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Dual role of miR-155 and exosomal miR-155 in tumor angiogenesis: implications for cancer progression and therapy

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Abstract

Tumor angiogenesis facilitates cancer progression by supporting tumor growth and metastasis. MicroRNA-155 (miR-155) plays a pivotal role in regulating angiogenesis through both direct effects on tumor and endothelial cells and indirect modulation via exosomal communication. This review highlights miR-155's pro-angiogenic influence on endothelial cell behavior and tumor microenvironment remodeling. Additionally, exosomal miR-155 enhances intercellular communication, promoting vascularization in several cancers. Emerging therapeutic strategies include miR-155 inhibition using antagomirs, exosome-mediated delivery systems, and modulation of pathways such as JAK2/STAT3 and TGF-β/SMAD2. Targeting miR-155 represents a promising approach to hinder tumor angiogenesis and improve cancer therapy outcomes.

Keywords Cancer, Angiogenesis, Exosome, MicroRNA-155

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Introduction

Angiogenesis—the formation of new blood vessels from pre-existing vasculature—is a highly regulated process essential for normal physiological functions such as embryonic development, wound healing, and tissue regeneration. However, in pathological conditions such as cancer, angiogenesis becomes dysregulated, leading to the formation of abnormal vasculature that supports tumor growth and metastasis. Various cancers, including melanoma, breast, colorectal, and lung cancers, exploit angiogenic pathways to sustain their proliferation and facilitate metastatic spread [1].

MicroRNAs (miRNAs) have emerged as critical regulators of gene expression involved in cellular processes such as differentiation, apoptosis, and immune response. Among them, miR-155 is notable for its multifaceted role in inflammation, immunity, metabolism, and oncogenesis. Elevated expression of miR-155 has been reported in numerous malignancies, where it contributes to tumor

progression by influencing the tumor microenvironment, enhancing angiogenesis, and modulating immune evasion [2–4].

In recent years, exosomes—small extracellular vesicles ranging from 40 to 100 nm—have emerged as important mediators of intercellular communication [5]. They are secreted by various cell types and carry molecular cargoes, including proteins, lipids, mRNAs, and non-coding RNAs such as microRNAs (miRNAs). Exosomes play a significant role in modifying the behavior of recipient cells and are increasingly recognized for their involvement in cancer biology, particularly in remodeling the tumor microenvironment, promoting metastasis, and enhancing angiogenesis. Given their stability in biological fluids and ability to reflect the physiological state of their originating cells, exosomes are also being explored as diagnostic biomarkers and therapeutic delivery vehicles in cancer [5].

Changes in the genes that encode microRNAs or the unequal expression of those genes have been proven to be substantial contributors to the development of a variety of disorders, including malignancies, according to research. Elevated levels of miR-155 have been discovered in several forms of human cancer. Research has demonstrated that in models including malignant cells and tissues, elevated levels of miR-155 enhance the growth of cancer. This is especially true for tumors that are associated with the gastrointestinal tract [6–8]. Researchers have established a link between higher miR-155 levels and dramatically lower survival rates in individuals with esophageal squamous cell cancer. There is a possibility that MiR-155 is capable of independently evaluating the situation regarding this condition [9]. In addition, microRNA-155 also plays a role in the increased aggressiveness and progression of cells that are associated with gastric cancer [6]. Despite extensive research, the precise function of miR-155 in gastrointestinal cancer and the mechanisms that underlie it are still unknown. Exosomal miR-155 is engaged in numerous molecular functions linked to cancer. These activities include angiogenesis and apoptosis (refer to Fig. 1), respectively. Consequently, miR-155 is crucial in managing immune

