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Emerging Role of MicroRNAs in mTOR Signaling

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Abstract

Mechanistic target of rapamycin (mTOR) is a conserved serine/threonine kinase that plays a critical role in the control of cellular growth and metabolism. Hyperactivation of mTOR pathway is common in human cancers, driving uncontrolled proliferation. MicroRNA (miRNA) is a class of short noncoding RNAs that regulate the expression of a wide variety of genes. Deregulation of miRNAs is a hallmark of cancer. Recent studies have revealed interplays between miRNAs and the mTOR pathway during cancer development. Such interactions appear to provide a fine-tuning of various cellular functions and contribute qualitatively to the behavior of cancer. Here we provide an overview of current knowledge regarding the reciprocal relationship between miRNAs and mTOR pathway: regulation of mTOR signaling by miRNAs and control of miRNA biogenesis by mTOR. Further research in this area may prove important for the diagnosis and therapy of human cancer.

Keywords

mTOR; microRNA; cancer; cell signaling pathway; biomarker

Introduction

Mechanistic target of rapamycin (mTOR) is an evolutionarily conserved serine/threonine kinase belonging to the phosphoinositide 3-kinase (PI3K) related kinase family. It lies at the nexus of a regulatory network and integrates extracellular and intracellular events, coordinating processes in growth and proliferation (Summarized in Figure 1). mTOR forms

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two distinct complexes called mTOR complex 1 (mTORC1), which is composed of raptor, and binds to the FKBP12-rapamycin complex and is inhibited by rapamycin. On the other hand, mTOR complex 2 (mTORC2) contains rector but does not bind to FKBP12-rapamycin or is directly inhibited by rapamycin^[1].

mTORC1 couples signals from diverse nutritional and environmental cues to promote cellular growth and metabolism. It achieves this by promoting anabolic processes such as mRNA translation and transcription of genes involved in ribosome biogenesis and metabolism, or limiting catabolic processes such as autophagy. Rheb (Ras homology enriched in brain) is a Ras-related small GTPase. When present in the GTP-bound form, it acts as a potent activator mTORC1 for in its GTP-bound form, which is negatively regulated by its GAP, the tuberous sclerosis complex (TSC) heterodimer. TSC2 integrates diverse upstream signals through phosphorylation by kinases such as AKT, ERK and p38, which causes either activation or inhibition of mTORC1, depending on the specific serine/threonine residues^[2]. Proline-rich AKT substrate 40kDa (PRAS40) is a negative regulator of mTORC1 by preventing the binding of mTOR to its substrates. Both AKT and mTORC1 can phosphorylate PRAS40, which results in PRAS40 dissociation from mTORC1, enhancing mTORC1 activity. mTORC2 regulates cellular survival, cytoskeletal dynamics, ion transport and growth by phosphorylating and activating AGC kinase family members, including AKT, SGK1, and PKC^[3].

mTOR acts downstream of class IA PI3Ks in response to tyrosine kinase receptors. Class IA PI3Ks are heterodimeric proteins consisting of a p110 catalytic subunit associated with a p85, p55, or p50 regulatory subunit. The major regulatory subunit p85 α is a multi-functional component that has both positive and negative roles in PI3K regulation. As a positive regulator, p85 α participates in trafficking of p110 to the cell membrane as an initial step in the PI3K-AKT signaling cascade. As a negative regulator, p85 α mediates basal inhibition of the p110 subunit, to keep PI3K activity low under non-stimulatory conditions. Furthermore, monomeric p85 α competes with p85-p110 dimers for activated receptor binding^[4, 5]. Upon PI3K activation, PDK1 phosphorylates AKT at Thr-308 to expose the Ser-473 residue, and mTORC2 phosphorylates AKT at Ser-473 for its full activation^[6] (summarized in Figure 1). Diverse upstream growth factors and cytokines enhance the PI3K/AKT/mTOR pathway, including IGF-1^[7], VEGF^[8], c-Met^[9], and BDNF^[10]. mTOR pathway is antagonized by negative regulators such as PTEN^[11,12], GSK3 β ^[13], LKB1/AMPK^[14], p53^[15], DDIT4^[16], PDCD4^[17], and IKK β ^[18]. Aberrant mTOR signaling pathway is known to be involved in many disease states particularly cancer. Previous studies from several laboratories, including our own, have shown that hyperactive mTOR signaling represents one of the major mechanisms that promote the pathogenesis and therapeutic resistance of various solid tumors and hematological malignancies^[19, 20].

