Review Article
Middle East Journal of Cancer; January 2022; 13(1): 14-24

MicroRNAs Contribute to Metastasis by Regulating Autophagy: Recent Concepts

Soussan Irani*, **, DDS, OMFP, PhD

**Dental Research Centre, Oral Pathology Department, Dental Faculty, Hamadan University of Medical Sciences, Hamadan, Iran*
***Lecturer at Griffith University, Gold Coast, Australia*

Please cite this article as: Irani S. MicroRNAs contribute to metastasis by regulating autophagy: Recent concepts. Middle East J Cancer. 2022;13(1):14-24. doi: 10.30476/mejc.2021.88044.1452.

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 adaption of cells to environmental or developmental changes and is a

♦Corresponding Author:
Soussan Irani, DDS, OMFP, PhD
Dental Research Centre, Oral Pathology Department, Dental Faculty, Hamadan University of Medical Sciences, Hamadan, Iran
Tel: +98813-8354250
Fax: +98813-8354220
Email: sousanirani@gmail.com

Received: September 06, 2020; Accepted: April 18, 2021

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 antiautophagy 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

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	*TP53*INP2	Melanoma

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-β1-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 CD44[56] 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 prerequisite 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 convers 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-1β (IL-1β), 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-κB 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-αB 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 100nm, with an endosomal origin. Exosomes contain several components, including lipids, proteins, mRNAs, and miRNAs. Increased production of exosomes in response to hypoxia

