

Review Article

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Running Title: miRNAs and Autophagy Contribute to Metastasis

MicroRNAs Contribute to Metastasis by Regulating Autophagy: Recent Concepts

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Abstract

Autophagy means self-eating and is the degradation process of cellular proteins and organelles. In cancers, autophagy has a conflicting function. While it acts as a tumor suppressor by inhibiting the accumulation of damaged organelles and proteins, it functions as an oncogene and accelerates tumor progression.

The related articles in the limited period of time of 2005 to mid-2020 were reviewed through searching PubMed, Google Scholar, and Scopus database. A total of 100 articles met all the selection criteria. The articles published in the last two decades related to the role of miRNAs in regulating autophagy and metastases were selected.

Both miRNAs and autophagy involve in different signaling pathways that are activated in cancers. MicroRNAs and autophagy are critical factors for prediction of prognosis in cancer patients. Significant advancement has been achieved over the last decades. The development in therapeutic strategies has improved the survival rate of cancer patients.

Metastasis is a multistep process; therefore, new detection biomarkers and treatment strategies are needed.

Keywords: Autophagy, Metastasis, MicroRNAs, Neoplasm, Therapy

Introduction

Cancer is believed to be a global problem that continues to demand action. Each year, several people are diagnosed with cancer around the world. In 2017, there were 24.5 million cancer cases worldwide and 9.6 million cancer deaths.¹ Cancer cells

have the ability to migrate and spread into nearby normal tissues, lymph nodes, and distant parts of the body. Metastasis is the main cause of cancer-related death around the world; therefore, identification of metastasis-associated biomarkers and

therapeutic targets would help to improve the prognosis.²

Autophagy means self-eating and is the degradation process of cellular proteins and organelles. The cells utilize this process in stress conditions. Autophagy facilitates the adaptation of cells to environmental or developmental changes and is a protective intracellular procedure.³ On the other hand, autophagy has a great impact on cancer development.⁴ During autophagy, a double-membrane autophagosome is formed to degrade damaged organelles and unfolded proteins. Autophagosome formation is regulated by autophagy-related genes (ATGs), such as ATG12, ATG5, and microtubule-associated protein light chain 3 (LC3).^{3,5} In cancers, autophagy has a conflicting function. While it acts as a tumor suppressor by inhibiting the accumulation of damaged organelles and proteins, it functions as an oncogene and accelerates tumor progression. Autophagy can also protect cancer cells from unpleasant conditions, for instance, chemotherapy or radiotherapy.⁶ In the early stages of cancer, autophagy helps the establishment of chromosomes and genomes, reduction of protein synthesis, and increasing protein degradation, which result in the inhibition of cancer cell proliferation and tumor growth.⁷ Later, it promotes tumor growth.⁵ Autophagy has been reported to be involved in modulating tumor cell motility and invasion, differentiation, and tumor cell escape from immune surveillance.⁸ Moreover, autophagy is a critical player for establishing the pre-metastatic niche and metastasis via induction of epithelial-mesenchymal transition (EMT) phenomenon.⁹ Several onco-proteins and onco-suppressors are involved in autophagy process.¹⁰ The expression of ATGs is a promising tool for prediction of cancer outcome. For example, in oral squamous cell carcinoma, autophagic markers, such as

LC3A and LC3B, are associated with poor prognosis and tumor recurrence.¹¹ Induction of autophagy could affect the therapeutic efficacy of drugs or chemoresistance; hence, it could be considered as a promising therapeutic target for cancers.⁶

MicroRNAs (miRNAs) are endogenous small non-coding RNAs which are involved in the modulation of various genes in the post-transcriptional level via interacting with the 3' untranslated region (3' UTR) of the target mRNAs. In cancers, miRNAs play essential roles in cancer cell proliferation, differentiation, apoptosis, survival, motility, invasion, and metastasis.^{12,13} The function of MicroRNAs as tumor suppressors or oncogenes depends on their target genes and differ between cancer types. Given that, miRNAs also regulate autophagy^{14,15} via their effects on different autophagy regulatory proteins which act at various stages of the pathway, such as induction, vesicle nucleation, vesicle elongation, retrieval, and fusion.¹⁶ miRNAs play a double role in autophagy regulation, including anti-autophagy and pro-autophagy roles.¹⁷ They change the levels of numerous proteins involved in the autophagy pathway, from upstream signaling pathways to later stages of autolysosomal degradation.¹⁶ Autophagy regulating miRNAs are able to decrease the expression of autophagy-related genes (ATGs), Beclin-1, LC3-phosphatidylethanolamine conjugate (LC3-II), and Sequestosome-1 (SQSTM1).¹⁸ For instance, in pancreatic cancer, miR-29a acts as a potent autophagy inhibitor by blocking autophagy through the accumulation of autophagosomes and autophagy markers, LC3B and p62. Additionally, miR-29a decreases the expression of autophagy proteins, such as ATG9A and TFEB, which are essential for autophagosome trafficking and lysosomal function, respectively.¹⁹ miR-214 regulates ATG12-mediated autophagy in colorectal cancer.²⁰ A better