The discovery of microRNAs (miRs or miRNAs) has added another layer of complexity to the control of gene expression. miRs are a class of short (18–22 nucleotides) noncoding RNAs that regulate the expression of a wide variety of genes. Conservative estimate shows that approximately 60% of all human mRNAs are regulated by miRNAs, covering virtually all cellular functions. Through base pairing with the 3'-untranslated region (3'UTR) of target genes, miRNAs were found to enhance mRNA degradation or inhibit

posttranscriptional translation^[21]. At least 50% of miRNA genes are located in cancer-associated genomic regions or in fragile sites and are aberrantly expressed in cancer, suggesting that these miRNAs have an important role in the pathogenesis of cancers. Overall, cancer is characterized by many up-regulated and repressed miRNAs, potentially exerting oncogenic and tumor-suppressive functions, respectively. While a subset of these miRNAs are overexpressed in cancers and shown to target tumor suppressor genes, hence termed oncogenic miRNAs or oncomiRs, some other miRNAs that target oncogenes are underexpressed in cancers, which are often called tumor-suppressor-like miRNAs. Certain miRNAs are known to have a dual role, either oncogenic or tumor-suppressive, depending on the cancer-specific context^[22].

Accumulating evidence indicates that miRNAs contribute to tumorigenesis and cancer metastasis by targeting different steps of mTOR pathway. While some miRNAs target mTOR directly, others act on mTOR signaling by targeting other components of the pathway such as PI3K and AKT. A comprehensive list of miRNAs targeting mTOR pathway is listed (Table 1). Much like mTOR, miRNAs regulate broad cellular functions, including proliferation, differentiation, apoptosis, and autophagy. This review intends to provide an overview of current knowledge regarding the miRNA profiles that intercept mTOR pathway, with special emphasis on the regulatory mechanism of miRNAs for mTOR signaling and the link between mTOR and miRNA biogenesis. A detailed understanding of their relationship has implications in cancer diagnosis, therapy and prognosis.

miRNAs that suppress upstream of mTOR pathway

There is a large number of miRNAs acting to oppose mTOR signaling. For instance, cancer development often associates with increased mTOR activity^[23], but with a loss of many miRNAs targeting this pathway^[24]. In particular, mTOR and miRNAs play opposite roles in regulating protein translation and mRNA stability, raising the possibility of close relationship between them^[25] (summarized in Figure 2).

miR-7

Mature miRNA-7 (miR-7) is derived from three miRNA precursors in human genome, miR-7-1 (9q21.32), miR-7-2 (15q26.1) and miR-7-3 (19p13.3). It has been implicated as tumor suppressor in multiple cancer types. miR-7 suppresses glioblastoma partially by directly inhibiting IRS-2 expression and subsequent AKT-mTOR signaling^[26]. In adrenocortical carcinomas, systemic delivery of miR-7 by nanoparticle delivery reduces growth of both cell line- and patient derived xenograft tumors^[27]. In hepatocellular carcinoma, miR-7 was shown to inhibit tumorigenesis and metastasis of HCC through direct targeting PIK3CD (encoding PI3K catalytic subunit p110 δ), mTOR and p70S6K^[28].

miR-99 family

The miR-99 family, consisting of miR-99a (21q21.1), miR-99b (19q13.41) and miR-100 (11q24.1), is one of the most ancient miRNA families. It plays a critical role in developmental timing and maintenance of tissue identity. Recent studies suggest that miR-99 also regulates various physiological processes in adult tissues, such as dermal wound

healing, and a number of disease processes, including viral infection and cancer^[29]. For example, miR-100 has been shown to inhibit human cytomegalovirus (HCMV) replication by targeting both mTOR and raptor during HCMV infection^[30]. miR-99 has been reported to be a tumor suppressor whose expression is frequently lost or reduced in various human cancers. Deregulation of the miR-99 family contributes to tumorigenesis at least partially, by direct and indirect targeting at multiple points in mTOR signaling pathway. In some cancer types, including metastatic CRC^[31], esophageal squamous cell carcinoma (ESCC)^[32, 33], clear cell ovarian cancer^[34], cervical cancer^[35], breast cancer^[36], prostate cancer^[12, 37], bladder cancer^[38], childhood adrenocortical tumor^[39], osteosarcoma^[40] and c-Src-transformed cells^[41], miR-99 family members suppress mTOR expression via direct targeting of its 3'-UTR in a post-transcriptional manner. Ectopic overexpression of miR-99 family members in these cancers reduces cell proliferation and migration, induces apoptosis and enhance sensitivity to the rapamycin analog RAD001 (everolimus). In some cancers, the miR-99 family regulates mTOR signaling by simultaneously targeting multiple genes. In HNSCC^[42] and HCC cells^[43], restoration of miR-99a and miR-100 reduce cell proliferation and migration, induce G1 cell cycle arrest and apoptosis by dual suppression of IGF1R and mTOR. In endometrial carcinoma^[44], NSCLC^[45] and cervical cancer^[35], miR-99a was reported to inhibit two major members of the PI3K/AKT/mTOR signaling pathway, AKT and mTOR. Loss of miR-99a appears to at least partially mediate hyperactivation of PI3K/AKT/mTOR signaling through AKT and mTOR, thereby inducing tumor initiation and progression. Restoration of miR-99a in these cancer cells induces a complex phenotype including blockage of the G1/S phase transition, induction of cell apoptosis, and suppression of cell proliferation, invasion and tumor metastasis.

