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REVIEW

Critical roles of miR-21 in promotions angiogenesis: friend or foe?

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Abstract
MiRNAs are small RNA strands that are managed following transcription and are of substantial importance in blood vessel formation. It is essential to oversee the growth, differentiation, death, movement and construction of tubes by angiogenesis-affiliated cells. If miRNAs are not correctly regulated in regard to angiogenesis, it can deteriorate the health and lead to various illnesses, which include cancer, cardiovascular disorder, critical limb ischemia, Crohn's disease, ocular diseases, diabetic microvascular complications, and more. Consequently, it is vital to understand the crucial part that miRNAs play in the development of blood vessels, so we can develop reliable treatment plans for vascular diseases. This write-up will assess the critical role of miR-21/exosomal miR-21 in managing angiogenesis associated with bone growth, wound recovery, and other pathological conditions like tumor growth, ocular illnesses, diabetes, and other diseases connected to formation of blood vessels. Previous investigations have demonstrated that miR-21 is present at higher amounts in certain cancerous cells, and it influences a multitude of genes that moderate the increased creation of blood vessels. Furthermore, studies demonstrated that exosomal miR-21 has the capacity to interact with endothelial cells to foster tumor angiogenesis. For that reason, this review explains the critical importance of miR-21/exosomal miR-21 in managing both healthy and diseased states of angiogenesis.

Keywords Angiogenesis · microRNA · miR-21 · Tumor angiogenesis · Wound healing

Introduction

The process of angiogenesis, which involves the creation of new blood vessels from pre-existing ones, is crucial at all stages of life; from prenatal development right through to one's final years. It is essential for the survival of all tissues by providing capillaries needed for the diffusion of necessary nutrients and metabolites, all of which are within a few hundred micrometers from newly formed capillaries [1]. Changes in metabolism directly affect angiogenesis, which alters the formation of capillaries. Oxygen is essential for maintaining proper balance in the body, and hemodynamic conditions are needed to maintain the stability of the vascular system as well as adjusting the walls of the vessels [1, 2]. Realizing how manipulating angiogenesis can help with medical issues has caused a great deal of excitement in these last forty years [1]. Increases in the production of blood vessels can have a positive effect on diseases such as ischemic heart disease, peripheral arterial disease, and aiding in the healing of wounds. Conversely, decreasing the formation of these vessels can be useful in treating cancer, eye disorders, rheumatoid arthritis, and other diseases. [3]. The number of capillaries in valid tissues is determined by the organism's functional needs. Exercise stimulates the growth of capillaries in the heart and muscles, while decreased physical activity results in a decrease in those capillaries. Additionally, when someone's body weight increases, the capillaries in fat tissues become more plentiful, and conversely, a decrease in body weight leads to the opposite effect. It is clear that angiogenesis is an ongoing process in life [1].

MicroRNAs (miRNAs) are short strands of RNA made up of 20 to 23 nucleotides, which do not create proteins. They can have an influence on the expression of genes by linking up with and possibly eliminating pertinent mRNA molecules or inhibiting their translation into proteins [4–6]. In 2006, the use of miRNA microarrays disclosed the miRNA activity levels in human endothelial cells, suggesting a possible role of miRNAs in the Angiogenesis process [7]. miRNAs have the capability to reduce the levels of proteins that block the formation of new blood vessels, such as Vascular Endothelial

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Growth Factor (VEGF) and basic Fibroblast Growth Factor (bFGF). This may prompt the formation of more blood vessels [8]. Of the miRNAs, miR-21 is one of the most studied and has been found to be elevated in pulmonary fibroblasts, non-small cell lung cancer and breast cancer. Recent studies have shown that miR-21 plays a crucial role in angiogenesis as it could influence on proteins and pathways involved in angiogenesis such as VEGF influencing both normal blood vessel growth, such as during bone healing, and abnormal angiogenesis in diseases like cancer, diabetic retinopathy, and other conditions associated with excessive or inhibited angiogenesis [9]. This study focuses on the critical role of miR-21 and exosomal miR-21 in regulating angiogenesis and its potential therapeutic applications in these disorders.

miR-21

The miR-21 gene is transcribed in the nucleus by the action of RNA polymerase II, giving rise to its primary transcript, pri-miR-21. This pre-miRNA then goes through processing by the Drosha enzyme and the DiGeorge syndrome critical region 8 (DGCR8) protein, which leads to the trimming of the transcript to approximately 72 nucleotides and the formation of a stem-loop configuration. After this modification, the finished miR-21 is considered to be mature [10].

In humans, the region on chromosome 17 where the miR-21 gene is found has been designated q23.1. MiR-21 is found inside Exon 10 of the Vacuolar Membrane Protein 1 (VMP1) gene, which is located downstream of the gene. This gene location is exclusive to certain species [11]. miR-21 expression is heavily influenced by transcribed proteins, which are integral to its regulation. Different transcription factors possess individual methods of regulating miR-21 expression in 293FT cells. PU.1 activates miR-21 through the activating of the AP-1. In contrast, a negative influence exists [12]. In patients with multiple myeloma, the Signal Transducer and Activator of Transcription (STAT)-3 transcription factor stimulates the switch on of a preceding enhancer of miR-21, while the presence of Interleukin (IL)-6 triggers the process of transcription of miR-21 [13]. In addition to control of miR-21 expression through modification of gene transcription, regulation of miR-21 expression also takes place at the post-transcriptional level. Transforming Growth Factor-beta (TGF-β) and Bone Morphogenetic Protein (BMP)-4 enhance the expression of miR-21 through stimulating the Drosha enzyme to convert pri-miR-21 transcripts into functioning forms [14]. In addition, Epigenetic modifications have been linked to the regulation of the amount of miR-21 generated. In individuals with relapsing–remitting Multiple Sclerosis, there is an increase in methylation of miR-21 within CD4 + T cells, which results in decreased miR-21 concentration. This then causes genes that miR-21 targets to become overexpressed [15, 16].

Angiogenesis

The essential difference between angiogenesis and vasculogenesis is that angiogenesis is the formation of new capillaries from pre-existing blood vessels, while vasculogenesis involves the development of new vessels from stem cells. The development of capillaries from existing blood vessels is known as angiogenesis and is usually triggered when the tissue experiences a lack of oxygen (hypoxia). In addition to this conventional "sprouting angiogenesis," vessels can also form from splitting, known as intussusception, in which there is an expansion of the pillars inside them to make two new vessels [17]. Intussusception can occur when there are changes to the circulation during development, physical activity, or when an underlying pathology (such as tumor formation) is present [18, 19]. It is absolutely necessary for the vascular system to keep up with the fluctuating conditions during postnatal development and in various physiological events by rebuilding the vasculature using either type of angiogenesis [17].

The formation of new vessels derived from pre-existing vessels that is called angiogenesis is a complex and varied procedure [20]. In the usual form, the generation of new blood vessels is prevented by natural angiogenesis inhibitors, such as endostatin, angiostatin, IL-12, IL-1, interferons, metalloproteinase inhibitors, and retinoic acid [21, 22]. Inhibitors of angiogenesis can prevent the development of additional blood vessels and help to get rid of existing pathways. Decreasing the levels of angiogenesis can disturb the typical functions of angiogenesis within the body, like aiding in fetal growth, healing injuries, and managing kidney operations. This is particularly important in the context of cancer treatments, as interference with the healing of injuries could result in a longer healing period after surgical procedures [23]. Preventing Vascular Endothelial Growth Factor A (VEGF-A) from functioning properly can lead to a drop in blood vessel volume, owing to enlarged NO production, causing a hike in blood pressure which can make clot formation more likely. This, in turn, can result in stroke or heart attack. These side effects may be a deterrent to the implementation of angiogenesis inhibition as a form of cancer treatment [24].