understanding of the role of miRNAs and autophagy in cancer metastasis would help the development of new markers and therapeutic strategies. We conducted the present review to provide updated knowledge about the role of miRNAs and autophagy in cancer metastasis.

Methods

Search Methods

The literature search was conducted through PubMed, Scopus database, and Google Scholar. The studies published since 2005 to mid-2019, with full text available, were considered for inclusion.

Quality Assessment of Articles

For further evaluation, research articles describing the contribution of miRNAs in the metastasis by controlling the autophagy were selected. Only the articles that fulfilled the selection criteria were included, read, and assessed in the present study.

Results

miRNAs, autophagy and angiogenesis

Angiogenesis plays a crucial role in cancer growth and distant metastasis. On the other hand, autophagy and miRNAs have essential roles in angiogenesis and metastasis. Several miRNAs regulate autophagy and angiogenesis. For example, miR-195 stimulates autophagy in endothelial progenitor cells by targeting the autophagy protein GABARAPL1.²¹ Decreased expression of miR-195 promotes angiogenesis and metastasis in hepatocellular carcinoma (HCC) via vascular endothelial growth factor (VEGF), the most potent angiogenic factor.²² Furthermore, lower expression of miRNA-199a-3p in HCC contributes to suppression of angiogenesis and lung metastasis by targeting VEGF-A.²³ Autophagy enables tumor cells to survive under stress conditions, such as hypoxia,²⁴ and in return,

hypoxia increases autophagy activity by inducing the accumulation of ATGs, such as ATG5, ATG7, and ATG12, and secretion of VEGF.^{25,26} Hypoxia-induced autophagy inhibits the killing of cancer cells by natural killer cells.²⁷

Table-1 summarizes the role of certain miRNAs in autophagy.

miRNAs, autophagy and EMT

The autophagic capacity of cancer cells has been considered as a determining factor.^{9,47} In non-small-cell lung carcinoma (NSCLC), down-regulation of miR-16 promotes TGF- β 1-induced EMT via activation of autophagy. This shows that autophagy has a great impact on the cancer metastasis through the induction of EMT.⁴⁸ EMT is a key process by which cancer cells lose their epithelial characteristics to acquire mesenchymal-like properties. The decreased expression levels of E-cadherin and β -catenin and elevated expression levels of vimentin, fibronectin and N-cadherin occur during EMT phenomenon. Therefore, EMT process involves the disruption of cell-cell adhesion and cellular polarity and is associated with enhancement of invasive properties. EMT promotes cellular plasticity during cancer metastasis.⁴⁹ miRNAs regulate both autophagy and EMT. For instance, miR-133a-3p, a tumor suppressor, defeats EMT phenomenon and metastasis through blocking autophagy-mediated glutaminolysis in gastric cancer.⁵⁰

miRNAs, autophagy and CSCs

A small subset of tumor cells is involved in tumor growth. These cells, cancer stem cells (CSCs), are capable of reproducing the whole phenotype of the original tumor and contribute to cancer initiation and metastasis. Accumulated evidence has demonstrated that cancer cells which acquire EMT characteristics also have the characteristics of CSCs.⁵¹ The main contributors to the maintenance of stemness in these cells are not known, yet some

studies have suggested that autophagy may play a critical role in this process.^{52,53} Interestingly, in certain tumors, such as glioma, enhancement of autophagy promotes differentiation of CSCs.⁵⁴ In addition, in colorectal CSCs, autophagy maintains pluripotency.⁵ miRNAs control CSC functions, such as tumorigenesis, invasion, and metastasis.⁵⁵ For example, miR-34a inhibits metastasis of prostate cancer by targeting CD44⁵⁶ and miR-21 promotes metastasis in renal cancer by targeting Large tumor suppressor gene 1 (LATS1).⁵⁷ Additionally, ectopic expression of miR-140-5p in CSCs inhibits their growth and sphere formation by disrupting autophagy through suppressing ATG12.⁴¹