miR-101

miR-101 (1p31.3 for miR-101-1, 9p24.1 for miR-101-2), is down-regulated in several cancer cell lines and cancer tissues. Studies have shown that miR-101 functions as a tumor suppressor that is associated with the growth and apoptosis of various human cancers^[46]. mTOR gene is a direct target of miR-101 and plays an important role in mediating miR-101's effects in cancer. Overexpression of miR-101 significantly decreases mTOR expression at both mRNA and protein levels in osteosarcoma cells, resulting in cell proliferation inhibition and apoptosis^[47]. miR-101 is down-regulated in anaplastic large-cell lymphoma (ALCL). Ectopic expression of miR-101 attenuates cell proliferation in anaplastic lymphoma kinase (ALK) positive ALCL through direct repression of mTOR^[48].

miR-122

miR-122 (18q21.31) expression is restricted to the liver. Reduced miR-122 level was first noticed to be associated with primary HCC^[49], and the c-Met/AKT/mTOR cascade axis seems to be involved in miR-122's functional mechanism^[50]. A recent study showed that miR-122 is a tumor suppressor in breast cancer, and overexpression of miR-122 inhibits BC cell growth both in vitro and in vivo. miR-122 regulates BC cell proliferation through the PI3K/AKT/mTOR signaling pathway, by concurrently targeting at least two major signaling molecules upstream of mTOR signaling, IGF1R and PI3CG (encoding PI3K catalytic subunit p110 γ)^[7].

miR-126

miR-126 (9q34.3), encoded by intron 7 of the epidermal growth factor-like domain 7 (*egfl7*) gene, plays an essential role in vascular integrity and angiogenesis. Recent results on the distribution and function of miR-126 indicate that it acts as a tumor suppressor through modulation of signaling pathways that control tumor cell proliferation, migration, invasion, and survival^[51]. In colorectal cancer (CRC), miR-126 target sites in the promoter of p85 β , a PI3K subunit that stabilizes and propagates PI3K signal, which is involved in the carcinogenesis of CRC^[52, 53]. miR-126 is frequently lost in CRC, whereas p85 β is commonly overexpressed, resulting in the hyperactivation of the downstream AKT/mTOR pathway. In gastric cancer, miR-126 regulates AKT/mTOR pathway by targeting VEGF-A. Downregulation of miR-126 expression increases the expression of VEGF-A and its downstream mTOR signaling. In contrast, restoration of miR-126 expression reduces the expression of VEGF-A and suppresses the activation of its downstream AKT and mTOR^[54].

miR-149

miR-149-3p (miR-149*) and miR-149-5p are processed from the 3-arm and 5-arm ends of pre-miRNA149 (2q37.3), respectively; miR-149-5p is the most abundant form. The role of miR-149-5p/miR149-3p in cancer progression is controversial and varies in different types of tumors, functioning as either a tumor suppressor or an oncogene^[55]. In some tumors, miR-149-5p/miR149-3p expression is downregulated and acts as a tumor suppressor by inhibiting mTOR signaling. miR-149-5p/miR149-3p induces apoptosis, and inhibits proliferation and invasion in Be2C, HeLa, glioma and HCC cells by directly targeting AKT1 and subsequently inhibiting the downstream signaling events^[56, 57]. Low miR-149 expression is associated with enhanced AKT/mTOR signaling in glioma and HCC tissues, and predicts tumor aggressiveness and unfavorable prognosis^[58]. Reintroduction of miR-149 significantly inhibited HCC cell proliferation and tumorigenicity by regulating the AKT/mTOR pathway^[59]. Because the sequences of miR-149-5p and miR-149-3p are different, it will be important to further characterize their unique roles in this context.

miR-155

miR-155 (21q21.3) is involved in various physiological and pathological processes, including malignant growth, viral infections, and cardiovascular diseases^[60]. It has been shown to target multiple aspects of mTOR pathway. miR-155 inhibits mTORC1 signaling through suppression of Rheb in macrophages, thus promoting autophagy to eliminate intracellular mycobacteria^[61]. miR-155 also interferes with mTORC2 signaling by targeting Rictor and TSC1 in the estrogen receptor (ER) α^+ breast cancer cells, which controls ER function and renders RAD001 sensitivity^[62]. In human nasopharyngeal cancer and cervical cancer cells, miR-155 targets multiple players in mTOR pathway, including Rheb, Rictor, and RPS6KB2 (encoding P70S6K2), by directly interacting with their 3'-UTRs. By downregulating mTOR signaling, miR-155 acts as a potent inducer of hypoxia-induced autophagy, attenuates cell proliferation, and induces G1/S cell cycle arrest in nasopharyngeal cancer and cervical cancer cells^[63].