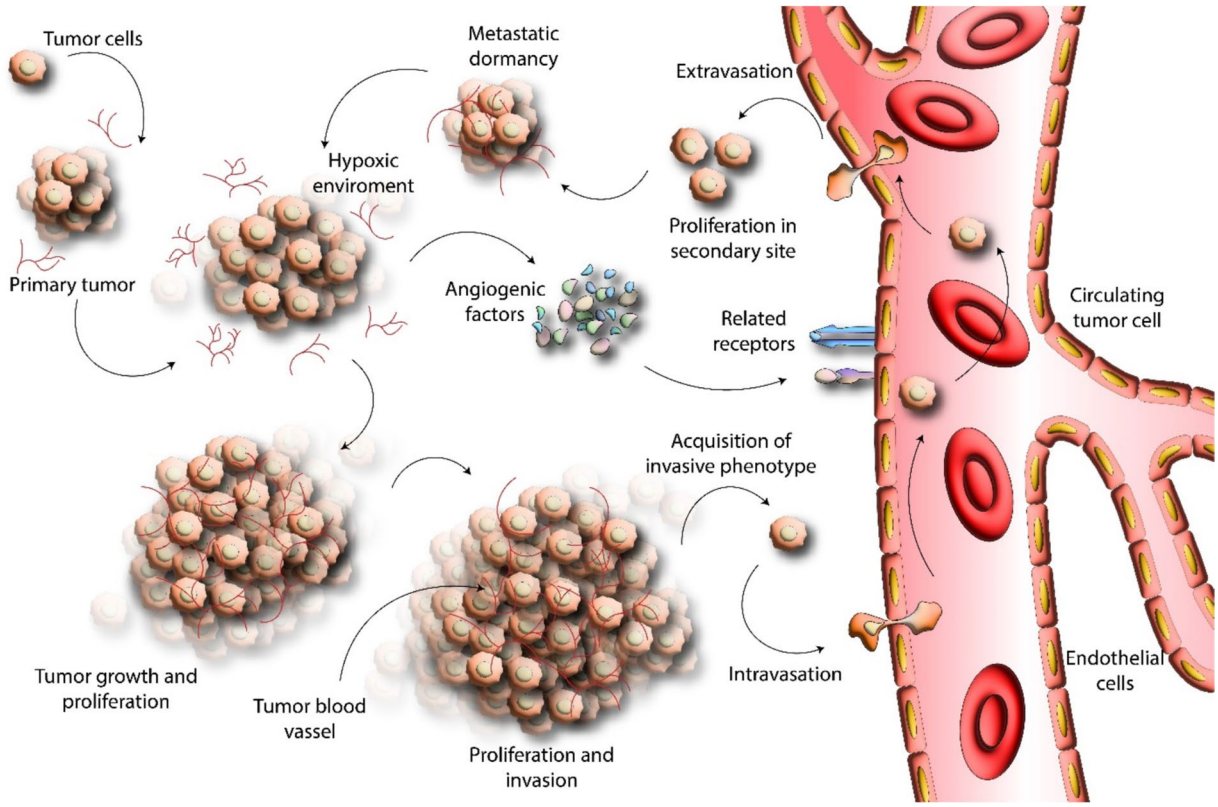

Fig. 1 The evolution of cancer through angiogenesis is driven by the fast proliferation of tumors, which has the effect of decreasing the oxygen supply. Angiopoietin, FGF, PDGF, and VEGF are among of the pro-angiogenic factors that are increased as a consequence of this. This leads in a low-oxygen tumor microenvironment (TME), which drives excessive blood vessel creation by boosting the levels of various pro-angiogenic proteins. An increase in the transport of oxygen and nutrients is made possible by the construction of new blood vessels, which in turn makes it easier for tumor cells to continue their growth, survival, and multiplication. As these cells become increasingly aggressive, they proliferate, expand, and promote the development of new blood vessels. Ultimately, they will penetrate and travel to distant regions via the bloodstream

responses [10]. Cells that are activated T and B lymphocytes, as well as monocytes and macrophages, are the cells that are responsible for the production of miRNA-155 [11, 12]. The production of blood cells, the maintenance of lymphocyte balance, and the development of immunological tolerance are all processes that are influenced by microRNA-155. It has been discovered that certain B cell malignancies that originate from myeloid cells have a negligible rise in the levels of miR-155. On top of that, research indicates that an increase in the expression of the miR-155 gene in mice may hasten the growth of cancer [13]. This review aims to comprehensively examine the dual role of miR-155 and exosomal miR-155 in tumor angiogenesis. We analyze their mechanisms of action, interactions with key signaling pathways, and potential as targets for therapeutic intervention, with the goal of informing novel anti-angiogenic strategies in cancer treatment.

Angiogenesis and cancer

A tumor is a form of biological tissue distinguished by its fast growth, high metabolic activity, and strong vitality, demanding a much greater supply of nutrients and oxygen compared to regular cells. When the tumor is in its early stages of development, it does not have its own blood vessels, which indicates that it is not aggressive and that it is dependent on the tissues that surround it to spread oxygen and nutrients in order to maintain its own survival [14]. Tumor blood vessel growth is limited or inactive because there are not enough factors that promote angiogenesis and because the extracellular matrix contains signals that inhibit vascular development. As a result, blood vessel formation within tumors occurs infrequently (refer to Fig. 1) [15]. Once a solid tumor grows larger than 1–2 mm^3, the neighboring tissues are unable to supply sufficient resources to sustain its continued development [16]. As a tumor grows, it establishes a microenvironment marked by ischemia, acidosis, hypoxia, and elevated interstitial pressure. This situation leads to the creation of a number of growth factors and cytokines, which in turn encourage the construction of new lymphatic and blood arteries to satisfy the metabolic demands of the tumor and to assist the evolution of the tumor [16, 17]. As tumor cells rapidly proliferate, areas distant from blood vessels within the tumor experience an increase in acidity, a lack of sufficient oxygen, and higher pressure in the spaces between tissues. This condition promotes the growth and aggressiveness of the tumor tissue (Fig. 1). Over time, this process evolves into carcinoma, acquiring the capacity for aggressive behavior and invoking a stromal reaction. This reaction comprises intratumoral angiogenesis, growth of fibroblasts, infiltration of leukocytes, and deposition of ECM, especially in tumors that are malignant [18–20]. Cancer cells consistently secrete or elevate the amount of various pro-angiogenic factors, which trigger the activation of ECs, pericytes, CAFs, endothelial progenitor cells, and immune cells. As a result of this stimulation, angiogenesis stays in a highly active state, leading to processes such as the development of new blood vessels, alterations in the extracellular matrix, the separation of pericytes, and the differentiation of endothelial cells. The formation, propagation, and metastasis of cancers are all significantly influenced by these mechanisms, which ultimately play a very important role [21–24]. Due of this tendency, tumors are commonly referred to as wounds that do not heal, providing an indirect explanation [25]. Additionally, tumors can undergo metabolic stress due to several factors, including immune system activation, inflammatory reactions, changes in oncogenes, and medical treatments. These factors promote tumor angiogenesis, which in turn enhances tumor invasion and metastasis [26].

MiR-155 and biological functions

miRNAs play an essential role as intermediaries within cells and are important for enabling cell-to-cell signal transduction [27, 28] [29, 30]. MiR-155, a type of microRNA, originates from the miR-155 host gene (miR-155HG) [31], miR-155 is crucial in various cellular functions, such as inflammation (refer to Fig. 2 for more information) [32, 33], immunity [34, 35], fibrosis [36, 37], autophagy [38–40], and carcinogenesis [34, 41, 42]. There is evidence from a number of studies that microRNA-155 is involved in the process of controlling the expression of about 250 genes [34, 43], Additionally, miR-155 regulates thiamine, an essential cofactor for certain enzymes involved in energy metabolism [44]. Various signaling pathways play a role in controlling miR-155 expression, with cytokines like TGF-β having the potential to either elevate or reduce its amounts [41, 45, 46]. On the other hand, IRF3 can mitigate neuroinflammation by regulating miR-155 expression [47]. Furthermore, miR-155 has been shown to affect inflammation linked to IL-17/IL-9 in the context of wound healing, emphasizing its promise as an effective therapeutic approach for reducing inflammatory responses in wound tissue [48]. Results from another research indicated that mice deficient in Ets2 exhibited a decreased miR-155 response upon LPS exposure [49]. Additionally, IL-10 suppresses Ets2, which leads in lower levels of miR-155. It has been revealed by Zheng and his colleagues that there is a specific place in the promoter region of the BIC gene, which includes miR-155, where NF-κB is able to bind itself [50]. The findings of a separate study revealed that glucocorticoids had the ability to reduce the levels of miR-155 by inhibiting the activation of NF-κB, which was a surprising