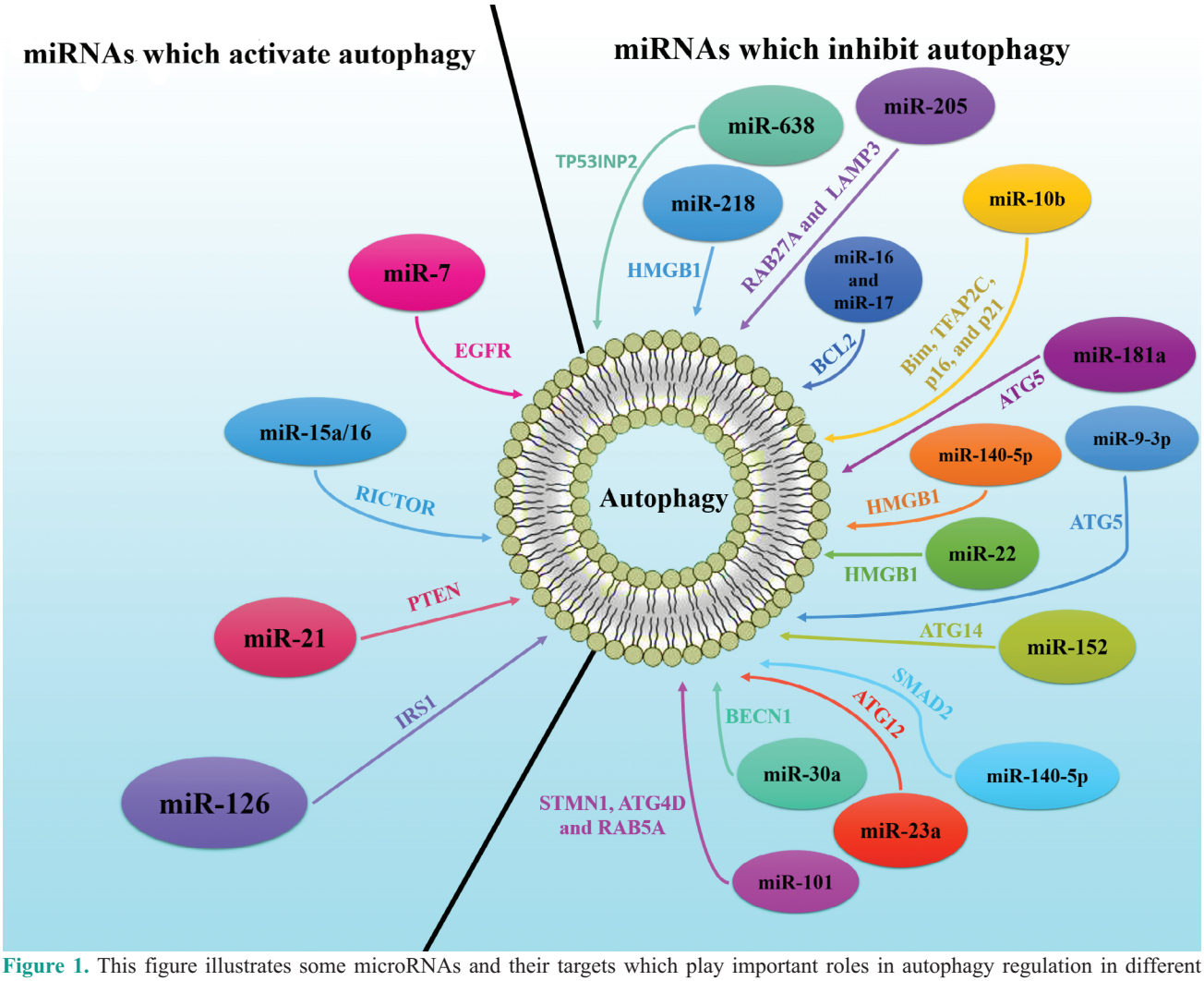

Figure 1. This figure illustrates some microRNAs and their targets which play important roles in autophagy regulation in different cancers.
miRNAs: MicroRNAs

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 upregulates 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 chemoresistance 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 (IkBα).[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.

Acknowledgments

I would like to thank Hamadan University of

Medical Sciences for financial support.

Conflict of Interest

None declared.

