miR-205: A dual regulator of angiogenesis in health and disease (Review)

MARIA OLTRA[1,2], MIRIAM MARTÍNEZ-SANTOS[1-3], MARIA YBARRA[1-3], MARIA PIRES[1-3], CHIARA CERESONI[1-3], CLARA GOMIS-COLOMA[1,2], CRISTINA MEDINA-TRILLO[1,2], JAVIER SANCHO[1,2] and JORGE BARCIA[1-3]

[1]Faculty of Medicine and Health Sciences, Universidad Católica de Valencia San Vicente Mártir, 46001 Valencia, Spain; [2]Centro de Investigación Traslacional San Alberto Magno, Universidad Católica de Valencia San Vicente Mártir, 46001 Valencia, Spain; [3]Escuela de Doctorado, Universidad Católica de Valencia San Vicente Mártir, 46001 Valencia, Spain

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Abstract. The present study evaluated the role of microRNA (miR)-205 as a dual regulator of angiogenesis, exhibiting both pro-angiogenic and anti-angiogenic effects depending on the biological context. miRs are small non-coding sequences that regulate gene expression at the post-transcriptional level and can be transported in extracellular vesicles (EVs), allowing them to modulate biological processes remotely. miR-205 is involved in multiple cellular processes, such as proliferation, migration, apoptosis and angiogenesis. In angiogenesis its function is contradictory: On one hand, it can inhibit blood vessel formation by suppressing pro-angiogenic factors such as VEGF and ANG-2, as demonstrated in diseases such as psoriasis, thyroid cancer and diabetic retinopathy. However, in other contexts, miR-205 promotes angiogenesis by inhibiting anti-angiogenic genes such as *PTEN* and *HITT*, facilitating the activation of the PI3K/AKT pathway and cell proliferation in ovarian cancer and thrombosis. Additionally, the present study highlighted the role of EVs in transferring miR-205 between cells, thereby influencing angiogenesis and disease progression. Studies in myocardial infarction and cancer models have demonstrated that EVs enriched in miR-205 can affect blood vessel formation and tumor progression. Similarly, in ocular diseases such as macular degeneration and diabetic retinopathy, miR-205 encapsulated in EVs has shown therapeutic potential by regulating VEGF levels. In conclusion, miR-205 emerges as a promising therapeutic target for angiogenic diseases. Its application in EV-based therapy could represent an innovative strategy for treating vascular disorders. However, further studies are needed to fully understand its mechanisms of action and optimize its clinical application.

Correspondence to: Professor Cristina Medina-Trillo, Faculty of Medicine and Health Sciences, Universidad Católica de Valencia San Vicente Mártir, Calle Quevedo 2, 46001 Valencia, Spain
E-mail: cristina.medina@ucv.es

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Contents

1. Introduction

Of the DNA in the genome ~ 95% is noncoding DNA among which are microRNAs (miRNAs/miRs), small non-coding RNA sequences (18-25 nucleotides), able to regulate the expression of one or more mRNAs (1,2). miRNAs were discovered in 1993 by Victor Ambros and colleagues in *Caenorhabditis elegans*, recently awarded 2024 Nobel Prize in Medicine for this discovery (3). These small non-coding sequences regulate gene expression at the post-transcriptional level (4). Despite constituting only 1% of the human genome, miRNAs influence up to 50% of genes (5), playing essential roles in development, cell proliferation, and apoptosis.

miRNAs regulate protein translation by targeting their complementary 3' untranslated regions (3'UTRs) mRNA and by repressing translation or degrading target mRNA. The specificity of miRNA-mRNA interactions is crucial for determining the regulatory outcome, which can vary from fine-tuning gene expression to more profound effects on cellular phenotypes. Each miRNA could regulate more than one mRNA involved in different biological processes including proliferation (6), cell survival (7), inflammation (8), angiogenesis (9), oxidative stress (10) and immune response (11) among

others. Some diseases are affected by miRNA dysregulation. A tissue-specific expression profile is needed to decipher the function and mechanism of individual miRNAs (12).