miR-193a-5p

The miR-193a gene is mapped to chromosome 17q11.2. It has been reported to negatively regulate mTOR pathway. miR-193a-5p functions as a tumor suppressor and has an important role in NSCLC metastasis through the PI3K/AKT/mTOR pathway. PIK3R3 (encoding PI3K regulatory subunit p55 γ and p50 γ) and mTOR were found to be direct targets of miR-193a-5p in NSCLC. Decreased miR-193a-5p expression is significantly associated with NSCLC tumor-node-metastasis (TNM) stage and lymph node metastasis. Reintroduction of miR-193a-5p inhibits NSCLC cell migration, invasion, epithelial-mesenchymal transition (EMT) in vitro and lung metastasis formation in vivo^[64].

miR-199a-3p

miR-199a-3p (1q24.3), a member of the miR-199 family, is located on the opposite strand of the orthologous intron of Dynamin genes (Dnm3os). The downregulation of miR-199a-3p occurs in various malignancies, and is accompanied by enhanced activity of the mTOR signaling pathway. MiR-199a-3p inhibits mTOR signaling through direct binding of the 3'UTR of mTOR. Restoration of miR-199a-3p leads to downregulation of mTOR and p-mTOR and increases cell populations at the G1-phase, resulting in restrained cellular growth, proliferation and migration in endometrial endometrioid adenocarcinomas^[65], glioma cells^[66], and osteosarcoma cells^[67]. In HCC cells, restoration of miR-199a-3p results in arresting G1-phase cell cycle and increasing sensitivity to doxorubicin-induced apoptosis^[68].

miR-204

miR-204 (9q21.12), also known as RDICC, has been reported to play important roles in smooth muscle cell calcification as well as the endoplasmic reticulum stress response in trabecular meshwork cells^[69, 70]. Recent reports have shown that genomic loci encoding miR-204 are frequently lost in ovarian cancers, pediatric renal tumors, breast cancers, peripheral nerve sheath tumors, endometrial cancer cell lines, papillary thyroid carcinomas, gastric cancers and CRCs, suggesting that it is potentially a tumor suppressor^[71]. The BDNF (Brain-derived neurotrophic factor)/AKT/mTOR/Rac1 signaling cascade is a major target of miR-204. Genomic loss of miR-204 results in BDNF/TrkB (tyrosine kinase receptor of BDNF) overexpression, promoting BDNF-induced cancer cell migration and invasion by activating AKT/mTOR signaling, leading to Rac1 translocation and act in reorganization^[10].

miR-214

miR-214 (1q24.3) is encoded by Dnm3os, the same gene that also encodes miR-199a-3p. miR-214 is often dysregulated in various cancers and its functions vary considerably, depending on the tissue types^[72]. IGF-1R is a direct target of miR-214 and reduced miR-214 expression contributes to increased IGF-1R levels in renal cancer cells. Increased IGF-1/IGF-1R level in turn results in phosphorylation and inactivation of PRAS40 in an AKT-dependent manner, leading to activation of mTORC1 signal transduction to increase phosphorylation of S6 kinase and 4E-BP1. Reintroduction of miR-214 significantly inhibits the AKT/PRAS40/mTORC1 axis in the IGF-1R signaling cascade, which dampens renal cancer cell proliferation^[73].

miR-218

Two distinct genes, miR-218-1 (4p15.31) and miR-218-2 (5q34), encode the same mature miR-218 sequence. miR-218 acts as a tumor suppressor and was found to play a pivotal role in tumorigenesis and progression^[74]. miR-218 inhibits the invasion and migration of CRC cells through regulation of PI3K/AKT/mTOR signaling by targeting PIK3C2A (encoding PI3K C2 subunit α) and PIK3R1 (encoding PI3K regulatory subunit p85 α)^[75]. PI3K/AKT/mTOR signaling is also involved in miR-218 suppression of ESCC growth and miR-218 enhancement of the chemosensitivity of ESCC cells to cisplatin^[76]. In cervical cancer^[77] and oral squamous cell carcinoma (OSCC)^[78], miR-218 targets Rictor, which directly regulates the phosphorylation of AKT at Ser-473 independently of the PI3K-AKT signaling pathway. Silencing of miR-218 and activation of mTORC2-AKT signaling is an important mechanism of carcinogenesis and cancer progression in OSCC. Ectopic expression of miR-218 reduces OSCC and cervical cancer cell growth in vitro and in vivo, and increases the chemosensitivity of cervical cancer to cisplatin.