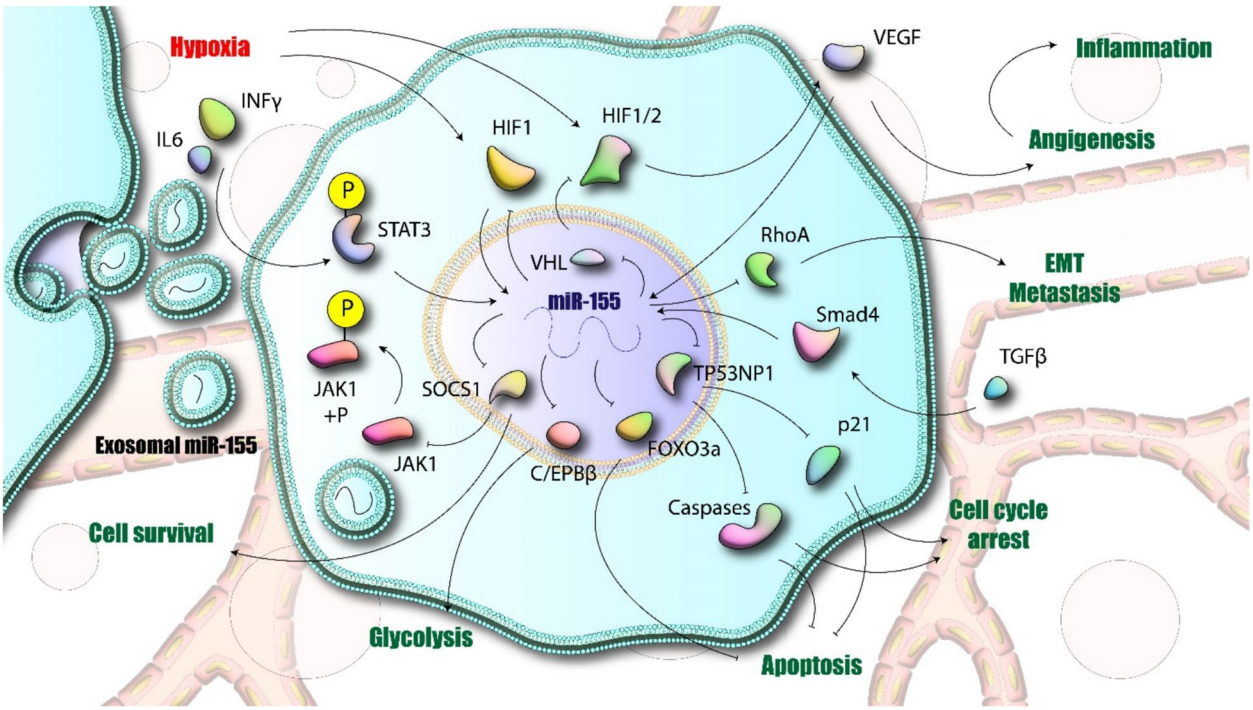

Fig. 2 miR-155 participates in multiple cellular functions. It is possible that hypoxic circumstances might lead to an increase in the production of miR-155 in cancer cells. This is because some response elements are present in the promoter region of miR-155. This particular microRNA has a strong connection to inflammation and exerts a major impact on lung cancer, ultimately having the capacity to alter the survival of cancer cells. In order to accomplish this objective, the levels of the tumor suppressor protein VHL are decreased, which in turn stimulates the development of new blood vessels. One-way TGF facilitates metastasis is by increasing miR-155 levels. This is accomplished through the action of Smad4. MiR-155 reduces RhoA protein levels, which breaks tight junctions and improves epithelial cell plasticity. This results in enhanced invasiveness and migration via enhancing epithelial–mesenchymal transition (EMT), which is triggered by transforming growth factor-beta 3. It is possible that lowering or inhibiting miR-155 could cause cells to halt in the G0/G1 phase of the cell cycle, which will signal the beginning of the process of programmed cell death. As a consequence of this, the growth of cancer cells in DLBCL and ccRC is restricted thanks to this. Another study showed that miR-155 inhibits Caspase 3 activity, which results in reduced cell death in nasopharyngeal cancer. Additionally, miR-155 has the potential to impact glucose metabolism by improving insulin sensitivity. This happens as a result of the suppression of C/EBPβ, which is a negative regulator in the insulin signaling pathway. This, in turn, leads to an increase in glycolysis. Ultimately, the presence of miR-155 is related with lowered levels of SOCS1 in non-small cell lung cancer (NSCLC), which might ultimately contribute to worse survival rates

yet significant discovery. Furthermore, new research on inflammation have indicated that the transcription factor FOXP3, which is associated to immunological response, can impact the expression of miR-155 [51]. Because of its capacity to regulate the expression of ZEB2 and SATB1 inside Treg cells, miR-155 plays a significant function in the immune system [52].

In a different line of research, studies have indicated that miR-155 regulates various genes that play roles in adipogenesis, as well as in carbohydrate and lipid metabolism [52]. MiR-155, originating from adipocytes, impacts participates and diet-induced obesity [53]. In order to evaluate the expression of miR-155, the research team that was directed by Miller conducted studies on male C57BL/6 wild-type mice as well as mice that lacked endogenous miR-155. Over the course of 6 months, both groups of mice were fed a diet that was heavy in fat. The results of their research demonstrated that the gene Nr1 h3 LXRα is affected by microRNA-155 and plays a crucial role in determining the liver features that are detected in mice that are lacking in microRNA-155 [54]. It is intriguing how the role of miR-155 varies depending on gender. Unlike male mice, female mice with a C57BL/6 genetic background lacking the miR-155 gene are protected against obesity resulting from a high-fat diet [55]. This occurrence, observed in female mice with specific gene deletions, is associated with safeguarding against obesity and changes in glucose metabolism. Consequently, the findings confirm that both female and male miR-155 knockout mice show reduced adipose tissue weight, although male knockout mice display increased liver steatosis [54, 55].