References

1. Global Burden of Disease Cancer Collaboration, Fitzmaurice C, Akinyemiju TF, Al Lami FH, Alam T, Alizadeh-Navaei R, et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 29 cancer groups, 1990 to 2016: A systematic analysis for the global burden of disease study. *JAMA Oncol*. 2018;4(11):1553-1568. doi: 10.1001/jamaoncol.2018.2706.
2. Irani S. Metastasis to head and neck area: a 16-year retrospective study. *Am J Otolaryngol.* 2011;32(1):24-7. doi: 10.1016/j.amjoto.2009.09.006.
3. Mathew R, Karantza-Wadsworth V, White E. Role of autophagy in cancer. *Nat Rev Cancer.* 2007;7(12):961-7. doi: 10.1038/nrc2254.
4. Arakawa S, Honda S, Yamaguchi H, Shimizu S. Molecular mechanisms and physiological roles of Atg5/Atg7-independent alternative autophagy. *Proc Jpn Acad Ser B Phys Biol Sci.* 2017;93(6):378-85. doi: 10.2183/pjab.93.023.
5. Yun CW, Lee SH. The roles of autophagy in cancer. *Int J Mol Sci.* 2018;19(11):3466. doi: 10.3390/ijms19113466.
6. Hua L, Zhu G, Wei J. MicroRNA-1 overexpression increases chemosensitivity of non-small cell lung cancer cells by inhibiting autophagy related 3-mediated autophagy. *Cell Biol Int.* 2018;42(9):1240-9. doi: 10.1002/cbin.10995.
7. Challapalli A, Carroll L, Aboagye EO. Molecular mechanisms of hypoxia in cancer. *Clin Transl Imaging.* 2017;5(3):225-53. doi: 10.1007/s40336-017-0231-1.
8. Mowers EE, Sharifi MN, Macleod KF. Autophagy in cancer metastasis. *Oncogene.* 2017;36(12):1619-30. doi: 10.1038/onc.2016.333.
9. Chen HT, Liu H, Mao MJ, Tan Y, Mo XQ, Meng XJ, et al. Crosstalk between autophagy and epithelial-mesenchymal transition and its application in cancer therapy. *Mol Cancer.* 2019;18(1):101. doi: 10.1186/s12943-019-1030-2.
10. Yang C, Zhang JJ, Peng YP, Zhu Y, Yin LD, Wei JS, et al. A Yin-Yang 1/miR-30a regulatory circuit modulates autophagy in pancreatic cancer cells. *J Transl Med.* 2017;15(1):211. doi: 10.1186/s12967-017-1308-3.
11. Liu JL, Chen FF, Lung J, Lo CH, Lee FH, Lu YC, et al. Prognostic significance of p62/SQSTM1 subcellular localization and LC3B in oral squamous cell carcinoma. *Br J Cancer.* 2014;111(5):944-54. doi: 10.1038/bjc.2014.355.
12. Irani S, Shokri G. The role of miR-143, miR-145, and miR-590 in expression levels of CD44 and vascular endothelial cadherin in oral squamous cell carcinoma. *Middle East J Cancer.* 2019;10(3):194-204. doi: 10.30476/mejc.2019.78667.
13. Maroof H, Irani S, Ariana A, Vider J, Gopalan V, Lam AK. Interactions of vascular endothelial growth factor and p53 with miR-195 in thyroid carcinoma: possible therapeutic targets in aggressive thyroid cancers. *Curr Cancer Drug Targets*. 2019;19(7):561-70. doi: 10.2174/1568009618666180628154727.
14. Yang Y, Liang C. MicroRNAs: an emerging player in autophagy. *Science Open Res.* 2015; 2015:10.14293/S2199-1006.1.SOR-LIFE.A181CU.v1. doi: 10.14293/S2199-1006.1.SOR-LIFE.A181CU.v1.
15. Liu L, He J. MicroRNA-20a-mediated loss of autophagy contributes to breast tumorigenesis by promoting genomic damage and instability. *Oncogene.* 2017;36(42):5874-84. doi: 10.1038/onc.2017.193.
16. Gozuacik D, Akkoc Y, Ozturk DG, Kocak M. Autophagy-regulating microRNAs and cancer. *Front Oncol.* 2017;7:65. doi: 10.3389/fonc.2017.00065.
17. Jamali Z, Taheri-Anganeh M, Shabaninejad Z, Keshavarzi A, Taghizadeh H, Razavi ZS, et al. Autophagy regulation by microRNAs: Novel insights into osteosarcoma therapy. *IUBMB Life*. 2020;72(7):1306-21. doi: 10.1002/iub.2277.
18. Aredia F, Scovassi AI. A new function for miRNAs as regulators of autophagy. *Future Med Chem.* 2017;9(1):25-36. doi: 10.4155/fmc-2016-0173.
19. Kwon JJ, Willy JA, Quirin KA, Wek RC, Korc M, Yin XM, et al. Novel role of miR-29a in pancreatic cancer autophagy and its therapeutic potential. *Oncotarget.* 2016;7(44):71635-50. doi: 10.18632/oncotarget.11928.
20. Hu JL, He GY, Lan XL, Zeng ZC, Guan J, Ding Y, et al. Inhibition of ATG12-mediated autophagy by miR-214 enhances radiosensitivity in colorectal cancer. *Oncogenesis.* 2018;7(2):16. doi: 10.1038/s41389-018-0028-8.
21. Mo J, Zhang D, Yang R. MicroRNA-195 regulates proliferation, migration, angiogenesis and autophagy of endothelial progenitor cells by targeting GABARAPL1. *Biosci Rep.* 2016;36(5). doi: 10.1042/BSR20160139.
22. Wang R, Zhao N, Li S, Fang JH, Chen MX, Yang J, et al. MicroRNA-195 suppresses angiogenesis and metastasis of hepatocellular carcinoma by inhibiting the expression of VEGF, VAV2, and CDC42. *Hepatology.* 2013;58(2):642-53. doi: 10.1002/hep.26373.
23. Ghosh A, Dasgupta D, Ghosh A, Roychoudhury S, Kumar D, Gorain M, et al. MiRNA199a-3p suppresses tumor growth, migration, invasion and angiogenesis in hepatocellular carcinoma by targeting VEGFA, VEGFR1, VEGFR2, HGF and MMP2. *Cell Death*