The miRNAs are transcribed as long primary miRNa (pri-miRNAby RNA pol II) (4). The pri-miRNA are cleaved by Drosha-DGCR8 generating the precursor (pre-miRNA). The pre-miRNA is transported to the cytoplasm by the Ran-GTP dependent Exportin-5 (13). Once in the cytoplasm, the Dicer enzyme processes the pre-miRNA, generating a mature miRNA as an 18-25 nucleotide RNA duplex. The mature miRNA is incorporated into the RNA-induced silencing complex assembled by Dicer to promote the post-transcriptional and mRNA target degradation (14).

In addition to its eminent intracellular role, in 2007, it was discovered that miRNAs can travel in extracellular vesicles (EVs), such as exosomes, facilitating intercellular communication (15,16). Additionally, they can travel outside of these nanospheres, although they are more predisposed to degradation by enzymes. Therefore, miRNAs are invaluable tools in probing different aspects of a disease such as diagnosis, progression, classification and treatment. In fact, a number of clinical fields are now focused on the study of miRNA for diagnosis or treatment purposes (17-19).

Angiogenesis is a multi-step process of new blood vessel formation from existing vasculature. The angiogenesis process can be summarized in four key steps: i) Matrix degradation with the activation of proteases able to digest matrix components; ii) migration of endothelial cells (EC); iii) proliferation of EC to supply new cells for the tube formation and, iv) EC survival, maturation and stabilization (20). Physiological angiogenesis is the normal process that occurs during growth, development and tissue repair. It is tightly regulated to ensure proper nutrient and oxygen supply to the tissue. The imbalance between pro- and anti-angiogenic factors leads to uncontrolled vasculature over-growth named pathological angiogenesis. Pathological angiogenesis is often associated with diseases such as cancer, diabetic retinopathy (DR), and chronic inflammation (21). In case of tissue damage, a temporary or permanent imbalance occurs. miRNAs are one of the mechanisms that can regulate this balance through the post-transcriptional regulation of pro- and anti-angiogenic genes.

The study of miRNA can be useful in a number of ways, from their use as biomarkers to their potential interest as therapeutic targets for different diseases. miR-205 is one of the most notable miRNAs, demonstrated in several studies and it is involved in the regulation of different processes such as angiogenesis, epithelial-mesenchymal transition and cell proliferation, all related to the progression of diseases such as cancer or DR. The aim of the present review is to delve into the role of miR-205 in regulating angiogenesis as well as to analyze the potential of its therapeutic window.

In short, miR-205 emerges as a critical factor, distinguished by its bifunctional activity that is strictly dependent on the biological context. This duality positions miR-205 as a master regulator of the angiogenic switch in both health and disease. On the one hand, miR-205 exerts a pronounced anti-angiogenic effect by repressing the expression of key pro-vascular factors such as vascular endothelial growth factor (VEGF) (22) and angiopoietin-2 (ANG-2) (23), acting as a protective mechanism in hypervascular pathologies including diabetic retinopathy, thyroid cancer, and psoriasis. On the other hand, in conditions requiring vascular recanalization or favoring malignancy, miR-205 adopts a pro-angiogenic role by inhibiting tumor suppressors and anti-angiogenic molecules such as phosphatase and tensin homolog (PTEN) (24) and the long non-coding RNA HITT (25), thereby activating survival and proliferation pathways, most notably the PI3K/Akt cascade. Furthermore, the therapeutic significance of miR-205 is reinforced by its ability to be encapsulated and transferred through EVs (26), enabling the paracrine modulation of angiogenesis at a distance, a mechanism with profound implications for tumor progression and for the development of innovative strategies in vascular regenerative medicine.

2. Characteristics of miR-205

Genomic location and conservation. miR-205 is a highly conserved miRNA in a number of species. In the human genome, miR-205 is located on locus 1q32.2 within a gene annotated as miR-205 host gene (*MIR205HG*) and is composed of a highly conserved structure. More specifically, miR-205 resides between the second and third exons of LOC642587 (27). The *MIR205HG* gene also acts as a noncoding RNA called LEADR/MIR205HG and is the host gene for miR-205.

Physiological expression and developmental roles. This miRNA is physiologically expressed in different epithelia as cornea, breast, esophagus, thymus and bladder and is one of the most highly expressed miRNAs in skin (28). Additionally, miR-205 is key in development because it is involved in embryogenesis, especially in epithelial morphogenesis, promoting endoderm and ectoderm differentiation (29,30). In early embryonic stages, miR-205 is expressed in trophoblasts cell-linage regulating placental development (31). miR-205 is involved in the early lacrimal gland (32) and cornea development (33). Genetic loss of miR-205 causes perinatal lethality due to an altered pathway in the epidermis inhibiting stem cell self-renewal leading to skin defects (28,34,35).