miRNAs, autophagy and microenvironment

The tumor microenvironment (TME) is a heterogeneous tissue created by the tumor. TME comprises proliferating cancer cells, tumor stroma, inflammatory cells, cancer-associated fibroblasts and fibroblasts, immune cells, tumor blood vessels, and lymphatic channels.⁵⁸ TME has a pivotal role in tumor evolution and metastasis by controlling the molecular and cellular events. Adaptation of cancer cells to microenvironment and formation of the metastatic niche promote metastasis.⁵⁹ Furthermore, different cytokines in TME stimulate angiogenesis, tumor cell migration, and metastasis. For instance, C-X-C motif chemokine ligand 12 (CXCL12), the identified target of miR-448, is absent in normal tissues, but its expression in ovarian cancer regulates metastasis.⁶⁰ Moreover, miRNA-101 decreases the ability of cancer-associated fibroblasts to stimulate lung cancer cell proliferation and metastasis by targeting CXCL12.⁶¹ Interestingly, the expression of miR-31 and miR-214 decreases in tumor-associated fibroblasts; however, the expression of miR-155 increases in these cells.⁶²

miRNA, autophagy and anoikis

The absence of cell attachment to extracellular matrix (ECM) leads to a particular form of apoptosis, called anoikis. Anoikis is a physiologic process that functions in the tissue development and homeostasis. It is an important mechanism in preventing non-adherent cell growth and the growth of cells in an inappropriate environment. In other words, separation of a normal epithelial cell from its ECM results in anoikis. Integrin receptors are the main mediators of cell-ECM interactions.⁶³ Augmentation of adhesion molecules correlates with anoikis-resistance. Anoikis-resistance enhances survival of cancer cells and has a great impact on tumor progression and metastasis.⁶⁴ Resistance against anoikis is a hallmark of EMT phenomenon and is a pre-requisite for metastasis.⁴⁹ At the early stages of metastasis, cancer cells detach from ECM and adjacent cells; however, they resist anoikis partly via activation of autophagy (65). Autophagy and anoikis play regulatory roles in metastasis.⁶⁶

Altered expression of miRNAs also regulates anoikis. The miRNAs which promote anoikis are often down-regulated in different cancers.⁶⁷ For instance, the decrease in the expression level of miR-26a in HCC promotes anoikis by increasing the expression of integrin alpha-5 (ITGA5).⁶⁸ In addition, the decrease in the level of miR-30a mediates Beclin 1 and ATG5-dependent autophagy which converts anoikis resistance in HCC cells.⁶⁹ On top of that, miR-125b inhibits anoikis in human mesenchymal stem cells.⁷⁰ On the other hand, overexpression of miR-451 promotes anoikis sensitivity in human glioma through inhibiting the expression of CAB39 and disrupting the P13K/Akt pathway.^{71,72}

miRNAs, autophagy and inflammation

Recently published studies have suggested that inflammation can trigger autophagy in some inflammatory cells, such

as monocytes and macrophages. Previous investigations have reported the role of autophagy in the production of certain cytokines, including interleukin-1 β (IL-1 β), IFN- γ , and tumor necrosis factor (TNF- α). Furthermore, autophagy enhances macrophage aging which causes some functional changes, reduced antigen presentation capacity and impaired maturation for instance. However, autophagy mediates anti-inflammatory responses.⁷³ Recently published data have indicated that chronic inflammation participates in tumorigenesis.^{74,75} In cancers, autophagy differentiates macrophages into tumor-associated macrophages (TAMs) and fibroblasts into cancer-associated fibroblasts (CAFs) which promote tumor growth, invasiveness, and metastasis.⁷⁴ An increasing number of studies have described the role of miRNAs in inflammatory responses in cancers. For example, miR-146/miR-155-axis, miR-17-92 cluster, miR-223, miR-23~27~24 cluster, and miR-181 target the NF- κ B pathway to regulate inflammation in cancers.^{76,77} miR-130a is overexpressed in high-grade serous ovarian carcinoma (HGSOC) and suppresses tuberous sclerosis 1 (TSC1) expression by targeting its 3'UTR. Ectopic TSC1 expression blocks the effects of miR-130a on HGSOC cell proliferation, migration, and autophagy. Additionally, NF- κ B up-regulates miR-130a expression in ovarian cancer cells.⁷⁸