miRNAs that activate mTOR pathway

Besides the miRNAs mentioned above that act as tumor suppressors by targeting mTOR and/or positive regulators upstream of mTOR signaling pathway, some other miRNAs are always overexpressed in cancers and are able to promote the development and/or progression of tumors by stimulating the mTOR signaling pathway. These are termed oncogenic miRNAs, or oncomiRs. Molecules that suppress mTOR pathway are always targeted by these oncomiRs (summarized in Figure 3).

miR-21

miR-21 (17q23.2) is overexpressed under many pathological conditions, including many types of cancers^[79]. Overexpression of miR-21 is correlated with enhanced cancer cell proliferation and survival, reduced apoptosis and autophagy, poor differentiation, lymph node metastasis, advanced TNM stage and unfavorable clinical outcomes. As an oncomiR, miR-21 affects major events of tumor development and progression. In particular, miR-21 targets multiple genes in mTOR pathway, including PTEN, p85 α and PDCD4. Besides promoting malignant growth, the miR-21/PTEN/PI3K/AKT/mTOR axis has been shown to influence anti-cancer effects of zoledronic acid^[80], triptolide^[81], Metformin^[82], Matrine^[83] and curcumin^[84], and modulate radiosensitivity^[85, 86] and chemosensitivity to tamoxifen, fulvestrant^[87], sorafenib^[88], cisplatin^[89, 90], imatinib^[91], gefitinib^[92], doxorubicin^[93], daunorubicin^[94], anti-EGFR tyrosine kinase inhibitors (TKI)^[95] and the CHOP chemotherapy regimen^[96]. miR-21 also influences PI3K/AKT/mTOR signaling via PIK3R1 that negatively regulates p110 subunit under certain circumstances. This miR-21/PI3K/AKT/mTOR axis has been shown to affect chemosensitivity of pancreatic ductal adenocarcinomas to gemcitabine^[97], modulate tumor cell migration, invasion, EMT and predict clinical outcomes of breast cancer^[98]. PDCD4 levels are decreased as a result of direct targeting of its 3'-UTR by miR-21, which regulates AKT and IKK β activation and contributes to activation of mTORC1 signaling. Furthermore, overexpression of miR-21 decreases the association between PDCD4 and Rictor, thereby stimulating mTORC2 signaling and

subsequently AKT activity. Both mechanisms enhance renal cancer cell migration and invasion, contributing to metastatic fitness of renal cancer cells^[17, 99].

miR-93

miR-93 (7q22.1) is encoded within the minichromosome maintenance 7 (MCM7) gene. As an oncomiR, miR-93 is overexpressed and contributes to the pathogenesis of osteosarcomas, ovarian cancers, breast cancers and others. PTEN is a putative target of miR-93. By directly targeting PTEN in osteosarcoma^[100], gliomas^[101] and HCC^[102], miR-93 promotes cancer cell proliferation, migration and invasion, while inhibiting apoptosis. In ovarian cancer^[11, 103] and HCC^[102], miR-93 is known to affect cisplatin and 5-FU chemosensitivity through suppression of PTEN expression.

miR-96

miR-96(7q32.2) is processed from a conserved polycistronic transcript. miR-96 functions as an oncomiR by promoting cellular growth, invasiveness and metastasis in breast cancer^[104], pancreatic cancer^[105] and HCC^[106]. miR-96 directly targets AKT1S1 that encodes for PRAS40, a negative regulator of mTOR kinase, which prevents the binding of mTOR to its substrates^[107]. miR-96 upregulation in prostate cancer cells has also been shown to lead to the downregulation of the AKT1S1, thereby unleashing mTOR signaling to promote prostate bone metastasis^[108].

miR-125b

MiR-125b belongs to the miR-125 family, and is transcribed from two loci located on chromosomes 11q23 and 21q21. It acts as an oncogene in several cancer types^[109]. MiR-125b is known to directly target the p53 tumor suppressor gene, which negatively regulates the expression of *PI3KCA* (encoding PI3Kcatalytic subunit p110 α). Elevated miR-125b expression leads to upregulation of *PI3KCA* and constitutive activation of PI3K/AKT/mTOR pathway and thus pathophysiology of cancer^[110, 111]. The miR-125b/PI3K/AKT/mTOR axis contributes to confer resistance to anastrozole and letrozole in breast cancer cells^[112].

miR-193-3p

miR-193-3p plays a critical role in regulating human gastric cancer through direct targeting of PTEN, which activates mTOR signaling. Downregulation of miR-193-3p inhibits tumor proliferation, migration and chemoresistance in human gastric cancer, by up-regulating the PTEN gene^[113].