Mir-21 and its mechanisms in angiogenesis

miR-21 plays a critical role in the regulation of angiogenesis by influencing several pathways that control the formation of new blood vessels. This miRNA is involved in both normal physiological angiogenesis and pathological conditions

like cancer and ischemia. The mechanism by which miR-21 regulates angiogenesis includes the modulation of key molecules such as VEGF, Hypoxia-Inducible Factor 1-alpha (HIF-1α), and TGF-β signaling pathways [25–29]. MiR-21 can target and downregulate inhibitors of angiogenesis, such as Sprouty (SPRY)-1, thus promoting the expression of VEGF [30]. VEGF is a potent pro-angiogenic factor that stimulates endothelial cell migration, proliferation, and tube formation. This is particularly crucial in tumors where increased VEGF expression supports the growth of new blood vessels to nourish the tumor cells.

miR-21 also impacts HIF-1α, a key regulator in response to hypoxic conditions [31]. In tumor cells, for instance, miR-21 promotes the stabilization of HIF-1α, which then upregulates the expression of other angiogenesis-related factors such as VEGF, thereby enhancing blood vessel formation in hypoxic tumors [27, 32]. In addition to these factors, miR-21 regulates TGF-β signaling, which is crucial in maintaining endothelial cell function and promoting angiogenesis [25, 33]. By modulating TGF-β receptors, miR-21 ensures the proper formation of new vessels in tissues requiring vascular support, like bone and muscle tissues post-injury [34, 35].

Role of angiogenesis in homeostasis

3.2.1. Angiogenesis is an essential part of the prenatal and postnatal periods, taking place only during the healing of wounds, expansion of the skeleton, the menstrual cycle, gestation, and certain ailments such as ocular disorders caused by neovascular formation, autoimmune diseases, psoriasis, and the growth of tumors.

Bone morphogenesis

Many bones in the body are created through endochondral ossification, which is when bone replaces non-vascularized cartilage [36]. Through this course of events, the chondrocytes inside the diaphysis of the cartilage or at the end of long bones' epiphyseal growth plates transition from a resting state to proliferating chondrocytes. These cells then enlarge and become the destination of an influx of blood vessels from the metaphysis, with the successive result of ossification nuclei forming within. The osteoclasts and osteoblasts have penetrated the area work together to break down the overgrown cartilage, then destroy and mineralize the extracellular matrix and bone. Inhibition of angiogenesis for creating it in cartilage, causes a decrease in the breakdown of hypertrophic chondrocytes and as a consequence, impedes bone formation. This indicates that VEGF-induced neovascularization is necessary for enabling the removal of cartilage and the development of new bones [37, 38]. Experts have hypothesized that RUNX2 is responsible for stimulating the production of VEGF-A, which is necessary for bone development and vessel formation. In specimens lacking Runt-related transcription factor (RUNX)-2, VEGF-A and Vascular Endothelial Growth Factor Receptor (VEGFR)s are under-expressed in the skeletal organization, preventing blood circulation and limb advancement within the bones, substantiating the supposition that VEGF-A is indispensable for the process of vascularization while bones are growing [39]. Later studies also showed that VEGF-A amounts and the HIF-1α pathway, which detects low-oxygen environments, have a close correlation with bone substance. Additionally, it was realized that neoangiogenesis is essential for making sure that osteogenic cells get to the right spots and providing the right conditions for bone formation [40].

Bone damage can be caused by injuries, infections, tumors, birth abnormalities, and certain skeletal health conditions, resulting in delayed or even no healing, in turn causing lifelong disability and disability [41, 42]. At present, using either one's own cells (autologous) or those of another individual (allogeneic) is the optimal solution for addressing bone deficiencies [43, 44]. Recently, a wide array of reconstructive materials has been made available, granting orthopedic surgeons more options to choose from; yet the most critical factor in bone reconstruction remains the ability to utilize secure, efficient, and attractive methods of filling structural gaps [45–47]. Studies have indicated that angiogenesis is a necessary feature of bone regeneration. Therefore, tissue engineering for bone repair requires a combination of different cellular components, biological molecules, frameworks, and bone-restorative elements to enhance both osteogenesis (bone formation) and angiogenesis (blood vessel formation) [48, 49]. Regarding enhancing angiogenesis and vascularization for bone regeneration, a number of inventive approaches have been explored including bio-functionalizing scaffolds, delivering growth factors and directing signaling pathways by miRNAs [50–52]. Studies conducted in the past have demonstrated that miR-21 is capable of stimulating the transition of MSCs into cells with the ability to form blood vessels and bone, as seen in a rabbit trial [53, 54]. Recently, findings of a separate investigation revealed that miR-21-enveloped robotic systems could foster integration between bone and implant by enhancing angiogenesis and cell adhesion [55].

Utilizing Bone Marrow Stromal Cells (BMSCs) is a desirable method to encourage bone and blood vessel growth in those having bone damage. As harvesting BMSCs from benefactors is rather straightforward, moreover these cells possess the aptitude for its osteogenic properties, and generate a small susceptibility to graft-versus-host disease. Nevertheless, direct implantation of BMSCs confronts different difficulties like demand for precise time and quantity, mediocre coping rate of transplanted cells, development of tumors and denial of acceptance by the immune system [56]. The regenerative functions of BMSCs in tissue also involve

the application of paracrine mechanisms, which can activate immunoregulatory pathways; moreover, these processes are believed to be tied to the release of small extracellular vesicles [57]. Exosomes and microvesicles, both membrane-bound structures measuring 50–150 nm in diameter, are discharged from cells into their external surroundings, carrying out a kind of cellular-communication process [58–65]. Exosomes have an indispensable part to play in preserving the integrity of the elements enclosed within them, for instance, mRNAs, miRNAs and proteins, while simultaneously ensuring that these factors are successfully transmitted to targeted cells to permit normal cellular activities [60, 61, 63, 65, 66]. The use of exosomes offers therapeutic properties similar to that of stem cells and can help to prevent many of the drawbacks of stem cell therapy. Of even more significance, exosomes do not include Major Histocompatibility Complex Class (MHC)-I or MHC-II proteins, thus succeeding in avoiding any of the issues of stem cell therapy and rarely resulting in any significant immune reactions [67]. Previous investigations have revealed that exosomes emitted from BMSCs show similar or indistinguishable curative functions from BMSCs in curing bone diseases, and miRNAs can possibly activate bone cell differentiation and bone formation s [68, 69]. Liu et al. discovered that exosomes created from BMSC carrying the miR-130a molecule can initiate the Phosphatase and Tensin Homolog (PTEN)/Protein Kinase B (AKT) signal pathway, which is responsible for controlling blood vessel formation and rebuild bone [70]. Given that exosomes obtained from BMSC that secrete miRNA-122–5p have the potential to boost the development of osteoblasts in patients with osteonecrosis of the femoral head [71]. Recently, Wu and their associates engineered a temperature-sensitive hydrogel that could be injected to enclose exosomes taken from bone mesenchymal stem cells. This showed an extended delivery and release period and considerably improved bone repair. To analyze the hydrogel's physical, chemical and biological properties, they conducted in vitro experiments which looked at osteogenic differentiation, cell division, and tube formation. The effectiveness of the hydrogels was further tested in rats to heal calvarial defects, with the results indicating a successful enhancement in bone healing. Their investigation revealed that BMSC-derived exosomal miR-21 had a role in fostering angiogenesis. The rise in miR-21 was credited to its ability to manage SPRY2 expression, which exhibited a prohibitive result on Human Umbilical Vein Endothelial Cells (HUVEC) migration, proliferation, and the generation of bFGF, VEGF and Angiopoietin (ANG)-1 growth factors. Experiments of gain and loss of function established that overexpression of SPRY2 in human umbilical vein endothelial cells (HUVECs) weakened, though did not completely nullify, the miR-21's ability to promote angiogenesis [72]. In conclusion, the research showed that the emission of exosomal miR-21 from BMSCs initiates angiogenesis and contributes to bone healing due to its targeting of SPRY2. This can offer a novel method of regenerating bones and tissues, indicating that it will have a promising application in the future.

Combating fractures with efficient healing has proven difficult, making weakened recovery from such an injury a major concern as our population ages [73, 74]. About five to ten percent of times, the mending of a fracture is either held back or weakened, which can lead to countless surgeries being required, and bring about extensive economic impacts [75, 76]. Angiogenesis is essential for the successful completion of bone regeneration and fracture healing [77]. Inadequate blood flow to the swelling at the broken bone stops medicines from being able to effectively help the tissue to rebuild, particularly [77, 78]. Thus, the factors related to angiogenesis, the process of stimulating the growth of new blood vessels, could be an effective remedy for improving fracture recovery and could be vitally important in the development of more effective biological processes. Zhang et al. [79] explored the role of umbilical mesenchymal stem cell exosomes (uMSC-Exos) on angiogenesis-mediated bone regeneration and fracture healing in patients suffering from Osteonecrosis of the Femoral Head (ONFH). Through in vivo and in vitro experiments, they found that the uMSC-Exo-induced angiogenesis was mediated by the highest abundant miRNA, miR-21. In particular, it was determined that miR-21 had an effect on the Phosphoinositide 3-Kinase (PI3K)/AKT signaling pathway in HUVECs through the negatively regulating of SPRY1, thereby increasing both proliferation, migration and angiogenesis. Furthermore, studies suggest that this miRNAs from uMSCs was able to promote growth within the local microvascular network and bone regeneration in living organisms. Summarizing, it can be seen from the evidence that exosomal miR-21 from uMSCs plays a major role in the process of vasculogenesis and the production of new bone through targeting SPRY1.