Dis. 2017;8(3):e2706. doi: 10.1038/cddis.2017.123.
24. Jin F, Wang Y, Li M, Zhu Y, Liang H, Wang C, et al. MiR-26 enhances chemosensitivity and promotes apoptosis of hepatocellular carcinoma cells through inhibiting autophagy. *Cell Death Dis.* 2017;8(1):e2540. doi: 10.1038/cddis.2016.461.
25. Li CJ, Liao WT, Wu MY, Chu PY. New insights into the role of autophagy in tumor immune microenvironment. *Int J Mol Sci.* 2017;18(7):1566: doi: 10.3390/ijms18071566.
26. Sung SJ, Kim HK, Hong YK, Joe YA. Autophagy is a potential target for enhancing the anti-angiogenic effect of mebendazole in endothelial cells. *Biomol Ther (Seoul).* 2019;27(1):117-25. doi: 10.4062/biomolther.2018.222.
27. Janji B, Berchem G, Chouaib S. Targeting autophagy in the tumor microenvironment: New challenges and opportunities for regulating tumor immunity. *Front Immunol.* 2018;9:887. doi: 10.3389/fimmu.2018.00887.
28. Pannuru P, Dontula R, Khan AA, Herbert E, Ozer H, Chetty C, et al. miR-let-7f-1 regulates SPARC mediated cisplatin resistance in medulloblastoma cells. *Cell Signal.* 2014;26(10):2193-201. doi: 10.1016/j.cellsig.2014.06.014.
29. Tazawa H, Yano S, Yoshida R, Yamasaki Y, Sasaki T, Hashimoto Y, et al. Genetically engineered oncolytic adenovirus induces autophagic cell death through an E2F1-microRNA-7-epidermal growth factor receptor axis. *Int J Cancer.*2012;131(12):2939-50. doi: 10.1002/ijc.27589.
30. Gundara JS, Zhao J, Gill AJ, Lee JC, Delbridge L, Robinson BG, et al. Noncoding RNA blockade of autophagy is therapeutic in medullary thyroid cancer. *Cancer Med.* 2015;4(2):174-82. doi: 10.1002/cam4.355.
31. Gabriely G, Yi M, Narayan RS, Niers JM, Wurdinger T, Imitola J, et al. Human glioma growth is controlled by microRNA-10b. *Cancer Res.*2011;71(10):3563-72. doi: 10.1158/0008-5472.CAN-10-3568.
32. Huang N, Wu J, Qiu W, Lyu Q, He J, Xie W, et al. MiR-15a and miR-16 induce autophagy and enhance chemosensitivity of Camptothecin. *Cancer Biol Ther.* 2015;16(6):941-8. doi: 10.1080/15384047.2015.1040963.
33. Chatterjee A, Chattopadhyay D, Chakrabarti G. MiR-16 targets Bcl-2 in paclitaxel-resistant lung cancer cells and overexpression of miR-16 along with miR-17 causes unprecedented sensitivity by simultaneously modulating autophagy and apoptosis. *Cell Signal.* 2015;27(2):189-203. doi: 10.1016/j.cellsig.2014.11.023.
34. He C, Dong X, Zhai B, Jiang X, Dong D, Li B, et al. MiR-21 mediates sorafenib resistance of hepatocellular carcinoma cells by inhibiting autophagy via the PTEN/Akt pathway. *Oncotarget.* 2015;6(30):28867-81. doi: 10.18632/oncotarget.4814.