Studies reveal that the PIK3R1-PDK/AKT-FOXO3a-cMYC signaling pathway stresses the relevance of miR-155 as a major regulator of glucose metabolism in breast cancer. This is achieved by enhancing the cells' energy

metabolism [56]. In a similar manner, the combination of the NF-κB-miR-146a pathway and the NF-κB-miR-155 pathway can have an impact on the regulation of the inflammatory response [57]. Importantly, the interaction between miR-155 and miR-146a generates a distinct regulatory framework that impacts a specific form of macrophage. Throughout the course of the inflammatory response, this particular structure is accountable for changing the activity of NF-κB inside the body [58]. MiR-155-5p is thought to contribute to demyelination by increasing the expression of the normal NgR and decreasing the Smad signaling pathways in male C57BL/6 mice that were fed a diet containing 0.2% cuprizone. This was discovered in a subsequent analysis by researchers, who found that the levels of miR-155-5p had significantly increased. This was seen in mice that were made to consume foods that contained 0.2% cuprizone [59]. Research has been carried out on living organisms as well as in controlled laboratory environments to examine the connection between miR-155 and allyl-isothiocyanate. These studies have shown that there is a considerable drop in the levels of miRNA-155 and interleukin-1β, which indicates that there is a significant reduction in inflammation [60].

miRNAs are closely linked with post-transcriptional gene expression regulation under various conditions and can regulate metabolic control [61]. The majority of studies on metabolic and immune-related disorders concentrate on the importance of miR-155 in these conditions. Research has shown that microRNA-155 is found in both immune cells and fat tissues, indicating its potential impact on various diseases, such as diabetes mellitus [52, 62, 63].

Under typical physiological circumstances, miR-155 contributes to sustaining healthy glucose levels by managing the equilibrium of blood sugar and insulin sensitivity [64]. Increased levels of miR-155 in adipose tissue and liver linked to skeletal muscles have been shown to have the potential to increase glycolysis, encourage IRS-1 phosphorylation, and stimulate the activation of the serine-threonine kinase AKT when insulin is present in mice that have undergone genetic modification (refer to Fig. 3). Additionally, microRNA-155 plays a role in regulating important inhibitors of insulin signaling, including HDAC4, C/EBPβ, and SOCS1 [65].

miRNAs can influence host immune homeostasis and immune responses by negatively regulating mRNA translation and balance [66]. miR-155 is a versatile microRNA found in immune system cells, essential for the body's immune function [67]. To make matters worse, miR-155 levels rise as a result of both infection and injury [68]. According to the findings of several studies, microRNA-155 has the ability to stimulate a wide variety of immune cells, such as T cells, B cells, dendritic cells, and macrophages [34, 66, 67]. Additionally, it is believed that miR-155 contributes to the body's typical immune reaction to specific inflammation-inducing substances [51, 69]. NF-kB and AP-1, two transcription factors that are well-known for their role in increasing inflammation, are responsible for controlling the amounts of miR-155 via controlling their expression [70–72]. AP-1 is responsible for directing how macrophages respond to TLR-3 and TNF-α, while NF-kB is in charge of guiding their reaction to the LPS receptor [70, 73].

MiR-155 has been shown to have a role in the remodeling of lung airways through the promotion of collagen formation and the infiltration of inflammatory cells, according to research conducted using knockout mice [74]. The lack of selection for high-affinity plasma B cells leads to a reduction in the generation of IgG1 antibodies, which in turn leads to a lessened B-cell memory response [71, 75]. Furthermore, BIC and miR-155 impact adaptive immunity by targeting B cells in the germinal centers of the tonsils [76]. An additional point to consider is that the activation of the ERK and JNK signaling pathways results in an increase in the expression of miR-155 in B-cell lines. Through the use of chromatin immunoprecipitation, researchers have showed that the activation of the B-cell receptor (BCR) leads to the recruitment of FosB and JunB, which then bind with the miR-155 promoter [72].

Various studies conducted on T cells have demonstrated that naïve T cells derived from mice that lack miR-155 have a greater propensity to evolve into Th2 cells. This mechanism results in the release of Th2 cytokines into the circulation. These cytokines include IL-5, IL-4, and IL-10 [72, 75]. In addition, when T cells are exposed to antigens, they have attenuated responses and a lower production of interferon and interleukin-2 [71, 74]. Furthermore, it is worth noting that miR-155 has an impact on IFN-γ in T cells, which implies that it hinders the transmission of IFN-γ signals in CD4 + T cells and encourages the development of Th1 cells [77].

Inflammation is an intricate biological and pathological reaction that encompasses the body's response to injuries and infections, and therefore, inflammatory processes are associated with various diseases [78, 79]. miRNAs is identified as key regulators of inflammation, as they influence multiple inflammatory pathways [78]. miRNAs have the ability to influence inflammation by either enhancing or reducing it, contingent upon the specific mRNAs they target [33, 78, 80, 81].

Multiple situations have been investigated to comprehend the function of miR-155 in inflammatory processes. For example, when considering atherosclerosis, miR-155 impacts the condition by suppressing downstream target