ONFH is a serious condition that mainly affects young people, and is considered a major contributing factor to the need for total hip replacements in this group of individuals [80]. Mesenchymal stem cells (MSCs) have the potential to be highly effective in treating ONFH in its early stages, but substantial obstacles have to be overcome, such as the fragility of the cells and their limited ability to differentiate osteogenetically. Additionally, the transplanted MSCs may be displaced by existing pathological bone cells in the target area [81, 82].

The destruction of endothelial cells and the inhibition of bone formation are two small but significant signs that glucocorticoids have led to a case of ONFH [83]. It has been proposed that stimulating angiogenesis and osteogenesis could be beneficial approaches to bone regeneration, and thus may be viable therapies to prevent or treat

ONFH [81]. So far, experiments have focused on seeing if Human Umbilical Cord Mesenchymal Stem Cell Exosomes (hucMSC-Exos)—which come from human umbilical cord mesenchymal stem cells—have the potential to help treat ONFH in rats by spurring the growth of new blood vessels in the hurt bone [84]. Understanding how angiogenesis and osteogenesis take place may help create clinical treatment for ONFH on a scientific level. The researchers [85] studied the impact of hucMSC-Exos that have miR-21-5p on the progression of ONFH. They discovered that the level of miR-21-5p was lower in cartilage tissue gotten from individuals with ONFH. They also found that exosomes secreted from hucMSCs had the effect of raising miR-21-5p in hFOB1.19 cells and HUVECs. Subsequent studies revealed that Exo-miR-21-5p had the power to enhance HUVEC angiogenesis and trigger the bone formation of hFOB1.19 cells. In addition, it was discovered that miR-21-5p particularly bound to the SRY-Box Transcription Factor 5 (SOX5) gene, leading to a decrease in its expression, and subsequently caused an increase in the transcription of Enhancer of Zeste Homolog 2 (EZH2). When SOX5 and EZH2 were either overexpressed or absent, the effects of Exo-miR-21-5p were weakened. HucMSC-Exos containing miR-21-5p decreased the amounts of SOX5 and EZH2, which in turn led to greater angiogenesis and osteogenesis [85]. The combination of these results implies that the comprehension of the causes of bone regrowth activated by exosomal miRNAs could be enhanced, which would in turn support the emergence of new treatments. Supplementary evidence is available in Table 1.

Wound healing angiogenesis

When an injury takes place, the first step in repairing the wound is generating a platelet plug and clot that are caused by compounds secreted from the endothelial cells in response to VEGF-A. Afterward, the wound healing process may be divided into three different phases: clotting and inflammation, new tissue formation, and tissue remodeling. When bleeding and irritation occur, platelets become activated and inflammatory cells, macrophages and fibroblasts congregate to help guard the wound from contamination. Subsequently, the injured area is replenished with fresh tissue and proteins to generate a new layer of connective tissue. Finally, the wound undergoes a remodeling process to restore the tissues to its original form [124]. Platelet-derived VEGF-A triggers a heightened amount of the same molecule in the area, triggering the growth of endothelial cells and allowing fibronectin to move from the bloodstream into the exterior of the cells. This fibronectin is then combined with fibrin and other extracellular matrix components to construct a clot [125]. VEGF-A binding to its receptor, VEGFR-2, stimulates the production of nitric oxide and prostacyclin, resulting in increased blood vessel permeability, as well as the mobilization of endothelial cells. [126]. Additionally, when the complement system is set off, platelets release their contents and decomposing bacteria (if present) draw inflammatory cells to the injured area for protection from invading organisms and to provide the cytokines, growth elements, and proteinases which are necessary for new tissue development. Moreover, thrombin in the ECM can induce platelets to emit VEGFA which attracts phagocytic macrophages and neutrophils [127, 128]. These cells possess the capacity to both ingest bacteria and create toxins such as proteases and reactive oxygen species to stop the wound from being infiltrated by outside agents [129].

In reaction to the launching of chemoattractants, keratinocytes assemble and begin to swiftly form a fresh epidermal layer to cover the wound. A sufficient blood supply must be created in order to mend the harmed dermis, prompting the emergence of vessels toward the edge of the wound through the presence of VEGF-A, activating granulation. VEGF-A adjusts the blood vessels by increasing the number of molecules, such as Matrix Metalloproteinase (MMP)-1, MMP-2, Urokinase Plasminogen Activator (uPA) and Tissue Plasminogen Activator (tPA), plus plasminogen activator inhibitor 1. This balance of proteins facilitates the disintegration of the fibrin blood clot and the expansion of cells during the formation of newly grown granulation tissue [130]. The wound healing process can be seen to be underway by noting the various components of the granulation, such as fibroblasts, collagen, immune cells, and blood vessels. Once the wound healing process is complete, the granulated tissue turns into scar tissue, and the cells decrease in number, resulting in the mature scar [131].

Injuries to the skin and underlying tissue are frequently seen as a consequence of accidental traumas, including fractures [132, 133]. The mending of skin/soft tissue damage necessitates a precise combination of cell movement and growth, the formation of collagen, creating of new blood vessels, and wound reconstruction [134]. Some pathological conditions interfere with normal wound healing, resulting in prolonged recovery and potentially chronic non-healing wounds like diabetic ulcers or keloid scars [134, 135]. The importance of minimizing recovery time and preventing scarring after skin and soft tissue trauma is evident. Although various attempts to aid in the healing process have been made, the perfect therapy has yet to be established. Studies have indicated that after wounding the skin, concentrations of miR-21 increase which may help to promote the transition of keratinocytes, thus aiding in the healing of the injured area [136]. The inhibition of miR-21 could lead to prolonged wound healing with fewer fibroblasts and lowered collagen formation in the affected area, which implies that miR-21 has a positive role in controlling fibroblast functions [136]. Very few investigations have figured out how miR-21

Table 1 Role of miR-21 in cancer angiogenesis

Diseases	Expression	Target	Sample	Induce/inhibit of angiogenesis	Refs
Lung cancer	Up	–	In vitro, In vivo	Induce	[86]
Acute monocytic leukemia (AML)	Up	IL-12	Human, In vitro	Induce	[87]
Prostate cancer	–	–	In vitro	Induce	[9]
Malignancy human bronchial epithelial (HBE)	–	–	In vitro	Induce	[88]
Colorectal cancer (CRC)	Up	KRIT1	Human, In vitro, In vivo	Induce	[89]
Breast cancer	–	–	In vitro, In vivo	Induce	[90]
Glioblastoma	Up	–	In vitro	Induce	[91]
Multiple myeloma	Up	–	In vitro	Induce	[92]
Renal cell carcinoma (RCC)	–	PDCD4	In vitro	Induce	[93]
OSCC	Up	RECK	In vitro, In vivo	Induce	[94]
Esophageal carcinoma (EC)	–	PTEN	In vitro	Induce	[95]
Thyroid cancer	Up	TGFBI and COL4A1	In vitro, In vivo	Induce	[96]
HUVEC	–	PTEN	In vitro	Induce	[97]
Chronic myeloid leukemia (CML)	–	RhoB	In vitro	Inhibition	[98]
Ovarian cancer	–	–	In vitro In vivo	Induce	[99]
Cervical cancer	–	–	In vitro	Induce	[100]
Bone-implant osseointegration	–	–	In vitro, In vivo	Induce	[55]
Bone defects	–	SPRY2	In vitro, In vivo	Induce	[72]
Bone regeneration	–	SPRY1	In vitro, In vivo	Induce	[79]
Bone-related diseases	–	–	In vitro, In vivo	Induce	[53]
Osteonecrosis of the femoral head (ONFH)	–	SOX5	In vitro, In vivo	Induce	[85]
Temporomandibular joint osteoarthritis (TMJOA)	–	SPRY1	In vivo	Induce	[101]
Osseointegration	–	–	In vitro, In vivo	Induce	[53]
Lumbar degenerative disc disease (DDD)	–	–	In vitro	Induce	[102]
Soft tissue wound healing	–	–	In vitro, In vivo	Induce	[103]
Corneal wound healing	–	SPRY2	In vitro	Induce	[104]
Diabetic wound healing	–	–	In vitro, In vivo	Induce	[105]
Choroidal neovascularization	–	RhoB	In vitro, In vivo	Inhibition	[106]
Choroidal neovascularization (CNV)	–	–	In vivo	Induce	[107]
Ischemic retina	–	TIMP3	In vivo	Induce	[108]
Proliferative diabetic retinopathy (PDR)	–	maspin	In vitro	Induce	[109]
Diabetic retinopathy (DR)	–	PTEN	In vivo	Induce	[110]
Type 2 diabetes	Down	PTEN and SMAD7	In vitro	Induce	[111]
Crohn's disease (CD)	–	–	In vivo	Induce	[112]
Critical limb ischemia (CLI)	–	–	In vitro	Induce	[113]
Renal ischemia/ reperfusion (I/R) injury	–	TSP-1	In vitro, In vivo	Induce	[114]
Deep venous thrombosis (DVT)	Down	FASLG	In vivo	Induce	[115]
Ischemic Stroke	–	–	In vitro, In vivo	Induce	[116]
Cerebral ischemia (CI)			In vivo	Induce	[117]
Acute Myocardial Infarction (AMI)	–	PTEN	In vitro, In vitro	Induce	[118]
Myocardial infarction (MI)	–	–	In vitro, In vivo	Induce	[119]
Atherosclerosis	Up	PTEN	In vitro	Induce	[120]
Coronary microvascular disease		–	In vitro	Induce	[29]
Traumatic brain injury (TBI)	Up	–	In vivo	Induce	[121]
Spinal cord injury	Up	TIMP3	In vitro, In vivo	Induce	[122]
Early ischemia and hypoxia of grafts	Up	–	In vitro	Induce	[123]