35. Guo S, Bai R, Liu W, Zhao A, Zhao Z, Wang Y, et al. miR-22 inhibits osteosarcoma cell proliferation and migration by targeting HMGB1 and inhibiting HMGB1-mediated autophagy. *Tumour Biol.* 2014;35(7):7025-34. doi: 10.1007/s13277-014-1965-2.
36. Wang P, Zhang J, Zhang L, Zhu Z, Fan J, Chen L, et al. MicroRNA 23b regulates autophagy associated with radioresistance of pancreatic cancer cells. *Gastroenterology.* 2013;145(5):1133-43.e12. doi: 10.1053/j.gastro.2013.07.048.
37. Zheng B, Zhu H, Gu D, Pan X, Qian L, Xue B, et al. MiRNA-30a-mediated autophagy inhibition sensitizes renal cell carcinoma cells to sorafenib. *Biochem Biophys Res Commun.* 2015;459(2):234-9. doi: 10.1016/j.bbrc.2015.02.084.
38. Frankel LB, Wen J, Lees M, Hoyer-Hansen M, Farkas T, Krogh A, et al. microRNA-101 is a potent inhibitor of autophagy. *EMBO J.* 2011;30(22):4628-41. doi: 10.1038/emboj.2011.331.
39. Sun Q, Liu T, Zhang T, Du S, Xie GX, Lin X, et al. MiR-101 sensitizes human nasopharyngeal carcinoma cells to radiation by targeting stathmin 1. *Mol Med Rep.* 2015;11(5):3330-6. doi: 10.3892/mmr.2015.3221.
40. Tomasetti M, Monaco F, Manzella N, Rohlena J, Rohlenova K, Staffolani S, et al. MicroRNA-126 induces autophagy by altering cell metabolism in malignant mesothelioma. *Oncotarget.* 2016;7(24):36338-52. doi: 10.18632/oncotarget.8916.
41. Zhai H, Fesler A, Ba Y, Wu S, Ju J. Inhibition of colorectal cancer stem cell survival and invasive potential by hsa-miR-140-5p mediated suppression of Smad2 and autophagy. *Oncotarget.* 2015;6(23):19735-46. doi: 10.18632/oncotarget.3771.
42. He J, Yu JJ, Xu Q, Wang L, Zheng JZ, Liu LZ, et al. Downregulation of ATG14 by EGR1-MIR152 sensitizes ovarian cancer cells to cisplatin-induced apoptosis by inhibiting cyto-protective autophagy. *Autophagy.* 2015;11(2):373-84. doi: 10.1080/15548627.2015.1009781.
43. Zhao J, Nie Y, Wang H, Lin Y. MiR-181a suppresses autophagy and sensitizes gastric cancer cells to cisplatin. *Gene*. 2016;576(2 Pt 2):828-33. doi: 10.1016/j.gene.2015.11.013.
44. Pennati M, Lopergolo A, Profumo V, De Cesare M, Sbarra S, Valdagni R, et al. miR-205 impairs the autophagic flux and enhances cisplatin cytotoxicity in castration-resistant prostate cancer cells. *Biochem Pharmacol.* 2014;87(4):579-97. doi: 10.1016/j.bcp.2013.12.009.
45. Ran X, Yang J, Liu C, Zhou P, Xiao L, Zhang K. MiR-218 inhibits HMGB1-mediated autophagy in endometrial carcinoma cells during chemotherapy. *Int J Clin Exp Pathol.* 2015;8(6):6617-26.
46. Bhattacharya A, Schmitz U, Raatz Y, Schonherr M, Kottek T, Schauer M, et al. miR-638 promotes