Exosomal microRNAs and autophagy in cancer metastasis

Exosomes are membrane bound extracellular vesicles (EVs), ranging in size between 40 and 100 nm, with an endosomal origin. Exosomes contain several components, including lipids, proteins, mRNAs, and miRNAs. Increased production of exosomes in response to hypoxia has also been demonstrated. On the other hand, hypoxic conditions promote autophagy in cancer cells.⁷⁹ Exosomal

miRNAs (exomiRs) are essential in regulating angiogenesis and cancer progression. Exosomal miRNAs are involved in cancer cell invasion and metastasis under hypoxic conditions.⁸⁰ In oral squamous cell carcinoma, exosomal miR-21 promotes cancer growth and metastasis.⁸¹ In lung cancer, miR-23a-enriched exosomes enhance angiogenesis and metastasis.⁸² In breast cancer, exosomal miR-221/222 mediates autophagy and angiogenesis.⁸³ Exo-miR-425-3p up-regulates the autophagic levels in lung cancer patients within the early and advanced disease stages.⁸⁴

miRNA, autophagy, chemoresistance and radioresistance

In metastatic cancers, chemotherapy has been considered as the first line of therapy. Meanwhile, chemoresistance is the main problem in cancer therapy. Despite great efforts, the exact molecular mechanism of the chemo-resistance remains unclear. Autophagy has been recognized as an important element of chemoresistance since it helps cancer cells to escape from fetal cell damage. Therefore, it has been suggested to target autophagy-related regulators.⁸⁵ Moreover, miRNAs regulate tumor sensitivity to radiotherapy in different cancers. For example, miR-668 enhances the radioresistance in human breast cancer through targeting nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha (I κ B α).⁸⁶ miR-183 inhibits autophagy in colorectal cancer cells by targeting ultraviolet radiation resistance-associated gene (UVRAG), a well-known regulator of autophagy; therefore, it has an oncogenic role in CRC.⁸⁷ Additionally, miR-22 regulates the autophagy pathway and modulates the drug sensitivity in CRC cells.⁸⁸ Figure 1 shows a schematic representation of signaling pathways that miRNAs and autophagy can control cancer metastasis.

Conclusion

Different signaling pathways, factors, and cells contribute to cancer development and metastasis, such as oncogenes, tumor suppressors, EMT, and CSCs. The altered expression of miRNAs contributes to the development of different cancers, invasion, and metastasis. miRNAs act as oncogenes or tumor suppressor genes, thereby contributing to tumor formation.¹² In physiological conditions, autophagy has a crucial role in discarding damaged organelles and proteins and in pathological conditions, such as cancers, it is known as a pro-survival or pro-death factor.⁸⁹ Several genes and pathways are involved in autophagy regulation. Recent investigations have shown the critical roles of miRNAs in the regulation of autophagy. Interactions between miRNAs and autophagy have a great impact on cancer development.⁹⁰ Both miRNAs and autophagy are involved in different signaling pathways which are activated in cancers. Numerous research sources have implied that miRNAs and autophagy-related proteins differ from one tumor type to another; therefore, they have prognostic values in cancers and could be considered as therapeutic targets. Regulation of autophagy by miRNAs has been extensively studied over the last decades^{91,92}. Exosomal and circulating microRNAs are biomarkers which facilitate the early and minimally-invasive diagnosis of cancers.^{93,94} In addition, they could be utilized as biomarkers for metastasis.⁹⁵ Certain previous studies have also found and validated the expression level of autophagy-related proteins in cancer tissues and urine samples.^{96,97}

Metastasis is a multistep process; thus, new treatment strategies are needed. Autophagy dysregulation occurs in human cancer cells, but the exact mechanism of the regulation of metastasis by autophagy is not clear yet.

Regulation of autophagy by miRNAs may be a potential tool for cancer diagnosis and treatment in the future. The clinical use of molecular markers is very demanding and this area of research is highly dynamic and promises novel approaches to cancer diagnosis and therapy. A better understanding of the interactions of miRNAs with autophagy is pivotal to cancer therapy.

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Conflict of Interest

None declared.

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Table 1. A summary of the role of miRNAs related to autophagy in cancer

miRNA (reference)	Effect on autophagy	Target gene	Type of cancer
miR-let7f1(28)	Inhibition	HMGB1	Medulloblastoma
miR-7(29)	Activation	EGFR	Esophageal cancer
miR-9-3p (30)	Inhibition	ATG5	Medullary thyroid carcinoma
miR-10b (31)	Inhibition	Bim, TFAP2C, p16, and p21	Glioblastoma
miR-15a/16 (32)	Activation	RICTOR	Cervical cancer
miR-16, miR-17 (33)	Inhibition	BCL2	Lung cancer
miR-21(34)	Activation	PTEN	Liver cancer
miR-22 (35)	Inhibition	HMGB1	Osteosarcoma
miR-23a (36)	Inhibition	ATG12	Pancreas cancer
miR-30a (37)	Inhibition	BECN1	Renal carcinoma
miR-101(38)	Inhibition	STMN1, ATG4D, RAB5A	Breast cancer
miR-101(39)	Inhibition	STMN1	Nasopharyngeal carcinoma
miR-126 (40)	Activation	IRS1	Malignant mesothelioma
miR-140-5p (41)	Inhibition	SMAD2	Colorectal cancer
miR-152 (42)	Inhibition	ATG14	Ovarian cancer
miR-181a (43)	Inhibition	ATG5	Gastric cancer
miR-205 (44)	Inhibition	RAB27A, LAMP3	Prostate cancer
miR-218 (45)	Inhibition	HMGB1	Endometrial carcinoma
miR-638 (46)	Inhibition	TP53INP2	Melanoma