impacts wound revascularization, yet the advantages of miR-21 on endothelial cell operation and the development of tumors have been considered[137, 138]. Recent research has found that increasing the levels of miR-21 can promote wound healing. Studies have shown that upping the level of miR-21 enables stem cells derived from human umbilical cord blood to perform better at wound healing. As a result, UCB may become an even more attractive source of stem cells for promoting skin wound healing due to its benefits of being easy to access, carries no risk to the donor, and having few cases of graft-versus-host disease [126, 139]. Despite the possible medical benefits, the application of stem cells for treatment is still restricted by various dangers, including the development of tumors, clotting, and undesirable immune reactions [140–142]. Administration of exosomes may provide much of the same regenerative benefits that stem cell therapies do, but without any of the ill effects resulting from stem cell transplantation treatments [143, 144]. Investigations have shown that upon localized injection directly into the skin of creatures with either diabetes or burn wounds, exosomes produced by human umbilical cord blood (UCB) stem cells can catalyze skin cell generation, migratory activity, angiogenesis (creation of new blood vessels) and wound closure. All these suggest that therapy based on exosomes could be a highly promising means of mending wounds. In addition to the stem cells, UCB is full of abundant exosomes [144–146]. In a recent experiment researchers explored the capacity of human umbilical cord plasma exosomes (UCB-exosome) to promote wound healing. When the exosomes were injected into the full-thickness skin wounds of mice, they observed an accelerated rate of re-epithelialization as well as lessened scar widths and improved new blood vessel growth. Additionally, UCB-exosome was found to augment fibroblast growth and migration and increase the pro-angiogenic effects of endothelial cells while cells were being cultured in the laboratory. The investigation also determined that a molecule called miR-21-3p, which diminishes the activity of PTEN and SPRY1, is predominantly present in UCB-exosome, and could potentially be accountable for the exosome's healing qualities [147]. All in all, miR-21-3p from umbilical cord blood (UCB) proves to be helpful in mending skin wounds by escalating the amount of angiogenesis, which is attributed to the regulation of PTEN and SPRY1. This is the first research to demonstrate that UCB-exosomes have the potential to aid in the regeneration of soft tissue wounds and analyze the cause in detail. Moreover, another study found that using human epidermal keratinocytes (HEKa)-microvesicles that contain miR-21 mimics can highly improve the healing of skin wounds in diabetic rats [105]. In addition to boosting the growth of fibroblasts, prompting them to move and contract, research has proven that miR-21 contained in microvesicles can also foster an angiogenic effect in endothelial cells and cause an inflammatory response. The microvesicular miR-21 has the possibility to target precise effector genes involved in fibroblasts, like MMP-1, Tissue Inhibitor of Metalloproteinase (TIMP) -3, TIMP-4 and MMP-3, thus increasing their expression and efficiency. Additionally, miR-21 has the ability to control Alpha-Smooth Muscle Actin (α-SMA) and N-cadherin, initiating the transformation of fibroblasts to myofibroblasts. Additionally, miR-21 found in microvesicles has been observed to boost the production and liberation of IL-8 and IL-6, intensifying the immune response. It has been determined that on a protein level, PTEN and Reversion-Inducing Cysteine-Rich Protein with Kazal Motifs (RECK) are decreased, while at the same time the Mitogen-Activated Protein Kinase (MAPK)/Extracellular Signal-Regulated Kinase (ERK) signaling cascade is stimulated, leading to the advancement of fibroblast operations [105]. The findings of this research imply that microvesicles loaded with miR-21 that are produced by human keratinocytes exert a powerful effect on the healing of wounds in diabetic rats by spurring new blood vessel formation. Hence, the use of miR-21 as a therapeutic target for wound healing is highly innovative. Additionally, the cornea's external layer, known as the corneal epithelium, serves a vital function of reducing the risk of infection by external agents by forming a barrier [148, 149]. Around 10 percent of the depth of the cornea is made up of its epithelial layer, which is kept in place and supplied due to the presence of restraints provided by the acellular and concentrated stroma of collagen fibers in a space which has no blood vessels [150, 151]. The presence of vessels inside the corneal epithelium disrupts its normal functioning, eventually resulting in decreased vision [152]. Studies have verified an increase in miR-21 levels in corneas that have been damaged by alkali burns when compared to the levels found in healthy corneas. Giving antagomir-21 to subjects in vivo largely decreased the amount of HIF-1α and VEGF-A present, resulting in a noteworthy decrease in the advancement of neovascularization. miR-21 is responsible for triggering the growth of new blood vessels that feed tumors in human prostate cancer cells by increasing the production of HIF-1α [9, 153]. Evidence suggests that HIF-1α can be found in the human cornea during processes such as neovascularization and angiogenesis. Moreover, suppressing HIF-1α in the cornea hampers neovascularization [154, 155]. It has been established that TGF-β1 plays a role in the response of the cornea to harm, and data has suggested that halting Smad3/TGF-beta signaling in an alkali burn situation in the cornea can reduce the volume of neovascularization [156]. TGF-β1 stimulates scar fibroblasts to divide and change into different types of cells by increasing miR-21 levels [157]. It is still not understood whether or not there is a relationship between TGF-β1, hypoxia, and the expression of miR-21 in corneal epithelial cells. In order to investigate the effects of miR-21 on corneal epithelial cell homeostasis,

a research study was conducted. Western blotting was used to detect the alterations in pro-angiogenic signaling and the epithelial-mesenchymal transition (EMT) phenotype after the miR-21 and SPRY2 were silenced. The tube formation assay was utilized to investigate how the conditioned medium affected the network of small blood vessels (angiogenesis) that was created. Additionally, the wound healing progression was evaluated with both migration and scratch experiments. The researchers discovered that miR-21 suppression was strengthened by either TGF-β1 or hypoxia, while miR-21 expression was hindered by both TGF-β1/hypoxia-induced HIF-1α and VEGF expression [104]. It was suggested that either TGF-β1 or miR-21, induced by hypoxia, could suppress SPRY2, and thus promote pro-angiogenic process, prevent epithelial development, and facilitate the healing process for corneal epithelial cell injury.

Pathological angiogenesis

A host of closely regulated cellular activities are necessary for the angiogenic process to take place, and when it comes to tumor growth, an oncogenic transformation may cause a switch to the angiogenic phenotype through different avenues [158, 159]. The major difference between them is that pathological angiogenesis does not cease when the necessary blood vessels have been set up, but carries on indefinitely. This angiogenic pathway carries on, driven by the established pathology.