melanoma metastasis and protects melanoma cells from apoptosis and autophagy. *Oncotarget*. 2015;6(5):2966-80. doi: 10.18632/oncotarget.3070.
47. Zada S, Hwang JS, Ahmed M. Control of the epithelial-to-mesenchymal transition and cancer metastasis by autophagy-dependent SNAI1 degradation. *Cells*. 2019;8(2). doi: 10.3390/cells8020129.
48. Wang H, Zhang Y, Wu Q, Wang YB, Wang W. miR-16 mimics inhibit TGF-beta1-induced epithelial-to-mesenchymal transition via activation of autophagy in non-small cell lung carcinoma cells. *Oncol Rep*.2018;39(1):247-54. doi: 10.3892/or.2017.6088.
49. Irani S, Jafari B. Expression of vimentin and CD44 in mucoepidermoid carcinoma: A role in tumor growth. *Indian J Dent Res.* 2018;29(3):333-40. doi: 10.4103/ijdr.IJDR_184_17.
50. Zhang X, Li Z, Xuan Z, Xu P, Wang W, Chen Z, et al. Novel role of miR-133a-3p in repressing gastric cancer growth and metastasis via blocking autophagy-mediated glutaminolysis. *J Exp Clin Cancer Res*. 2018;37(1):320. doi: 10.1186/s13046-018-0993-y.
51. Irani S, Dehghan A. Expression of vascular endothelial-cadherin in mucoepidermoid carcinoma: Role in cancer development. *J Exp Clin Cancer Res.* 2017;7(6):301-7. doi: 10.1186/s13046-018-0993-y.
52. Sharif T, Martell E, Dai C, Kennedy BE, Murphy P, Clements DR, et al. Autophagic homeostasis is required for the pluripotency of cancer stem cells. *Autophagy*. 2017;13(2):264-84. doi: 10.1080/15548627.2016.1260808.
53. Pan H, Cai N, Li M, Liu GH, Izpisua Belmonte JC. Autophagic control of cell 'stemness'. *EMBO Mol Med*. 2013;5(3):327-31. doi: 10.1002/emmm.201201999.
54. Zhao Y, Huang Q, Yang J, Lou M, Wang A, Dong J, et al. Autophagy impairment inhibits differentiation of glioma stem/progenitor cells. *Brain Res*. 2010;1313:250-8. doi: 10.1016/j.brainres.2009.12.004.
55. Asadzadeh Z, Mansoori B. microRNAs in cancer stem cells: Biology, pathways, and therapeutic opportunities. *J Cell Physiol.* 2019;234(7):10002-17. doi: 10.1002/jcp.27885.
56. Liu C, Kelnar K, Liu B, Chen X, Calhoun-Davis T, Li H, et al. The microRNA miR-34a inhibits prostate cancer stem cells and metastasis by directly repressing CD44. *Nat Med.* 2011;17(2):211-5. doi: 10.1038/nm.2284.
57. An F, Liu Y, Hu Y. miR-21 inhibition of LATS1 promotes proliferation and metastasis of renal cancer cells and tumor stem cell phenotype. *Oncol Lett.* 2017;14(4):4684-8. doi: 10.3892/ol.2017.6746.
58. Balkwill FR, Capasso M, Hagemann T. The tumor microenvironment at a glance. *J Cell Sci.* 2012;125(Pt 23):5591-6. doi: 10.1242/jcs.116392.
59. Ingangi V, Minopoli M, Ragone C, Motti ML, Carriero MV. Role of microenvironment on the fate of disseminating cancer stem cells. *Front Oncol*. 2019;9:82. doi: 10.3389/fonc.2019.00082.
60. Lv Y, Lei Y, Hu Y, Ding W, Zhang C, Fang C. miR-448 negatively regulates ovarian cancer cell growth and metastasis by targeting CXCL12. *Clin Transl Oncol.* 2015;17(11):903-9. doi: 10.1007/s12094-015-1325-8.
61. Zhang J, Liu J, Liu Y, Wu W, Li X, Wu Y, et al. miR-101 represses lung cancer by inhibiting interaction of fibroblasts and cancer cells by down-regulating CXCL12. *Biomed Pharmacother.*2015;74:215-21. doi: 10.1016/j.biopha.2015.08.013.
62. Braga EA, Fridman MV, Kushlinskii NE. Molecular mechanisms of ovarian carcinoma metastasis: Key genes and regulatory microRNAs. *Biochemistry (Mosc)*. 2017;82(5):529-41. doi: 10.1134/S0006297917050017.
63. Paoli P, Giannoni E, Chiarugi P. Anoikis molecular pathways and its role in cancer progression. *Biochim Biophys Acta*. 2013;1833(12):3481-98. doi: 10.1016/j.bbamcr.2013.06.026.
64. Mak CS, Yung MM, Hui LM, Leung LL, Liang R, Chen K, et al. MicroRNA-141 enhances anoikis resistance in metastatic progression of ovarian cancer through targeting KLF12/Sp1/survivin axis. *Mol Cancer.* 2017;16(1):11. doi: 10.1186/s12943-017-0582-2.
65. Folkerts H, Hilgendorf S, Vellenga E, Bremer E, Wiersma VR. The multifaceted role of autophagy in cancer and the microenvironment. *Med Res Rev.* 2019;39(2):517-60. doi: 10.1002/med.21531.
66. Satyavarapu EM, Das R, Mandal C, Mukhopadhyay A, Mandal C. Autophagy-independent induction of LC3B through oxidative stress reveals its non-canonical role in anoikis of ovarian cancer cells. *Cell Death Dis.* 2018;9(10):934. doi: 10.1038/s41419-018-0989-8.
67. Weiswald LB, Richon S, Validire P, Briffod M, Lai-Kuen R, Cordelieres FP, et al. Newly characterised ex vivo colospheres as a three-dimensional colon cancer cell model of tumour aggressiveness. *Br J Cancer.* 2009;101(3):473-82. doi: 10.1038/sj.bjc.6605173.
68. Zhang X, Cheng SL, Bian K, Wang L, Zhang X, Yan B, et al. MicroRNA-26a promotes anoikis in human hepatocellular carcinoma cells by targeting alpha5 integrin. *Oncotarget*. 2015;6(4):2277-89. doi: 10.18632/oncotarget.2956.
69. Fu XT, Shi YH, Zhou J, Peng YF, Liu WR, Shi GM, et al. MicroRNA-30a suppresses autophagy-mediated anoikis resistance and metastasis in hepatocellular carcinoma. *Cancer Lett*. 2018;412:108-17. doi: 10.1016/j.canlet.2017.10.012.
70. Malagobadan S, Nagoor NH. Evaluation of microRNAs regulating anoikis pathways and its