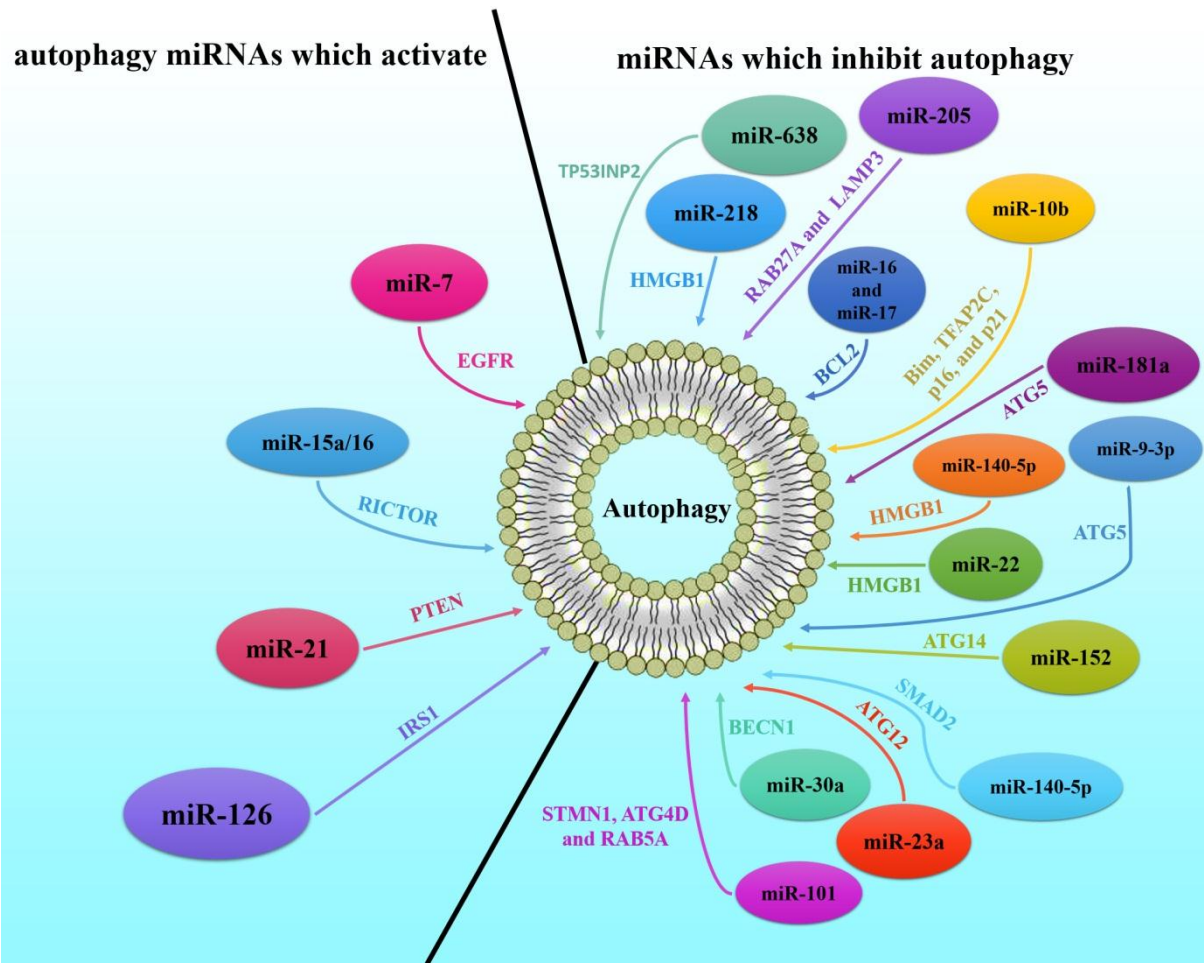


Figure 1. This figure illustrates some microRNAs and their targets which play important roles in autophagy regulation in different cancers.

miRNAs: MicroRNAs