Tumor angiogenesis

As rapidly growing tumors necessitated oxygen and nutrients to survive and multiply, they were found to be densely supplied with blood vessels, and dormant tumors were not. These observations caused Judah Folkman to suggest that in order for a tumor to progress, it must be supplied with newly formed blood vessels [160]. In addition, Folkman discovered a tumor-generated factor that caused the development of blood vessels and hypothesized that stopping the pathways leading to angiogenic stimulation could prevent new vessels from forming and result in the tumor being inactive [20, 161]. A great deal of enthusiasm was generated in the research world as a result of this interesting idea, leading to an abundance of attempts to detect pro-angiogenic substances created by tumors and trace their communicating signals [162]. A clinical trial in 2003 found that when chemotherapy was paired with humanized antibodies that target the VEGF, subjects with metastatic colorectal cancer had a significantly extended lifespan. This FDA approval provided evidence that anti-angiogenic therapy is an effective way of treating cancer [163]. The initial authorization of several antibodies and tyrosine kinase inhibitors designed to suppress cancer progression via anti-angiogenic therapy has been limited. However, the successes of these treatments have been limited. These interventions generally achieved short-term reductions in tumor size yet had little impact on long-term mortality. This has been hypothesized to be due to tumors adapting alternative ways of angiogenesis and building resistance, not to mention that cancer cells can get blood supply from existing vasculature, thereby removing the need for tumor angiogenesis [164]. Although some particular brain, lung, and liver tumors may be able to proliferate without requiring new blood vessels to develop, angiogenesis is generally necessary in order for a tumor to grow [165–167].

The production of molecules that either promote or inhibit angiogenesis in tumor cells is controlled by miRNAs, which therefore regulates the growth and movement of endothelial cells in a paracrine fashion [168]. It has been found that around 10% of the four hundred known human miRNAs regulate the processes of endothelial cell function and angiogenesis. Furthermore, research suggests that miRNAs are likely to be involved in the control of angiogenesis since they show a major presence in endothelial cells [169, 170]. There are generally two different types of miRNAs: those that promote angiogenesis (a growth of new blood vessels) and those that inhibit it [171]. miR-21 is a type of miRNA which has a dual effect by impacting multiple parts of the same cell; this has been seen in the angiogenic effects of different types of cancer (Table 1). Moreover, this example serves to demonstrate that miRNA can have a wide range of influences on cells.

Zheng et al. [172] determined that miR-21 is linked to the formation of blood vessels in diffuse large B cell lymphoma tumors. Activating endothelial cells to interact with regulatory T cells seems to boost the amount of Inducible T-Cell Costimulator (ICOS) that appears on regulatory T cells when miR-21 is present. This turns on the ICOS/inducible T cell costimulator ligand pathway, resulting in tumor blood vessel formation. This is important in speeding up the progression of the disease and making the lymphoma resistant to chemotherapeutic treatments [172]. Non-Hodgkin's lymphoma patients had significantly higher levels of circulating miR-21 compared to healthy people. The levels of circulating VEGF were also higher in the patients with non-Hodgkin's lymphoma compared to healthy subjects. The concentration of interleukin 12 in the THP-1 cell supernatant went up after inserting miR-21 mimetic, which is identified as an immediate target of miR-21 which further showed the angiogenic ability of this miRNA [87]. A research study revealed the presence of an anti-miR-21 with similarity to the 3′ end of pri-miR30. This anti-miR-21 targeted miR-21, inhibiting the transcription or translation of genes, while also reducing the level of miR30 that is involved in pathways controlling the development of vessels and regulating their size and quantity [173]. Recently, it was proposed by Fan et al. [93] showed miR-21 expression could result in an augmentation of the

structural organization of HMEC-1 cells into tubular formations and negatively affect the Programmed Cell Death (PDCD)-4/c-Jun signaling pathway. Additionally, miR-21 is linked to both tumor angiogenesis and the progression of renal cell carcinoma (RCC) by means of modifying the levels of ANG-1 and VEGFA. Accordingly, it was proposed that miR-21 boosts RCC blood vessel formation by influencing the PDCD4/c Jun signal route. Additionally, research has suggested that the miR-21 expression is higher in human oral squamous cell (OSCC) carcinomas. In addition to this, miR-21 has been determined to play a role in modulating the activity of RECK, a glycoprotein composed of cysteine-rich Kazal-like domains and found in the membranes of cells. This particular protein is assumed to be able to alter the external matrix by advancing the functioning of matrix metalloproteinases, and is perceived to be highly capable of thwarting tumor interaction, progression to distant regions, and the formation of new blood vessels [174–177]. MiR-21 has been shown to increase the development of blood vessels in a hamster buccal pouch (HBP) cancer model. Nimbolide has the potential to inhibit the process of angiogenesis in oral squamous cell carcinoma (OSCC) cells by stimulating the activity of RECK and subsequently reducing the MiR-21 expression levels [174].

Arsenic, which can be found in many places in the environment, has been proven to cause cancer in humans [178]. The studies conducted by epidemiologists suggest that prolonged exposure to arsenic may be responsible for the development of skin, lung, and bladder cancer in humans [179]. Arsenic poisoning is seen as having its greatest influence on the lungs [153, 180]. Studies have found that small doses of arsenite trigger mutations in human bronchial epithelial cells by obstructing the p53 tumor suppressor which is linked to hypoxia-inducible factor-2 [181]. Despite the solid proof of arsenic's ability to induce cancer in humans, the way in which it triggers tumor growth remains unclear. Zhao and his team have looked into the means of arsenite-promoted angiogenesis for better insight [86]. Investigations revealed that tumors that had formed from human bronchial epithelial (HBE) cells which had been altered by arsenite had grown new blood vessels, something that could be deterred by decreasing miR-21 levels. Observations showed that miR-21 had an exceptionally high expression in transformed HBE cells that was accompanied by an elevated amount of VEGF suggesting the pro-angiogenic role of arsenite.

The high death rate among colorectal cancer patients is mostly because of recurring tumors and cancer that spreads to other parts of the body [182]. A treatment known as anti-angiogenic therapy has been seen as a potential solution for CRC. Unfortunately, there are individuals that have either originally or eventually grown immune to the drugs which can lead to low or no positive outcomes [183]. Consequently, it is extremely crucial to recognize a possible biomarker and fresh treatment objective for colorectal cancer sufferers of the anti-angiogenic therapy. As reported by He and colleagues [184] was shown that targeting miR-21-5p to endothelial cells by exosomes, there was an increase in the quantity of miR-21-5p in the recipient cells. The increase in miR-21-5p quantity in HUVECs suppressed Krev Interaction Trapped 1 (KRIT1) and initiated β-catenin signaling, which then set off a chain of effects, resulting in a rise in VEGFa and Ccnd1 downstream targets. As a result, the creation of new blood vessels and the allowing of fluid to pass through them increased in colorectal cancer. In addition, there was a correlation between KRIT1 expression levels and miR-21-5p concentration that was seen near the cancer cell, in which when one decreased, the other went up. Additionally, exosomes in the circulation of individuals with colorectal cancer exhibited significantly higher levels of miR-21-5p than those from healthy patients [184]. Evidence suggests that exosomes released by glioma stem cells can stimulate angiogenesis, which is the growth of new blood vessels, by increasing miR-21 levels [91]. Additionally, miR-21 that is present in exosomes from cancer-associated fibroblasts promotes angiogenesis in multiple myeloma [92].