Regulation of miR-205 expression. Precise regulation of miR-205 expression is essential for development, onset and progression of different alterations. Epigenetic modifications, such as CpG DNA methylation, are mechanisms for gene expression regulation which may be key miR-205 modulators. Specifically, mature miR-205 expression is inversely associated to DNA methylation. miR-205 under expression is related to high hypermethylation and chromatin changes leading to epithelial-mesenchymal transition (EMT) and cell migration (36,37). miR-205-5p transcription is commonly repressed via miR-205 locus hypermethylation and then, over-activates miR-205 targets. This fact has been associated with poor prognosis in cancer (38,39). Moreover, there are different transcription factors for miR-205, such as the p53 family, closely involved in cell cycle and apoptosis (40). P53 stimulates miR-205 expression levels promoting cell proliferation and EMT in cancer (41). Hypoxia inducible factor 1 α (HIF-1α) is a member of the p53 family. This is a transcriptional factor that represses miR-205 expression inducing EMT, angiogenesis and tumor aggressiveness (42,43). Sp1

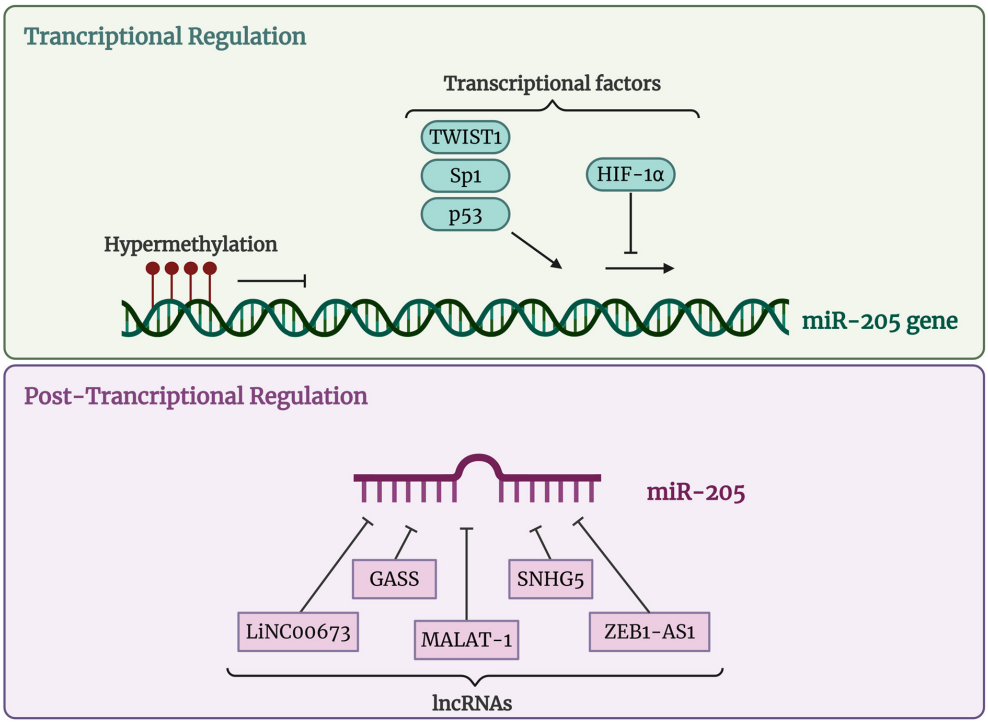

Figure 1. miR-205 transcriptional and posttranscriptional regulation. Created in https://BioRender.com. miR, microRNA; TWIST1, Twist-related protein 1; Sp1, Specificity protein 1; p53, Tumor protein p53; HIF-1α, Hypoxia-inducible factor 1-alpha; lncRNA, long non-coding RNA; LINC00673, Long intergenic non-protein coding RNA 673; GAS5, Growth arrest-specific 5; MALAT-1, Metastasis-associated lung adenocarcinoma transcript 1; SNHG5, Small nucleolar RNA host gene 5; ZEB1-AS1, Zing finger E-box binding homebox 1 antisense RNA 1.