miR-221

miR-221 (Xp11.3) overexpression has been observed in a number of advanced malignancies, including pancreatic cancer, thyroid papillary carcinomas, breast cancers, glioblastomas, HCCs and lung cancers^[114]. miR-221 directly targets DNA damage-inducible transcript 4 (DDIT4), which is an essential negative regulator of mTOR kinase through stimulation of the tuberous sclerosis tumor suppressor TSC1/2 complex^[115]. In this fashion, the miR-221/DDIT4/TSC/mTOR axis contributes to HCC cell proliferation and tumor development^[116].

miR-451

miR-451 is located on chromosome 17q11.2, which is in close proximity to ERBB2 (17q12), a region frequently amplified in human cancer^[116, 117]. miR-451 has attracted increasing attention due to its critical role in several types of cancers. In multiple myeloma, miR-451 regulates stemness of side population cells via the PI3K/AKT/mTOR signaling pathway, by specifically targeting TSC1, the upstream negative regulator of mTORC1. Inhibition of miR-451 potentiated the anti-myeloma effect by increasing apoptosis, and decreasing clonogenicity and MDR1 mRNA expression^[118]. In CRC cells, overexpression of miR-451 inhibits AMPK activation, causing mTORC1 hyper-activation, and hence enhanced migration and proliferation of cancer cells^[119]. In glioma cells, miR-451 regulates LKB1/AMPK/mTOR signaling through direct targeting of CAB39, a component of the active LKB1 complex, which acts as a conditional switch controlling glioma cell proliferation and migration. Under conditions of abundant energy, miR-451 expression is high, which suppresses LKB1/AMPK signaling that allows cells to maintain elevated proliferation via unrestrained mTOR signaling. In contrast, under conditions of glucose limitation, miR-451 is downregulated, leading to AMPK activation and suppression of cell proliferation as well as increase in cell survival and migration. This miR-451/LKB1/AMPK/mTOR axis may represent a common mechanism that controls cellular adaptation to glucose availability^[120].

Regulation of miRNA expression by mTOR pathway

Although the biological importance of miRNAs has been well recognized a decade ago, the regulatory mechanism for miRNA expression remains elusive. Previous studies have largely focused on individual miRNAs that regulate mTOR pathway. However, whether and how mTOR regulates miRNA biogenesis is not well understood. It has been shown in cancer cells that chronic rapamycin treatment leads to significant alterations in miRNA profiles, and these changes correlate with rapamycin resistance^[121]. Inactivation of TSC complex, an essential repressor of mTOR activation, also causes broad down-regulation of precursor and mature microRNA processing in mouse and human cells. Consistently, targeted mutation of Raptor, an essential component of mTORC1, increases miRNA biogenesis^[25]. It has been shown that mTOR activation broadly downregulates miRNA biogenesis through Mdm2-dependent ubiquitinylation of Drosha, an essential RNase dedicated to processing primary miRNA (pri-miRNA) to produce precursor miRNA (pre-miRNA)^[25]. These studies provide a missing link between mTOR and miRNA biogenesis, and given the broad function of miRNAs, these data raise the intriguing possibility that a significant portion of mTOR function may act through its ability to control miRNA biogenesis. Recently, several individual miRNAs have been confirmed to be regulated by mTOR signaling, including miR-21, miR-143, miR-125b and miR-1, which are known to be involved in cancer and other physiological conditions (summarized in Figure 4).

miR-21

Positive feedback has evolved between miR-21 and mTOR signaling. While miR-21 targets multiple genes in the mTOR signaling pathway as discussed above, miR-21 expression is modulated by mTOR and Stat3 in spontaneous tumors. The upregulated miR-21 level in

cancer is decreased by mTOR or Stat3 inhibitors. Active mTOR and Stat3 signaling has been shown to augment miR-21 expression, conferring increased aggressiveness and metastatic properties to tumor keratinocytes, both in vitro and in vivo^[15].

miR-143

miR-143 (5q32) is encoded by a fragile site of chromosome 5, which is frequently deleted in various types of cancers. miR-143 is downregulated following mTOR activation, via an unknown mechanism. mTOR-miR-143 signaling is known to regulate cancer glycolysis by targeting hexokinase 2 (HK2), an enzyme that phosphorylates glucose to produce glucose-6-phosphate, the first step in glucose metabolism pathway. The mTOR-miR-143/HK2 axis has been shown to enhance cancer cell proliferation and tumor formation by promoting glucose metabolism in human lung cancer^[122].