therapeutic potential. *Biomed Res Int*. 2015;2015: 716816. doi: 10.1155/2015/716816.
71. Wang XC, Tian LL, Jiang XY, Wang YY, Li DG, She Y, et al. The expression and function of miRNA-451 in non-small cell lung cancer. *Cancer Lett.* 2011;311(2):203-9. doi: 10.1016/j.canlet.2011.07.026.
72. Tian Y, Nan Y, Han L, Zhang A, Wang G, Jia Z, et al. MicroRNA miR-451 downregulates the PI3K/AKT pathway through CAB39 in human glioma. *Int J Oncol.* 2012;40(4):1105-12. doi: 10.3892/ijo.2011.1306.
73. Wu TT, Li WM, Yao YM. Interactions between autophagy and inhibitory cytokines. *Int J Biol Sci.* 2016;12(7):884-97. doi: 10.7150/ijbs.15194.
74. Ngabire D, Kim GD. Autophagy and inflammatory response in the tumor microenvironment. *Int J Mol Sci.* 2017;18(9). doi: 10.3390/ijms18092016.
75. Neagu M, Constantin C, Caruntu C, Dumitru C, Surcel M, Zurac S. Inflammation: A key process in skin tumorigenesis. *Oncol Lett.* 2019;17(5):4068-84. doi: 10.3892/ol.2018.9735.
76. Hirschberger S, Hinske LC, Kreth S. MiRNAs: dynamic regulators of immune cell functions in inflammation and cancer. *Cancer Lett.* 2018;431:11-21. doi: 10.1016/j.canlet.2018.05.020.
77. Jeffries J, Zhou W, Hsu AY, Deng Q. miRNA-223 at the crossroads of inflammation and cancer. *Cancer Lett.* 2019;451:136-41. doi: 10.1016/j.canlet. 2019.02.051.
78. Wang Y, Zhang X, Tang W, Lin Z, Xu L, Dong R, et al. miR-130a upregulates mTOR pathway by targeting TSC1 and is transactivated by NF-?B in high-grade serous ovarian carcinoma. *Cell Death Differ.* 2017;24(12):2089-100. doi: 10.1038/cdd. 2017.129.
79. Fan Q, Yang L, Zhang X, Peng X, Wei S, Su D, et al. The emerging role of exosome-derived non-coding RNAs in cancer biology. *Cancer Lett.* 2018;414:107-15. doi: 10.1016/j.canlet.2017.10.040.
80. Wang M, Yu F, Ding H, Wang Y, Li P, Wang K. Emerging function and clinical values of exosomal microRNAs in cancer. *Mol Ther Nucleic Acids.* 2019;16:791-804. doi: 10.1016/j.omtn.2019.04.027.
81. Li L, Li C, Wang S, Wang Z, Jiang J, Wang W, et al. Exosomes derived from hypoxic oral squamous cell carcinoma cells deliver miR-21 to normoxic cells to elicit a prometastatic phenotype. *Cancer Res.* 2016;76(7):1770-80. doi: 10.1158/0008-5472.CAN-15-1625.
82. Hsu Y, Hung J, Chang W, Lin Y, Pan Y, Tsai P, et al. Hypoxic lung cancer-secreted exosomal miR-23a increased angiogenesis and vascular permeability by targeting prolyl hydroxylase and tight junction protein ZO-1. *Oncogene.* 2017;36(34):4929-42. doi: 10.1038/onc.2017.105.
83. Wei Y, Lai X, Yu S, Chen S, Ma Y, Zhang Y, et al. Exosomal miR-221/222 enhances tamoxifen resistance in recipient ER-positive breast cancer cells. *Breast Cancer Res Treat.* 2014;147(2):423-31. doi: 10.1007/s10549-014-3037-0.
84. Yuwen D, Ma Y, Wang D, Gao J, Li X, Xue W, et al. Prognostic role of circulating exosomal miR-425-3p for the response of NSCLC to platinum-based chemotherapy. *Cancer Epidemiol Biomarkers Prev.* 2019;28(1):163-73. doi: 10.1158/1055-9965.EPI-18-0569.