Studies are demonstrating the complexity of the tumor microenvironment, a combination of the extracellular matrix and accommodating cells. Cancer cells are dependent on the TME for preserving their life, spreading, penetrating, and relocation [185, 186]. The higher level of permeability of the blood vessels in the tumor aids in cancer expansion and metastasis, allowing a constant supply of oxygen and nutrients to cancer cells, enabling the cells to spread more readily and (forming) the precursors to successful metastases [187]. A lack of oxygen, known as hypoxia, has been found to be a critical factor when it comes to the microenvironment that surrounds tumors. Researchers have reported that cancer cells respond to hypoxia by creating and releasing bioactive substances that can affects the neighboring environment, resulting in the formation of new blood vessels, known as tumor angiogenesis. Papillary thyroid cancer (PTC) displays a threefold higher angiogenecity compared to normal thyroid tissue, which is connected with the greater frequency of endothelial cell activation, increased permeability of capillary cells, and heightened perfusion [188]. Under normal levels of oxygen, HIF-1α is altered by enzymes called prolyl hydroxylases, (PHD1, PHD2, and PHD3). However, when oxygen levels are low, these enzymes become inactive, enabling HIF-1α to move to the nucleus and control the making of RNA from DNA [189]. A recent study [190] showed that exosomes extracted from PTC, BCPAP, and KTC-1 cells—all of which are types of papillary thyroid cancer—were more adept at stimulating angiogenesis in HUVECs than exosomes collected from the standard thyroid cell type, Nthy-ori-3-1. This was established in both laboratory testing and live animal studies. Additionally, exosomes taken

from BCPAP cells in low oxygen environments showed a prominent rise in miR-21-5p. When miR-21-5p was suppressed, the ability of the cells to stimulate angiogenesis was reduced. Besides, it was seen that miR-21-5p specifically targeted TGFBI and COL4A1, thus leading to an uptick in the formation of endothelial tubes. A considerable amount of miR-21-5p in exosomes was present in the serum of individuals with PTC, which stimulated the growth of HUVECs angiogenesis through inhibition of TGFBI and COL4A1 expression [95, 190]]. The activation of PTEN/Akt signaling in endothelial cells was shown to be strongly linked to the presence of miR-21 [95]. The results of this data implicate that exosomal miR-21 plays a role in the angiogenesis and increased blood vessel permeability that occurs in cancerous cells. Thus, miR-21 has potential as a new therapeutic target in order to reduce cancerous growth. Additionally, existing literature indicates miR-21 has an inhibiting role in the angiogenesis of chronic myeloid leukemia (CML) [98]. It is imperative to examine the impact of miR-21 on the growth of new blood vessels in cancer as the role of miR-21 contained in exosomes could vary between distinct forms of cancer and potentially between different cellular types. By doing so, we could draw more precise conclusions about how miR-21 regulates cancer angiogenesis. Furthermore, thorough examination and enriched research are necessary before miRNA-based therapeutics can be successfully used in clinical practice due to the need to evaluate the potency, stability, and side effects. Taverna et al. [98] demonstrated that treatment of Curcumin leads to a decrease in miR-21 in CML cells and at the same time, there is an elevation of miR-21 level in the exosomes. The introduction of CML control-derived exosomes to HUVECs resulted in a rise in IL-8 and Vascular Cell Adhesion Molecule 1 (VCAM1) concentrations. Nevertheless, by including Curcu-exosomes, the angiogenic qualities of the system were diminished. This anti-angiogenic activity was verified with in vitro and in vivo tests. Scientists concluded that Curcumin alters molecular properties, leading to diminished pro-angiogenic proteins in the exosomes and greater amounts of anti-angiogenic proteins. Also, miR-21 stopping the growth of new vessels in HUVECs blocks the crucial regulator of actin equilibrium named Ras Homolog Family Member B (RhoB) [98]. RhoB is a certain type of GTPase protein in the Rho family that is reactive to multiple kinds of stimuli such as growth promoters. This family of proteins interacts with the cell membrane to alter its structure, largely through changes to the actin cytoskeleton that is attached to it. Furthermore, it is known that Rho proteins in endothelial cells influence ICAM1-induced signals. In general, Rho proteins can be activated through signals delivered from the cell surface to the cytoskeletal actin [191, 192]. The combination of curcumin-exosomes works by limiting the amount of RhoB that is present at both the protein and mRNA level through miR-21. As a result, these cells can no longer increase angiogenesis [98]. More studies are shown in Table 1

Intraocular neovascular disorders

The beginning of research pointed to an angiogenic factor called X, believed to be responsible for assisting both beneficial vascular development and excess, irregular development within the eye through its permeation of the tissue of the retina [193]. Recently, studies have demonstrated that VEGF-A has similar properties to factor X, such as the capacity to disperse, target cells that are endothelial specifically, and being susceptible to being induced by hypoxia. Plus, the presence of VEGF-A mRNA is found to match up with where and when there is neovascularization present in experiments dealing with ischemia in the retina of animals [194, 195]. Studies have shown that in people suffering from diabetes and other conditions causing proliferative retinopathy, expansions in the levels of VEGF-A can be seen in the aqueous humor and vitreous humor of the eye [196, 197]. The outcomes of testing done on animals with different VEGF-A inhibitors demonstrate that VEGF-A is critical for the emergence of intraocular neovascularization that is caused by a lack of blood supply [198–200].

VEGF-A is not solely responsible for increased expression in the eye, it is also seen in a variety of other ischemic retinal disorders. Age-related macular degeneration (AMD) leads to choroidal neovascularization, which can result in the leakage of fluid and bleeding into the macula (the central part of the retina, providing high-definition, central vision) causing vision impairment [201]. The types of AMD can be classified into two main classes, dry and wet. Evidence from the mid-1990s demonstrated that VEGF-A, a cell growth promoting factor, could be identified in the thin micro-capillaries that start to form beneath the retinal pigment epithelium in individuals having wet AMD [202, 203]. Despite wet AMD being less frequent (only making up between 10 and 20% of AMD instances) than the more common dry AMD, it is more severe and accounts for around 80–90% of AMD related vision loss [201]. Clinical trials have demonstrated notable outcomes when VEGF-A inhibitors are utilized to treat wet age-related macular degeneration and two of those inhibitors, pegaptanib and ranibizumab, have been officially authorized for therapeutic use [204–206]. Administering ranibizumab to curb the production of VEGF-A not only mitigated the degradation of vision in wet AMD patients, but also enabled them to enjoy consistent and substantial gains in vision. Similarly, macular edema due to branch and central retinal vein occlusion have also reported noteworthy improvements in visual acuity [207]. The research findings revealed that the dependency of intraocular angiogenesis on VEGF signaling is significantly more intense than it is on tumors. Treatments for Retinal Neovascularization (RNV)

often include the use of pan-retinal laser photocoagulation and anti-VEGF intravitreal injections, although desired outcomes are not always achieved and side-effects can occur. To address this health condition, a deepened understanding of the molecular roots of RNV is required, with the aim of developing safer and more reliable therapeutic and diagnostic tools [208]. This is a significant and potentially life-threatening health issue that is related to retinopathies, including proliferative diabetic retinopathy, retinopathy of prematurity, and retinal vessel occlusion [209, 210]. To this point, medical treatments for RNV have included pan-retinal laser photocoagulation and intravitreal injections of anti-VEGF, yet these tactics do not always prove productive and might lead to undesired repercussions [211, 212]. Gaining a deeper understanding of how molecular processes influence the start and development of RNV can give us new insights and assist in finding more efficient treatment and examination options. Though RNV can have different reasons for arising in different ocular conditions, some frequently found components of the pathology have been recognized. Notably, increased production of VEGF is among them [213, 214], activation of MMPs [215, 216]. Several studies have found that the STAT-3 transcription factor is activated in the ischemic retina, and this is associated with both pro-inflammatory and pro-angiogenic processes [217–219]. Studies have shown that STAT-3 plays an essential role in controlling the production and function of VEGF molecules in the tiny blood vessels of the endothelial cells [217, 219]. Furthermore, the disruption of STAT-3 reduces risk of RNV, indicating that activating STAT3 may be a major contributing factor for RNV [220, 221].