is a transcriptional factor for miR-205 upregulation (44) in contrast to Twist1 (45). Beyond DNA methylation, histone modifications add a second layer of epigenetic control. Repressive marks such as H3K27me3 and H3K9me2 are associated with the silencing of MIR205HG, while activating marks such as H3K4me3 and histone acetylation (H3K9ac and H3K27ac) promotes an open and transcriptionally active chromatin state (37,38). These chromatin changes interact with transcription factors such as p53, Sp1 and HIF-1α integrating cellular stress and environmental signals into the regulation of miR-205 (40-44). Finally, long noncoding RNAs (lncRNAs) regulate miRNAs availability by sponging them. Increasing evidence has indicated that lncRNAs play important roles in human disorders, however, the functional implications have only been studied in a few of them. One of the most important lncRNAs related to miR-205 is MALAT1. It has been observed that under hyperglycemic conditions, MALAT1 act as a sponge for miR-205, thereby releasing its target ZEB1 from inhibition, which in turn represses E-cadherin expression and consequently induces EMT (46). In osteosarcoma, it has been observed that MALAT1 is upregulated and acts as a suppressor of miR-205, thereby releasing SMAD4 from miR-205-mediated inhibition and promoting cell proliferation through activation of TGF-β/SMAD4 signaling pathway (47). Similarly, MALAT1 sponges miR-205, inhibiting its function in cerebral ischemia and thereby leading to PTEN overexpression, which in turn modulates the PI3K/Akt signaling pathway and promotes apoptosis (48). There are other lncRNAs, such as LINC00673 (49), SNHG5 (50), GAS5 (51) and ZEB1-AS1 (52) capable of sequestering miR-205 and promoting the malignancy of tumor. Notably, it has been observed that lncRNA SNHG5 functions as a competing endogenous RNA (ceRNA) for miR-205-5p, suppressing its activity and increasing ABR expression, which in turn activates the RAF/MEK/ERK pathway and contributes to imatinib resistance in chronic myeloid leukemia (50). In line with these findings, lncRNA GAS5 has also been shown to suppress cervical cancer tumorigenesis by downregulating miR-196a and miR-205, thereby restoring the expression of their targets FOXO and PTEN, and consequently inhibiting the PI3K/Akt pathway, which leads to reduced cell proliferation and invasion (51). Finally, ZEB1-AS1 has been shown to regulate colorectal cancer progression through the miR-205/YAP1 axis, acting as a sponge for miR-205 and thereby increasing YAP1 expression, which promotes cell proliferation, migration and EMT via activation of Hippo signaling pathway (52). CircRNAs such as circ_0003520 have also been shown to act as sponges for miR-205-5p (53). Together, these findings highlight the pivotal role of lncRNAs as upstream regulators of miR-205, modulating their availability across diverse pathological contexts. By acting as molecular sponges, these lncRNAs fine-tune miR-205-mediated repression of key targets such as ZEB1, SMAD4, PTEN, ABR and YAP1, ultimately influencing major signaling pathways, including PI3K/Akt, TGF-β/SMAD, RAF/MEK/ERK, and Hippo, that govern cell proliferation, apoptosis, migration, and EMT (Fig. 1).

Context-dependent functions. The basic mechanisms of miRNAs regulation involve mRNA translation blocked upon base complementarity binding to the 3'UTR region. In this regard, miR-205 plays opposing roles depending on cellular contexts, cell types and target gene. In the context