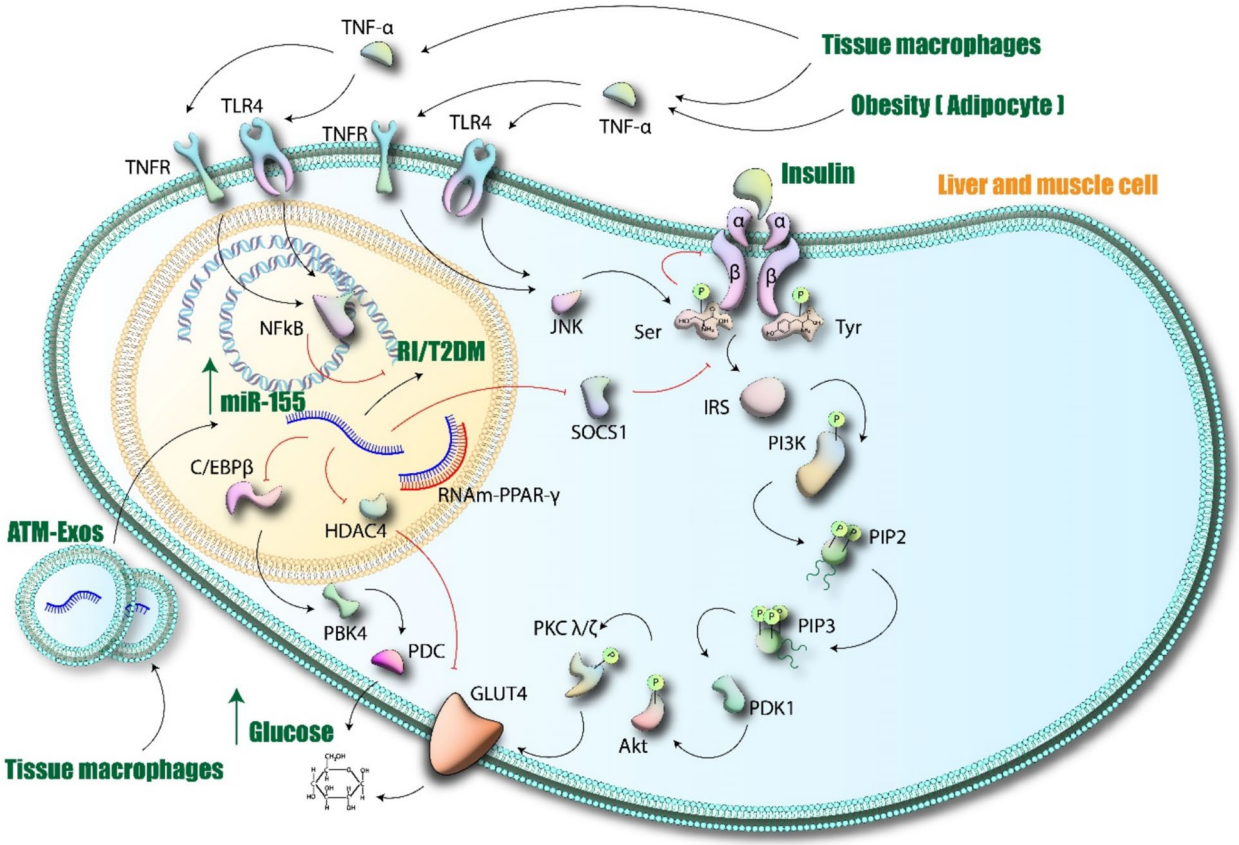

Fig. 3 Mechanistic overview of miR-155 in regulating insulin signaling and glucose metabolism. MiR-155 enhances insulin sensitivity by targeting key inhibitors of the insulin signaling pathway, including SOCS1, HDAC4, and C/EBPβ. Upon insulin binding to its receptor (IR), phosphorylation of insulin receptor substrates (IRS-1/2) activates PI3 K, leading to the conversion of PIP2 to PIP3. This cascade stimulates PDK1 and Akt, promoting GLUT4 translocation and increased glucose uptake. MiR-155 indirectly supports this process by enhancing AKT phosphorylation and glycolytic activity. Additionally, miR-155 counteracts TNF-α and JNK-mediated pathways that contribute to insulin resistance, thus playing a protective role in maintaining glucose homeostasis

genes like MAP3 K10, HBP1, and Bcl-6 [82, 83]. Furthermore, research indicates that miR-155 is crucial in retinal neovascularization. Lowering miR-155 levels reduces retinal neovascular growth by influencing the phosphorylation of components in the PI3 K/Akt signaling pathway within cells [84]. Furthermore, microRNA-155 is responsible for the enhancement of the expression of scavenger receptors including CD36, CD68, and LOX-1 in macrophages that are produced from THP-1 monocytes. This, in turn, leads to an increase in the cholesterol absorption carried out by these cells [85]. According to the findings of another investigation, increasing the levels of miR-155 in macrophages enhances the inflammatory response to lipopolysaccharide (LPS). The modification of SOCS-1, which in turn makes it more difficult to remove cholesterol from the cells, is the means by which this will be done [86]. Moreover, miR-155 is suggested to act as a regulatory point for adjusting the immune system by impacting various molecules that govern immune responses, including SMAD2 and FOXO3a [87–89]. In addition, the rapid inflammatory response in macrophages is significantly influenced by miR-155's inhibition of Bcl6 [82]. The discovery of the TLR/IL-1 inflammatory pathway has been made possible by the utilization of microarray technology. This advancement has brought to light the route's function as a prominent target for miR-155 and its direct influence on the levels of TAB2, which is an essential signaling protein [69].

On many occasions, it has been demonstrated that the levels of miR-155-5p in mouse pancreatic β-cells rise during endotoxemia, a condition that is associated with elevated levels of blood lipids. This rise enhances glucose metabolism, aiding β-cells in adapting to the insulin resistance induced by obesity (see Fig. 2) [90]. A compelling in vivo study on NAFLD indicated that increased miR-155 levels reduce liver fat accumulation by inhibiting the LXRα-dependent lipogenic pathway. Furthermore, increasing miR-155 levels greatly boosts glucose

metabolism, and HK2 is recognized as an indirect target in this process [91].

A number of genes are regulated by the miR-155 gene, which results in an increase in glucose metabolism (Fig. 3). In the process of insulin binding to the α-subunit of the insulin receptor (IR), the signaling proteins IRS-1 and IRS-2 of the insulin receptor phosphorylate the p85 regulatory subunit of PI3 K. The transition of PIP2 into the secondary messenger PIP3 is brought about as a result of the activation of PI3 K. This cascade activates PDK-1 and Akt, leading to the phosphorylation of PKCλ/ζ isoforms and GLUT4 storage vesicles. The development of insulin resistance is associated to the suppression of PPAR-γ. TNF-α, which stands for tumor necrosis factor-alpha, has the ability to alter the way in which insulin signals are processed inside tissue macrophages. This modification can result in insulin resistance and contribute to the progression of type 2 diabetes mellitus (T2DM). JNK promotes insulin resistance by directly adding a phosphate group to IRS proteins. Additionally, ATM can release exosomes containing miRNA, which can affect insulin target cells and promote glucose intolerance and insulin resistance.