Conclusions and Future Perspectives

miRNAs have been clearly demonstrated to have close relationships with mTOR signaling pathway. Current evidence shows that the interactions between miRNAs and mTOR signaling occur in most cancer types. In addition, their interaction has been reported in many other diseases and physiological conditions. For instances, mTORC1 was shown to regulate miR-125b and miR-1 biogenesis, which is a mechanism to govern skeletal myogenesis^[123, 124]. The Let-7/mTOR axis is known to regulate glucose metabolism^[125], neurodegenerative diseases^[126] and organ regeneration^[127]. Let-7 was found to coordinately suppress components of an amino acid sensing pathway to repress mTORC1 and induce autophagy^[128]. These findings suggest that miRNA interaction with the mTOR signaling pathway is a general mechanism involved in broad biological processes in eukaryotes.

Dysregulation of miRNAs is a key characteristic of cancer. Expression profiling of miRNAs has been extensively used to understand the development, invasion and progression in different types of cancers. By targeting mTOR signaling, miRNA interferes with many different cellular processes and according to the cellular context, acts as a tumor suppressor or oncogene, to promote uncontrolled growth, metabolism and metastasis. Because mTOR is a validated therapeutic target for cancer, targeting miRNAs may provide a novel approach to facilitate an integrated anti-cancer therapy. Two therapeutic strategies may be used: inhibition or replacement. Through the delivery of antagomiRs to silence endogenous oncomiRs, or via the ectopic replacement of tumor suppressive miRNAs by delivery primary miRNA or miRNA synthetic mimics to restore miRNA levels in cancer cells and tissues, it is possible to achieve blockage of key mTOR signaling event that drives oncogenesis^[129].

To date, a large body of evidence demonstrates that miRNA expression correlates well with various aspects of pathological features of human cancer. Therefore, miRNAs are also promising biomarkers for cancer diagnosis and prognosis, as well as predictive biomarkers for therapeutic response. Compared with other molecular markers such as proteins, miRNAs, particularly when used as signatures, can provide unparalleled accuracy and sensitivity. Moreover, circulating miRNAs may be captured for liquid biopsy. Moreover, the specificity and sensitivity may be further improved by combining miRNAs with key protein molecules in mTOR signaling pathway. For instance, osteosarcoma patients with miR-99a-

high/mTOR-low expression have better outcomes, while the miR-99a-low/mTOR-high patients have worse outcomes. The miR-99a-low/mTOR-high co-expression may be used as an independent prognostic indicator for osteosarcoma^[40]. As several clinical investigations are ongoing, there is a great expectation for the power of integrating miRNAs with cancer signaling cascades to fulfill clinical needs.

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Abbreviations

AMPK	Adenosine 5'-monophosphate-activated protein kinase
BDNF	Brain-derived neurotrophic factor
DDIT4	DNA damage-inducible transcript 4
4E-BP1	eIF4E-binding protein 1
IGF-1/IGF1R	insulin-like growth factor 1/insulin-like growth factor 1 receptor
IKKβ	I κ B kinase β
IRS	insulin receptor substrate
LKB1	Liver kinase B1
microRNA	miRNA
mTOR	mechanistic/mammalian target of rapamycin
mTORC1/2	mTOR complex 1/2
p70S6K	70kDa ribosomal protein S6 kinase
PDCD4	Programmed cell death 4
PI3K	phosphoinositide 3-kinase
PRAS40	Proline-rich AKT substrate 40kDa
PTEN	phosphatase and tensin homolog
Rheb	Ras homology enriched in brain
Stat3	signal transducer and activator of transcription 3
TSC1/2	tuberous sclerosis 1/2
VEGF	Vascular Endothelial Growth Factor

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Fig. 1. PI3K/AKT/mTOR signaling pathway

mTOR pathway integrates signals from growth factors and nutrients to regulate diverse cellular processes, including translation, autophagy and transcription of genes involved in ribosome biogenesis and metabolism.

Fig. 2. Tumor-suppressive miRNAs that inhibit mTOR pathway

A large number of miRNAs display tumor suppressive activity by directly targeting mTOR and/or upstream positive regulators of mTOR.

Fig. 3. Oncogenic miRNAs that activate mTOR pathway

Many oncogenic miRNAs are overexpressed in human cancers that promote the development and/or progression of tumors by stimulating mTOR signaling through down-regulation of negative regulators of mTOR.

Fig. 4. mTOR pathway controls expression of miRNAs

mTOR broadly regulates miRNA biogenesis in mammals through Mdm2-dependent ubiquitination and degradation of Drosha.