Nevertheless, preventing this transcription factor may cause severe damage to the neuroretina. It is essential to give more attention to the downstream effectors since they are the ones that truly produce the pro-inflammatory properties and pro-angiogenic [222]. Recent research has demonstrated that STAT-3 is a protein that can control the level of miRNA transcription [223, 224]. More and more data are gathering to confirm that miRNAs play a role in various diseases in humans, such as ischemic retinopathies [225, 226]. Gutsaeva and their team conducted studies on HREC in an artificial laboratory environment, as well as using a mouse model of Oxygen-Induced Retinopathy (OIR) in a living organism, in order to look into how the miR-21 functions and is regulated under hypoxic situations amid an ischemic retina and its relationship with the STAT3 and TIMP3 pathways. The study employed both strategies which increased and decreased the function of the subject, respectively [108]. They discovered that miR-21 works as an agent supporting the action of STAT-3 inside the ischemic retinas and its ability to spur retinal neovascularization (RNV) by suppressing TIMP-3. To test this, they used HREC (human retinal endoichthalmic cells) which were put under hypoxia and also a mouse OIR model. Both of these experiments showed a diminished level of TIMP-3 expression, which went in line with the activation of the STAT3 and an increase in miR-21. Subsequently, by repressing STAT3 or blocking miR-21 on the HREC, TIMP-3 expression was brought back to normal. Finally, by using an antisense to shut down miR-21 in the mouse model of OIR, RNV could be stopped which was directly related to the restoring of TIMP-3 expression [108]]. The findings of their investigation have revealed that miR-21 plays a part in the pro-angiogenic consequences resulting from STAT-3 activity observed in ischemic retinas. This suggests that blocking miR-21 could act as a potential treatment to inhibit or prevent the progression of choroidal neovascularization (CNV) and any associated sub-retinal fibrosis, which remain a major cause of vision loss. In particular, this treatment may be beneficial for patients who cannot respond to anti-VEGF therapies or who experience frequent recurrences [227–230]. Xiong et al. have conducted a study to look into the results of stopping miR-21 in an exploration of CNV in a laboratory setting [107]. In their study, the CNV (choroidal neovascularization) induced in C57Bl/6J mice by laser injury to Bruch's membrane was further suppressed when the mice were intraorbitally injected with the miR-21 Locked Nucleic Acid (LNA) inhibitor. It was found that the neovascularization peaked around day 14 post-injury before showing a mild decline at day 21 in the untreated CNV mice. Collagen I (Col1) staining showed that fibrosis progressed further beyond 14 days in the untreated CNV mice. Analysis demonstrated that after seven days, mice that had been given the miR-21 inhibitor had notably diminished areas when tested with Col1 and Isolectin B4 compared to the mice that had been administered the scramble antagomir or those that had not been administered any treatment. In addition, expression of fibrosis and EMT markers (alpha SMA) was significantly suppressed in the miR-21 injected mice. Furthermore, the miR-21 inhibitor was also noted to cause a decrease in neovascular lesions and improved retinal architecture, as confirmed by a decrease in retinal thickness and H&E staining suggesting the therapeutic role of miR-21 through inhibition of it in eye neovascularization. In contrast, Sabatel et al. [106] reported that increased miR-21 activity suppresses angiogenesis in both human umbilical vein cells (HUVECs) and mouse models of choroidal neovascularization. This inhibition is achieved by targeting the gene RhoB [106]. It is essential to carry out further research to analyze the influence of miRNA on ocular angiogenesis since the effect of miR-155 may vary in different kinds of cell lines.

Diabetes and angiogenesis

Diabetic retinopathy provides an example that shows how diabetes can cause many changes in different blood vessel

systems. In the early stages, it is linked to a decrease in the number of pericytes, which makes blood capillaries shrink and leads to the formation of tiny bulges in the vessels and fluid leaking out of them [231]. Abnormalities in the retina can result in a lack of blood supply (ischemia) which can lead to the growth of new blood vessels (angiogenesis). However, this new blood vessel growth is often weak and can lead to bleeding and an inadequate blood flow to the retina. This can result in possible vision impairment or loss, but with effective control of blood pressure and sugar levels, the risk of microvascular complications can possibly be lessened [232, 233]. The blood vessels of the kidneys are affected by the metabolic issues caused by diabetes, leading to an irregular thickness and leaking of the glomerular-podocyte connection. This damages the ability to filter, potentially causing kidney failure [234]. Heart attack, stroke, and decreased blood flow in the limbs are the primary sources of illness and loss of life in individuals with diabetes, and the formation of new blood vessels is a significant part of the body's natural response to these events. Subjects with diabetes tend to experience worse effects from major cardiovascular events, like gangrene after limb ischemia, due to a reduction in their body's ability to form new blood vessels in areas that are not receiving enough blood or oxygen [235, 236]. It is widely thought of as paradoxical that while some vascular beds show decreased angiogenesis, certain areas such as the retina have too much. However, although diabetes exhibits varied outcomes within different types of vascular beds, it can generally be stated that diabetes results in capillary loss and a decreased ability to form new vessels that are both structurally and functionally sound [237].

Three-quarters of patients with diabetes who have had the condition for longer than 15 years are at risk of diabetic retinopathy (DR). After 25 years, this risk drastically increases, with 20% of those developing signs of proliferative diabetic retinopathy (PDR) [238]. By 2050, it is expected that an estimated 3.4 million people over the age of 40 and 1.9 million people over the age of 65 who have diabetes will be at risk of developing a sight-threatening condition called Proliferative Diabetic Retinopathy (PDR) [239]. Patients who suffer from PDR will experience higher levels of glucose within their bloodstream which then causes additional growth of retinal tissue on the back of the eye and the creation of blood vessels in the retina [240]. In the most serious circumstances, hemorrhage and separation of the retina happen, eventually culminating in total blindness. It is vital to control prolonged and excessive increases in blood sugar levels that lead to an increase in new blood vessels in order to stop PDR from getting worse. Current treatments for DR focus on reducing the likelihood of loss of sight or blindness, and these treatments, like closely managing glucose levels and blood pressure, can reduce the probability of losing vision and developing DR [241]. The main role that Endothelial Cells (ECs) play in retinal ischemic vasculopathy is initiating a microvascular disorder in DR. This process commences with a continual inflammatory reaction in the endothelial cells of the retina, leading to the formation of pro-inflammatory molecules, a rise in blood vessel permeability, the death of endothelial cells, and the development of new blood vessels [242]. Recently, Lu et al. [110] looked into how miR-21 would affect the viability and angiogenesis of retinal vascular endothelial cells (RVEC) in rats with DR by using Sprague Dawley (SD) rats to create DR models. It was found that miR-21 expression was increased in the retinas of the DR rats, leading to the inactivation of PTEN and the activation of the PI3K/Akt/VEGF signaling pathway. When a miR-21 inhibitor was used on the RVECs, the results showed an enhancement in RVEC viability and angiogenesis, but a decrease of apoptosis. This implies that the suppression of PTEN expression by miR-21 is capable of stimulating RVEC viability and angiogenesis in rats suffering from DR through aiding the activation of the PI3K/Akt/VEGF pathway [110]. In a separate study, it has been discovered that the restriction of miR-21-5p can moderate the augmented growth and development of human retinal microvascular endothelial cells caused by high glucose levels by influencing the AKT and ERK pathways through maspin [109]. The results of these experiments demonstrate the possible efficacy of miR-21 as a remedy for DR. Subsequently, more focus should be applied to managing and subduing angiogenesis caused by miR-21 in DR in future studies.

Other angiogenesis-dependent diseases

Ischemia–reperfusion injury has been linked to a heightened risk of developing chronic kidney illness in the future and is a major cause of acute kidney damage. In other words, IRI is a significant factor leading to Acute kidney injury (AKI) and raising the likelihood of Chronic Kidney Disease (CKD) in the coming years [243]. The likelihood of experiencing kidney IRI is largely raised due to urologic procedures like partial nephrectomy, renal transplantation and other circumstances present in a clinical environment [243]. The exact source of Ischemia–Reperfusion Injury (IRI) is still unspecified. However, damage to the tissue covering the tubules in the kidney appears to be a major factor contributing to the disease's development. Evidence implies that trauma and recuperation of the microscopic blood vessel endothelial cells may be a contributing factor to the onset of acute renal failure [243, 244]. Following injury from a period of reduced blood flow, a decrease in the amount of peritubular capillaries could result in prolonged oxygen deprivation in the kidneys and may play a large role in the advancement of chronic kidney disease. Angiogenesis is one of the body's ways of trying to repair the damage to the kidneys caused by Ischemia/Reperfusion (I/R) and can