MiR-155 and cancer angiogenesis

HIF-1α is a transcription factor essential for cellular response to low oxygen conditions. It is vital for the proliferation of malignancies and the formation of new blood vessels. HIF-1α is well acknowledged to have a significant role in the progression of recurrent colorectal cancer (RCC) due to its capacity to limit the development of tumors. One-way MiR-155 facilitates the advancement of RCC is by decreasing HIF-1α levels. It has been shown by research that elevating the levels of miR-155 by the use of arsenic trioxide might potentially limit the formation of new blood vessels in prostate cancer patients [92, 93]. Moreover, the genes NR3 C2, E2 F2, PEG3, FOXO3a, FOXO3, and BACH1 have been recognized as targets of miR-155. These genes play a role in controlling transcription, monitoring the cell cycle, reacting to DNA damage, and modulating inflammatory processes. They are crucial in either inhibiting or promoting the development of tumors [94–107]. Studies indicate that miR-155 enhances the growth and spread of ccRCC by attaching to the 3′UTR of specific mRNAs. On the contrary, research has shown that MiR-155 acts as an inhibitor in prostate cancer. It accomplishes this by reducing the levels of VEGF and limiting the creation of new blood vessels. This is accomplished by inhibiting the TGF-β/SMAD2 signaling pathway [108].

Numerous studies have demonstrated that arsenic trioxide has the ability to increase the levels of miR-155, which in turn inhibits the growth and proliferation of blood vessels in persons who have prostate cancer [108], [109].

Through their research, Chen and his colleagues have established that the expression of miR-155–5p is lowered in bladder cancer cell lines [110]. Studies show that triggering the Notch signaling pathway and suppressing MTGR1, increased miR-155-5p levels can obstruct cell migration, new blood vessel formation, and cell invasion [110].

According to the findings of a recent study, elevating the levels of miR-155 in tumor-associated macrophages (TAMs) results in a reduction in the production of cytokines and is related with the promotion of their transition from an M2 to an M1 polarization state [111]. There is a significant lack of clarity regarding the precise function of microRNA-155 in tumor-associated macrophages that originate from endothelial cells. The fibroblast growth factor 2 (FGF2), which belongs to the family of fibroblast growth factors, is widely recognized for its ability to promote the development and maturation of several cell types, including cancer cells and fibroblasts [112]. An important signaling molecule, FGF2 performs a significant function in starting the development of blood vessels [113]. MiR-155 has been demonstrated to have an effect on the production of FGF2, which in turn has an effect on the angiogenesis process in non-small cell lung cancer (NSCLC), according to a prior research [114]. Recent study gives insufficient insight of how miR-155 affects TAMs in the context of FGF2 generated from EC.

In a research study, scientists investigated how miR-155 impacts TAMs originating from EC [115]. In this research, scientists employed Western blotting and quantitative real-time PCR techniques to measure the quantities of miR-155 and FGF2 in both tissue samples and laboratory conditions. These constructs were delivered into TAMs by the process of transfection, and then the culture medium of the TAMs was collected for further examination. ELISA was utilized in order to determine the levels of inflammatory cytokines and FGF2 in the body. Transwell analysis and CCK8 assays assessed invasion, migration, and cell viability, while Matrigel angiogenesis assays explored vascular formation in HUVECs. The results of the research showed that the levels of miR-155 were lower and the levels of FGF2 were greater in the EC tissue and the cell lines as compared to the levels that were found in the normal controls. The introduction of the miR-155 mimic into TAMs resulted in a rise in the levels of IL-12, TNF-α, and iNOS, while at the same time causing a decrease in the levels of IL-10, IL-22, and Arg-1 in the surrounding environment. TAMs with greater miR-155 levels demonstrated lower angiogenic activity and impacted the migration, survival, and invasiveness of ECA109 cells. However, the higher FGF2 levels inhibited

the effects of miR-155 on cell survival, tumor-like activity, and angiogenesis. The study's results reveal that miR-155, controlled by TAM, can inhibit the migration, proliferation, and penetration of EC cells. Furthermore, it may limit the creation of new blood vessels by changing the expression of FGF2. Consequently, targeting miR-155 to control FGF2 presents a possible therapeutic method to limit the evolution of EC [115].

The research conducted by Kong and his colleagues indicated that miR-155 interacts directly with the VHL gene, which in turn stimulates the development of new blood vessels in breast cancer affected individuals [116]. Research indicates that boosting miR-155 levels in HUVECs artificially improves their ability to form networks, invade, proliferate, and migrate. In contrast, decreasing miR-155 expression results in inhibitory effects on these processes. Furthermore, introducing ectopically expressed miR-155 into the mammary fat pad led to marked angiogenesis, tumor growth, necrosis, and the recruitment of pro-inflammatory cells, including TAMs. On the other hand, the study found that the presence of VHL counteracts the effects caused by miR-155. Additionally, there is an inverse link between miR-155 and VHL expression. The development of triple-negative breast cancer (TNBC) is linked to elevated levels of miR-155, which is related with advanced stages of cancer, metastasis to lymph nodes, poor patient outcomes, and progression of the disease. Through the process of down-regulating VHL, miR-155 plays a role in the development of tumor angiogenesis, which ultimately results in a more aggressive course of the illness [116].

Exosome biogenesis and function

Exosomes are extracellular vesicles (EVs) ranging from 40 to 100 nm in diameter, formed within multivesicular bodies (MVBs) of the endosomal pathway. Their biogenesis begins with the inward budding of the endosomal membrane, forming intraluminal vesicles (ILVs) within MVBs. Upon fusion of MVBs with the plasma membrane, ILVs are released into the extracellular environment as exosomes. Exosomes possess a lipid bilayer membrane enriched in cholesterol, sphingomyelin, and lipid rafts. This structure contributes to their stability in circulation and facilitates selective cargo loading. They also express surface proteins such as CD63, CD81, and CD9, which serve as markers for identification and are involved in cell targeting [117–119]. Exosomes carry a diverse cargo that includes: proteins e.g., tetraspanins, heat shock proteins, MHC molecules; lipids**:** sphingolipids, phosphatidylserine and nucleic acids**:** microRNAs (miRNAs), long non-coding RNAs (lncRNAs), mRNAs, and DNA fragments. The content of exosomes reflects the physiological or pathological state of their cell of origin. [120]. Exosomes serve as key mediators of intercellular communication. Their functional roles include: modulating immune responses, remodeling the tumor microenvironment, promoting angiogenesis, facilitating metastasis and inducing drug resistance. In cancer, tumor-derived exosomes influence surrounding cells (e.g., endothelial cells, fibroblasts, immune cells) to support tumor progression. [120]. Table 1 shows various features of exosomes.