85. YiRen H, YingCong Y, Sunwu Y, Keqin L, Xiaochun T, Senrui C, et al. Long noncoding RNA MALAT1 regulates autophagy associated chemoresistance via miR-23b-3p sequestration in gastric cancer. *Mol Cancer.* 2017;16(1):174. doi: 10.1186/s12943-017-0743-3.
86. Luo M, Ding L, Li Q, Yao H. miR-668 enhances the radioresistance of human breast cancer cell by targeting IκBα. *Breast Cancer.* 2017;24(5):673-82. doi: 10.1007/s12282-017-0756-1.
87. Huangfu L, Liang H, Wang G, Su X, Li L, Du Z, et al. miR-183 regulates autophagy and apoptosis in colorectal cancer through targeting of UVRAG. *Oncotarget.* 2016;7(4):4735-45. doi: 10.18632/oncotarget.6732.
88. Xie T, Huang M, Wang Y, Wang L, Chen C, Chu X. MicroRNAs as regulators, biomarkers and therapeutic targets in the drug resistance of colorectal cancer. *Cell Physiol Biochem.* 2016;40(1-2):62-76. doi: 10.1159/000452525.
89. Czaja MJ, Ding WX, Donohue TM Jr, Friedman SL, Kim JS, Komatsu M, et al. Functions of autophagy in normal and diseased liver. *Autophagy.* 2013;9(8):1131-58. doi: 10.4161/auto.25063.
90. Jing Z, Han W, Sui X, Xie J, Pan H. Interaction of autophagy with microRNAs and their potential therapeutic implications in human cancers. *Cancer Lett.* 2015;356(2 Pt B):332-8. doi: 10.1016/j.canlet. 2014.09.039.
91. Yin Q, Feng W, Shen X, Ju S. Regulatory effects of lncRNAs and miRNAs on autophagy in malignant tumorigenesis. *Biosci Rep.* 2018;38(5):BSR 20180516. doi: 10.1042/ BSR20180516.
92. Chen L, Zhou Y, Sun Q, Zhou J, Pan H, Sui X. Regulation of autophagy by miRNAs and their emerging roles in tumorigenesis and cancer treatment. *Int Rev Cell Mol Biol.* 2017;334:1-26. doi: 10.1016/bs.ircmb.2017.03.003.
93. Wang Y, Yin W, Lin Y, Yin K, Zhou L, Du Y, et al. Downregulated circulating microRNAs after surgery: potential noninvasive biomarkers for diagnosis and prognosis of early breast cancer. *Cell Death Discov.* 2018;4:21. doi: 10.1038/s41420-018-0089-7.
94. Salehi M, Sharifi M. Exosomal miRNAs as novel cancer biomarkers: Challenges and opportunities. *J Cell Physiol.*2018;233(9):6370-80. doi: 10.1002/jcp.26481.
95. McGuire A, Brown JA, Kerin MJ. Metastatic breast

cancer: the potential of miRNA for diagnosis and treatment monitoring. *Cancer Metastasis Rev.* 2015;34(1):145-55. doi: 10.1007/s10555-015-9551-7.

96. Liu H, He Z, Bode P, Moch H, Simon HU. Downregulation of autophagy-related proteins 1, 5, and 16 in testicular germ cell tumors parallels lowered LC3B and elevated p62 levels, suggesting reduced basal autophagy. *Front Oncol.* 2018;8:366. doi: 10.3389/fonc.2018.00366.
97. Eissa S, Matboli M, Awad N, Kotb Y. Identification and validation of a novel autophagy gene expression signature for human bladder cancer patients. *Tumour Biol.* 2017;39(4):1010428317698360. doi: 10.1177/1010428317698360.