help to restore balance following endothelial cell death or destruction. Stimulating this growth of new blood vessels can help to protect the kidneys from harm and improve the outlook for acute kidney injury [245, 246]. Hence, Xu et al. [114] studied the role of miR-21 in the angiogenesis induced by HIF-1α, and their findings revealed that expression of the predicted target gene, Thrombospondin (TSP)-1, is inversely related to the upregulated miR-21 in both an in vitro and an in vivo setting. Additionally, they validated that miR-21 targets TSP-1 in vitro. Furthermore, they found that HIF-1α, when increased as a consequence of hypoxia and CoCl2, improved renal function in mice through increased angiogenesis. The decrease in the protective action of HIF-1α when miR-21 was blocked points to the possibility that both HIF-1α and miR-21 are likely playing a role in safeguarding the kidney against ischemia/reperfusion injuries [114]. The development of angiogenesis, resulting from hypoxia, is partially caused by the production of the protein VEGF and the blockade of the protein TSP-1 by miR-21. Stroke is a major factor in death and impairment on a global scale [247]. So far, the only approved pharmaceutical treatment for acute cerebrovascular insufficiency is a tPA, with the role of a thrombolytic agent. However, its clinical use is severely restricted due to its tight therapeutic time frame and the possibility of lethal bleeding [248]. Consequently, it is essential to form innovative plans to accelerate the recovery level of those affected by ischemic stroke. Various studies have indicated that stem cell therapy is an emerging solution to ischemic stroke treatment [249, 250]. MSCs are conveniently accessible and can be quickly multiplied in a laboratory setting, making them an optimal choice for cell-based treatment approaches [251]. Multiple studies have shown that implanting MSCs could stimulate the generation of nerves and blood vessels, which in turns helps to speed up the healing process from a stroke [252, 253]. It was initially suggested that MSCs had the capability to migrate to injured or ischemic tissues and differentiate to take the place of the damaged cells. The precise mechanism behind this phenomenon was not fully understood [254]. Subsequent studies showed that MSCs transplanted to ischemic regions did not survive or integrate into the tissue well enough to explain how MSCs induce differentiation [255]. Up to this point, it is hypothesized that the positive effects of mesenchymal stem cells may be due to their secretion of paracrine factors, like growth factors and extracellular vesicles known as exosomes. [256, 257]. Recently, Hu et al. [258] explored the potential of BMSC-exosomes to augment angiogenesis in ischemic stroke mice via miR-21-5p. Their study revealed that BMSC-exosomes successfully improved neurological performance and restricted the ischemia-induced infarct size, resulting in a heightened number of microvessels and a boost in miR-21-5p expression. Furthermore, BMSC-exosomes bolstered the performance of HUVECs in the context of cell proliferation, migration and tubular formation. Analysis of the exosome-treated HUVECs revealed augmented expression of VEGF, VEGFR2, Ang-1 and Tyrosine kinase with immunoglobulin and EGF-like domains (Tie)-2. Nevertheless, the miR-21-5p inhibitor prevented the angiogenic impact of BMSC-exosomes on HUVECs [258]. The conclusion of these results signifies that BMSC-exosomes may be a viable solution to stroke recovery due to their ability to stimulate angiogenesis through the enhanced production of miR-21-5p. The most common cause of cardiac dysfunction is AMI, resulting in ischemic cardiomyocyte death [258]. Acute Myocardial Infarction (AMI) has become an increasingly prevalent health concern globally, leading to reduced oxygen circulation to the heart [259, 260]. The major contributing factors to the risk of Acute Myocardial Infarction (AMI) include having smoking, high levels of lipids in the blood, hypertension and diabetes [261]. Gaining insight into the molecular workings of AMI might provide more information about how to effectively handle the illness. Recent studies have shown a correlation between PTEN and the increasing prevalence of heart failure in mice [262, 263]. Results of research have shown that when the PTEN gene was stopped from being expressed, VEGF secretion was increased, migrating and multiplying of cells was increased, and the growth of small tubes (tubule development) in pancreatic cancer cells was activated [264]. Research has demonstrated that various forms and subtypes of VEGF demonstrate different levels of expression in a heart post myocardial infarction, making it possible to monitor changes in VEGF expression after a cardiac episode [265]. Recently, researchers conducted an experiment using immunodeficient mice with significant limb ischemia. During the experiment, it was witnessed that the miR-21 indication resulted in a reduction of the PTEN protein level and an augmentation of VEGF production [266]. Yang et al. [99] revealed that miR-21 could be linked to the 3′-UTR of PTEN, resulting in decreased expression of PTEN. Having more miR-21 copies was associated with a decrease in infarct size and decreased levels of markers for injury, achieved by raising VEGF expression and controlling PTEN expression. Furthermore, laboratory experiments showed that lenti-PTEN and VEGF siRNA could successfully nullify miR-21's effect on cell expansion, apoptosis, and angiogenesis. [118]. In summary, miR-21 appears to have a protective function when it comes to damage to the inner lining of blood vessels that has occurred due to acute myocardial infarction (AMI). This protection is enabled by miR-21 influencing the PTEN/VEGF pathway. Similarly, Yu et al. [119] demonstrated that administering astragaloside could boost miR-21 expression, which in turn nurtures the development of fresh blood vessels subsequent to a heart attack through the positive control of VEGF and AKT production [119].

A spinal cord injury is a devastating condition of the central nervous system that causes paralysis and often diminishes motor functions and sensations. Research results show that the average age of those who suffer from Spinal Cord Injury (SCI) in the USA is 41 years, and it typically affects grown-ups [267]. SCI involves both a primary injury caused by a physical impact or trauma and a secondary injury caused by biochemical reactions following the initial incident [268]. All of these factors have an impact on the post-secondary injury associated with spinal cord injury (SCI). The loss of connectivity between vessels, restricted blood supply due to lack of oxygen or insufficient perfusion, and a decrease in the number of microvascular endothelial cells all work in tandem to weaken the body's healing process following the initial injury [269, 270]. Following a SCI, a healing process occurs, consisting of restoring blood vessels and the nervous system [271, 272]. This requires a process of repairing the body's neurovascular system. Studies have shown that miR-21 is highly expressed in rats that have experienced spinal cord injury. In addition, when antagomir, which is a molecule used to lower the levels of miR-21, was administered it correlated with an increase in apoptotic cells and decreased functional deficits [273]. Hu et al. conducted an investigation to assess the impact of miR-21 on the formation of new blood vessels following a SCI [122]. The researchers found that providing an increased amount of miR-21 can help promote survival, spreading, and the development of vascular tissue of endothelial cells, while lessening TIMP-3 expression and boosting MMP-2 and MMP-9 activity and production. On the contrary, lowering the amount of miR-21 by utilizing antagomir had a detrimental effect. It is widely known that survival, movement, and tube formation of endothelial cells are essential components for angiogenesis when damage occurs. The results of a dual-luciferase reporter assay suggested that TIMP-3 was the precise target of miRNA-21. To demonstrate this further, small interfering RNA was used to inhibit TIMP3, leading to an increased rate of tube formation and greater expression of MMP-2 and MMP-9 at the protein level. When miR-21 was downregulated, angiogenesis after spinal cord injury in rats was hampered. To sum up, it appears that miR-21 may protect vascularization by decreasing cellular death and propelling cell endurance, relocation, and network construction through its possible restraint of TIMP-3 and MMP-2 and MMP-9 [122]. Investigating how miRNA-21 aids the growth of new blood vessels could offer a promising solution to treating secondary spinal cord injury, which necessitates the formation of new vessels for healing.

Conclusion and future perspectives

This study demonstrated that miR-21 could be seen as a potential therapeutic target due to its fundamental role in controlling angiogenesis (Table 1). miR-21 or exosomal miR-21 targets different proteins and pathways to form a complex network to boost angiogenesis. Advanced miRNA nanocarrier systems have been built to also support the clinical applicability of this miR-21-based therapy. Though the effects of miR-21 in stimulating angiogenesis have already been identified, its function in assisting various types of tissues to repair angiogenesis-related disorders needs to be explored further. The growing information on the role of miR-21 is proving its importance in various biological processes, including angiogenesis. Even though much progress has been made in comprehending the way miR-21 is regulated, the precise mechanisms causing its elevation are not fully understood. In the past, researchers have investigated that the regions that control miR-21 production hold multiple binding sites for various transcriptional regulators, one of them being STAT-3. Despite this, not all genes controlled by those factors show increased levels of activity as miR-21 does in medical problems such as heart failure [223, 224, 274]. Further research is needed to understand what could be causing the post-transcriptional regulation of mature miR-21 expression. If the underlying mechanisms can be determined, then it may be possible to manipulate miR-21 through medications or drugs, allowing for improved therapeutic treatment [10].

Future studies should pay more attention to some of the restrictions concerning miRNAs, which potentially presents an encouraging therapeutic strategy for regulating levels of the targeted miRNA [275]. Understanding the transcriptional and processing control of miRNAs during its biogenesis, as well as its exact role in tumorigenesis, is key for utilizing miRNAs as a therapeutic approach. In order to avoid any undesired outcomes and devise a successful regimen, it is essential to conduct more research on the immunogenic and cytotoxic impact of miRNA delivery when administered in a living organism. We also suggested that miRNAs may form a regulatory network like the one involving transcription factors [275, 276]. Therefore, because of delivery issues and an unavailable safe and efficient delivery method, knocking down miRNAs using anti-miRNAs oligo is currently not possible. A potential solution for targeted delivery is the use of biological vectors such as adeno-associated viruses (AAV) and lentivirus, however, it is necessary to standardize this approach in order to avoid the potential for unintended cell changes.

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Declarations

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