Exosomal miR-155 and angiogenesis in cancer

The signaling pathway known as JAK2/STAT3 is frequently activated in a wide variety of tumors. This pathway has a function in controlling the creation of blood vessels, the proliferation of cells, and the migration of malignant cells. Upon JAK2 activation, STAT3 gets phosphorylated, leading to dimerization and its movement into the nucleus. Following its entry into the nucleus, STAT3 forms attachments to specific DNA sequences, which in turn triggers the production of gene-specific information [127]. Research indicates that the JAK2/STAT3 signaling pathway influences blood vessel development. This is accomplished by controlling the

Table 1 Various features of exosomes

Feature	Description	Relevance in cancer	References
Size	40–100 nm	Enables circulation in various body fluids	[121]
Origin	Formed inside multivesicular bodies (MVBs) via endosomal pathway	Reflects cellular state of origin (normal vs. malignant)	[122, 123]
Membrane	Lipid bilayer rich in cholesterol and tetraspanins (CD63, CD81, CD9)	Facilitates cell targeting and cargo protection	[122]
Cargo	miRNAs, lncRNAs, mRNAs, DNA, proteins (e.g., HSPs, MHCs), lipids	Enables gene regulation in recipient cells	[124]
Functions	Intercellular communication, immune modulation, angiogenesis, metastasis	Alters tumor microenvironment; supports progression and drug resistance	[125]
Applications	Diagnostics, prognostics, drug delivery, therapeutic targets	Liquid biopsy potential; engineered exosomes for miRNA delivery	[126]

production of pro-angiogenic molecules, such as FGF2 and VEGFa, as well as enzymes, such as MMP9, that are involved in the breakdown of proteins [128–130]. SOCS proteins suppress JAK kinases and prevent STAT from interacting with receptors. SOCS1 plays a crucial role in inhibiting the JAK2/STAT3 signaling pathway. Studies have revealed a relationship between lower levels of this suppressor and numerous human malignancies, as well as the creation of new blood vessels in tumors [131, 132].

Zhou and colleagues discovered that melanoma cell lines, whether highly metastatic (B16 F10) or weakly metastatic (B16), produce exosomes containing miR-155, which in turn activate cancer-associated fibroblasts (CAFs). This activation causes an increase in factors that promote angiogenesis, including FGF2, MMP9, and VEGFa, within cancer-associated fibroblasts (CAFs). Exosomal microRNA-155 is responsible for the enhancement of pro-angiogenic activity. By blocking SOCS1, which in turn stimulates the JAK2/STAT3 signaling cascade, it is able to achieve this goal. When it comes to the fight against melanoma, the findings of this study point to a potential target for anti-angiogenic therapy [133].

Exosomes are created by hepatocellular carcinoma (HCC) cells when they are exposed to low oxygen levels. Throughout the course of their research, Matsuura and his colleagues explored how these exosomes influence the process of blood vessel creation in endothelial cells. Additionally, it was shown that the creation of tubes in HUVECs was considerably enhanced by exosomes that were produced under circumstances of low oxygen [134]. They discovered that the level of miR-155 grew greatly in both cells and exosomes when exposed to low oxygen circumstances in each kind of habitat. Decreased miR-155 levels in HCC cells resulted in less exosome-induced tube formation in HUVECs under low oxygen conditions. Additionally, a strong link was discovered between high amounts of exosomal miR-155 in the plasma prior to surgery and the chance of an early recurrence. The findings demonstrate that exosomes coming from hepatocellular carcinoma (HCC) cells in low-oxygen settings accelerate the development of tube-like structures in human umbilical vein endothelial cells (HUVECs). Furthermore, there is a potential that exosomal miR-155 contributes to the angiogenesis that is associated with HCC [134].

Due to the fact that triple-negative breast cancer is the most prevalent kind of breast cancer, it is essential to identify possible therapy targets in order to create drugs that are successful. In TNBC, angiogenesis supports tumor growth and metastasis, with miR-155 contributing to this process. Exosomes, which are small vesicles, transport various cargoes, including microRNAs. A study investigated how delivering a miR-155 antagomir via exosomes affects tumor migration, invasion, and angiogenesis in TNBC [135]. The findings indicated that employing exosomes to transport miR-155 antagomirs into HUVEC cells notably reduced miR-155 expression while increasing the levels of PTEN and DUSP14. Furthermore, the formation of tubular structures by HUVEC cells was significantly impaired after being treated with exosomes containing miR-155 antagomirs, a result that was validated by a CAM assay. Moreover, after the MDA-MB-231 cells were exposed to exosomes containing miR-155 antagomirs, their migration and invasion were considerably reduced. For the purpose of reducing migration, invasion, and the development of new blood vessels in triple-negative breast cancer, the utilization of exosomes for the transportation of miR-155 inhibitors has been demonstrated to be effective. This is due to the influence that it has on PTEN and DUSP14 [135].

