489 suppresses proliferation and induces apoptotic cell death in cervical tumor by decreasing PI3K/Akt expression and stimulation of p53 [180]. Another study has investigated the potential of miRNA-489 as being used for predicting survival rate of breast tumor patients. It has been shown that breast cancer patients who have high expression of miRNA-489, demonstrate higher 3-year survival rate, showing the relationship between miRNA-489 and desirable prognosis [181] (Table 1). Hence, following conclusions can be made:

- miRNA-489 is associated with desirable prognosis [181],
- It is a diagnostic tool,
- It has onco-suppressor role,
- And its down-regulation occurs during cancer progression (Fig. 3).

5. Conclusion and remarks

miRNA-489 is an emerging miRNA located on chromosome 7q21.3. The recently published studies have shown that how miRNAs can contribute to suppressing/promoting tumor progression. miRNAs tightly modulate tumor progression by targeting various factors. Besides, molecular pathways including lncRNAs regulate miRNA expression in tumors. These topics were discussed in this review for miRNA-489 to shed some light on the function and regulation of this new

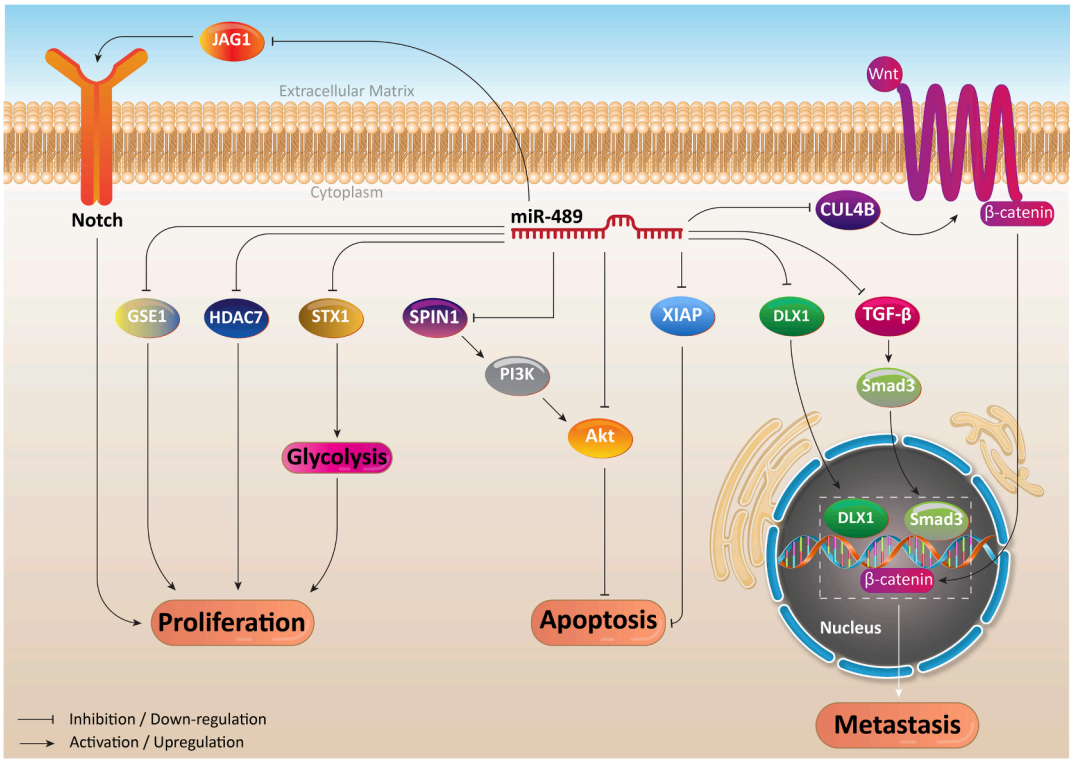

Fig. 3. The regulation of different molecular pathways by miRNA-489 in cancer cells. The complexity of molecular pathways that are modulated by miRNA-489, and how this affects tumor progression.

miRNA in different cancers. First of all, studies have shown that miRNA-489 is an onco-suppressor factor and elevating its expression can be considered as a promising strategy in cancer therapy. Chemoresistance is an increasing challenge nowadays and it has been reported that miRNA-489 modulates response of cancer cells to chemotherapy. In enhancing sensitivity of cancer cells to chemotherapy, miRNA-489 negatively targets proliferation (down-regulation of Akt3) and metastasis (inhibition of EMT via TGF-β/Smad3 down-regulation) of cancer cells. Furthermore, miRNA-489 disrupts XIAP and SPIN1/PI3K/Akt signaling networks in sensitizing cancer cells to chemotherapy. These studies clearly demonstrate that miRNA-489 is a potential chemosensitizer and its overexpression is efficient in overcoming chemotherapy failure. Furthermore, chemically modification of miRNA-489 by removing Uracil and replacing it with 5-FU shows high efficacy in chemotherapy and triple-negative breast cancer suppression [202].

LncRNAs can function as upstream mediators of miRNA-489 in various cancers. To date, just oncogenic lncRNAs such as LINC00460, CHRF and LINC01133 have been identified that down-regulate expression of miRNA-489 in promoting proliferation and metastasis of cancer cells. Future studies can focus on revealing other oncogenic lncRNAs and discovering onco-suppressor lncRNAs with regulatory effect on miRNA-489. Interestingly, studies have examined how miRNA-489 affects proliferation and invasion of cancer cells. The inhibitory effect of miRNA-489 on proliferation of cancer cells is mediated via stimulation of apoptosis and suppressing Warbrug effect. In this way, molecular signaling pathways such as SIX1, GSE1 and Notch are affected. For inhibiting migration of cancer cells, miRNA-489 affects molecular pathway DLX1 and is correlated with better survival of patients with cancer. Although we discussed different molecular pathways as downstream targets of miRNA-489, we devoted two sections into describing relationship among miRNA-489, PI3K/Akt and Wnt/β-catenin signaling pathways. Notably, miRNA-489 as an onco-suppressor factor, interferes with proliferation and metastasis of cancer cells via down-regulation of PI3K/Akt and Wnt. Finally, it was revealed that miRNA-489 can be considered as potential diagnostic and prognostic factor in cancer. As it was mentioned earlier, miRNA-489 is a new emerging miRNA and there is still a long way in revealing its role in different cancers.

Declaration of competing interest

The authors declare no conflict of interest.

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