Table 1

miRNAs target different steps of mTOR signaling pathway

Component	Direct Target	miRNA	Cancer Types	Function
PTEN	PTEN	miR-21	1.Breast cancer 2.NSCLC 3.RCC 4.CML 5.HCC 6.Gastric cancer 7.ALL(Ph+) 8.DLBCL	Oncogenic
		miR-93	1.Osteosarcoma 2.Ovarian cancer 3.Breast cancer 4.Glioma 5.HCC	Oncogenic
		miR-193a-3p	1.Gastric cancer	Oncogenic
PI3K	IGF/IGFR	miR-99	1.HNSCC 2.HCC	Tumor-suppressive
		miR-122	1.Breast cancer	Tumor-suppressive
		miR-214	1.RCC	Tumor-suppressive
	IRS	miR-7	1.Glioblastoma 2.Adrenocortical carcinoma	Tumor-suppressive
	BDNF	miR-204	1.Ovarian cancer 2.Pediatric renal tumor 3.Peripheral nerve sheath tumor 4.CRC 5.Breast cancer 6.Endometrial cancer 7.Papillary thyroid carcinoma 8.Gastric cancer	Tumor-suppressive
	VEGF	miR-126	1.Gastric cancer	Tumor-suppressive
	c-Met	miR-122	1.HCC	Tumor-suppressive
	PDCD 4	miR-21	1.Renal cancer	Oncogenic
	P53	miR-125b	1.Breast cancer	Oncogenic
	PI3K	miR-7	1.HCC 2.Adrenocortical carcinoma	Tumor-suppressive
		miR-21	1.Pancreatic ductal adenocarcinoma 2.Breast cancer	Oncogenic
		miR-122	1.Breast cancer	Tumor-suppressive
		miR-126	1.CRC	Tumor-suppressive
		miR-193a-5p	1.NSCLC	Tumor-suppressive
		miR-218	1.CRC 2.ESCC	Tumor-suppressive
AKT	AKT	miR-99	1.Endometrial carcinoma 2.NSCLC 3.Cervical cancer	Tumor-suppressive
		miR-149	1.Neuroblastoma 2.Cervical cancer 3.Glioma 4.HCC	Tumor-suppressive
TSC1	PDCD 4	miR-21	1.Renal cancer 2. NSCLC	Tumor-suppressive
	TSC1	miR-155	1.Breast cancer	Tumor-suppressive
		miR-451	1.Multiple myeloma	Oncogenic
TSC2	DDIT 4	miR-221	1.Pancreatic cancer 2.Thyroid papillary carcinoma 3.Breast cancer 4.Glioblastoma 5.NSCLC 6.SCLC 7.HCC	Oncogenic
	CAB3 9	miR-451	1.Glioma	Oncogenic
	AMP K	miR-451	1.CRC	Oncogenic
Rheb	Rheb	miR-155	1.Nasopharyngeal cancer 2.Cervical cancer	Tumor-suppressive
mTORC1/mTORC2	PRAS 40	miR-96	1.Breast cancer 2.Pancreatic cancer 3.Prostate cancer 4.HCC	Oncogenic
	mTOR	miR-7	1.HCC 2.Adrenocortical carcinoma	Tumor-suppressive
		miR-99	1.Metastatic CRC 2.Clear cell ovarian cancer 3.Cervical cancer 4.Breast cancer 5.Prostate cancer 6.HCC 7.ESCC 8.Childhood adrenocortical tumor 9.Osteosarcoma 10.Endometrial carcinoma 11.NSCLC 12.HNSCC 13.Bladder cancer	Tumor-suppressive
		miR-101	1.Osteosarcoma 2.Anaplastic large-cell lymphoma	Tumor-suppressive

Component	Direct Target	miRNA	Cancer Types	Function
	Rictor	miR-193a-5p	1.NSCLC	Tumor-suppressive
		miR-199a	1.Endometrioid adenocarcinoma 2.Glioma 3.Osteosarcoma 4.HCC	Tumor-suppressive
		miR-155	1.Nasopharyngeal cancer 2.Cervical cancer 3.Breast cancer	Tumor-suppressive
		miR-218	1. Cervical cancer 2. OSCC	Tumor-suppressive
S6K1	S6K1	miR-7	1.HCC 2.Adrenocortical carcinoma	Tumor-suppressive
		miR-155	1.Nasopharyngeal cancer 2.Cervical cancer	Tumor-suppressive

Abbreviations: NSCLC(Non-small-cell lung cancer), RCC(Renal cell carcinoma), CML(Chronic myeloblastic leukemia) HCC(Hepatic cellular cancer), ALL(Acute lymphoblastic leukemia), Ph+(Philadelphia chromosome positive), DLBCL(Diffuse large B-cell lymphoma), HNSCC (Head and neck squamous cell carcinoma), CRC (Colorectal cancer), ESCC(Esophageal squamous cell carcinoma), SCLC(Small cell lung cancer),OSCC(Oral squamous cell carcinoma)