One of the most aggressive forms of cancer, pancreatic ductal adenocarcinoma (PDAC) is often linked with a bad prognosis. This is a commonly held belief among medical professionals. The density of blood vessels has a favorable correlation with the advancement of triple-negative breast cancer. Recent study reveals that tumor-associated macrophages (TAMs) might be involved in the formation of new blood vessels, albeit the particular pathways responsible for this impact are not yet completely known [104]. The number of microvessels in pancreatic ductal adenocarcinoma tissues was found to have a positive correlation with the presence of M2 macrophages, according to the findings of several studies. Furthermore, it was shown that exosomes produced from M2 macrophage-derived extracellular vesicles were able to stimulate angiogenesis in mouse aortic endothelial cells when subjected to experimental circumstances. In mice, M2 MDEs result in increased blood vessel density and assist in the development of tumors under the skin. Additionally, unlike M0 MDEs, M2 MDEs display elevated amounts of miR-155-5p and miR-221-5p, which are then passed on to MAECs due to their heightened expression. This shows a relationship between tumor-associated macrophages (TAMs) and the creation of new blood vessels in pancreatic ductal adenocarcinoma (PDAC), which is enhanced by the dissemination of exosomes. According to this relationship, targeting microRNAs in exosomes that originate from TAMs may have tremendous promise for both diagnostic and therapeutic applications in the treatment of pancreatic ductal carcinoma [104]. Figure 4 depicts the formation process of exosomal miR-155.

Conclusion

MiR-155 and its exosomal form have emerged as crucial regulators in cancer progression, particularly through their role in promoting angiogenesis, modulating immune responses, and influencing the tumor

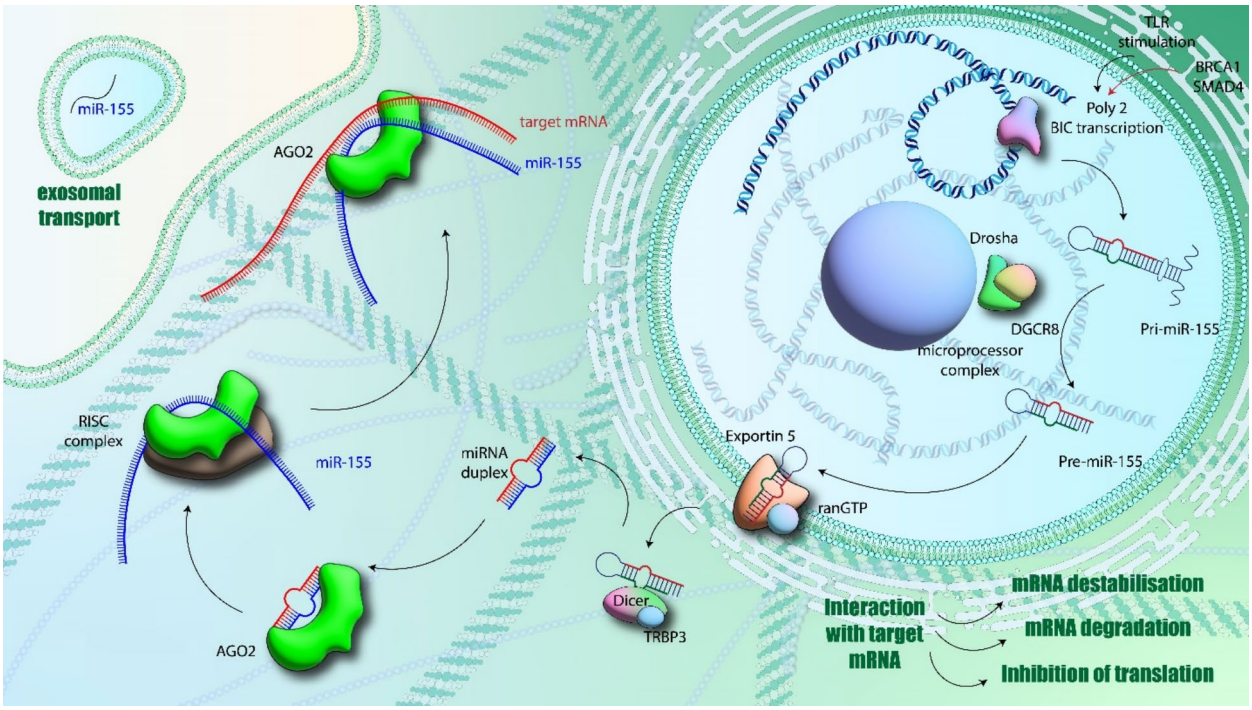

Fig. 4 Biogenesis and release of exosomes containing miR-155. Exosomes are nano-sized extracellular vesicles (40–100 nm) formed within multivesicular bodies (MVBs) through inward budding of endosomal membranes. Upon fusion of MVBs with the plasma membrane, exosomes are released into the extracellular space. They are enriched in lipids, proteins, and nucleic acids, including microRNAs such as miR-155. These vesicles can be taken up by nearby or distant recipient cells, enabling intercellular communication. The figure illustrates how exosomes derived from tumor or immune cells serve as carriers of miR-155, modulating gene expression in target cells and contributing to tumor angiogenesis and progression

microenvironment. Their dual capacity to act within cancer cells and to mediate intercellular communication via exosomes makes them attractive, yet complex, therapeutic targets.

Despite growing evidence of miR-155's oncogenic potential, several knowledge gaps remain. First, the context-dependent role of miR-155—acting as both a promoter and suppressor of angiogenesis in different cancers—requires deeper mechanistic exploration. Second, the precise molecular targets of exosomal miR-155 within endothelial cells and other components of the tumor stroma are not yet fully defined. Understanding how these interactions vary across tumor types and microenvironmental conditions (e.g., hypoxia, inflammation) is essential.

Furthermore, standardized methods for detecting and quantifying exosomal miR-155 in clinical samples are lacking, limiting its current application as a biomarker. Future research should focus on developing sensitive, non-invasive diagnostic tools, including liquid biopsies, to monitor exosomal miR-155 levels as indicators of angiogenic activity or treatment response.

From a therapeutic standpoint, novel delivery systems such as exosome-based carriers, nanovectors, or gene-editing platforms (e.g., CRISPR/Cas9) offer promising strategies to modulate miR-155 activity. However, these approaches must overcome challenges related to specificity, stability, immune clearance, and off-target effects.

In conclusion, while miR-155 is a compelling target in cancer biology, future studies must clarify its diverse roles, validate clinical utility across patient populations, and refine delivery technologies. Addressing these challenges will be key to translating miR-155-targeted interventions from bench to bedside, potentially transforming anti-angiogenic cancer therapies.

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