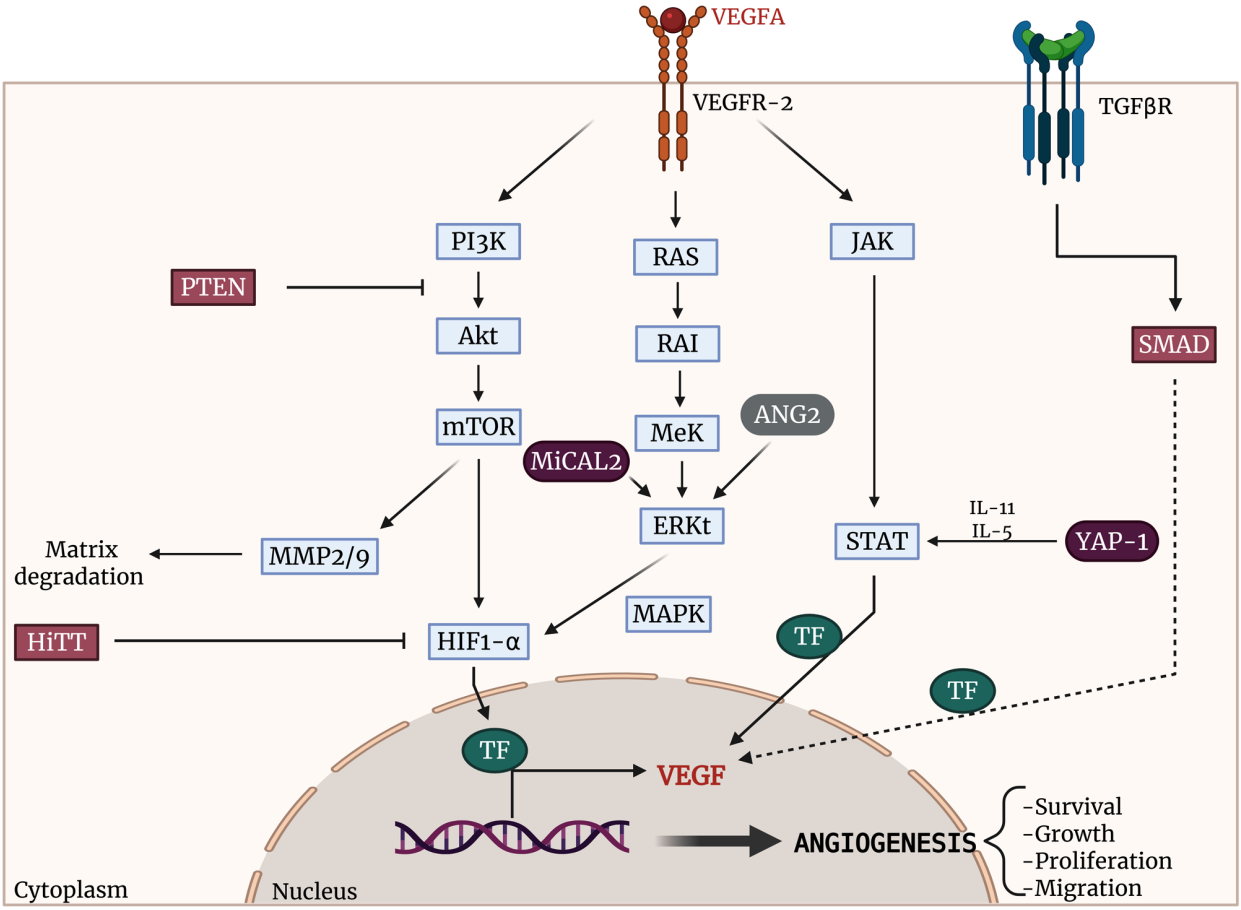

Figure 2. Representation of the main regulatory pathways of angiogenesis and the targets of miR-205. The direct targets of miR-205 are highlighted in purple. Created in https://BioRender.com. miR, microRNA; VEGFA, vascular endothelial growth factor A; VEGFR-2, vascular endothelial growth factor receptor 2; TGFβR, transforming growth factor β receptor; PI3K, phosphoinositide 3-kinase; Akt, protein kinase B; mTOR, mechanistic target of rapamycin; RAS, rat sarcoma viral oncogene homolog; RAI, Ras-associated/activated inhibitor; MEK, mitogen-activated protein kinase kinase; ERK, extracellular signal-regulated kinase; MAPK, mitogen-activated protein kinase; JAK, Janus kinase; STAT, signal transducer and activator of transcription; PTEN, phosphatase and tensin homolog; HIF-1α, hypoxia-inducible factor 1-alpha; TF, transcription factor; MiCAL2, microtubule-associated monooxygenase, calponin and LIM domain-containing 2; HiTT, HIF-1α inhibitor at the transcriptional level (lncRNA); YAP-1, yes-associated protein 1; SMAD, SMAD signaling proteins; ANG2, angiopoietin-2; MMP2/9, matrix metalloproteinases 2 and 9; IL-11, interleukin-11; IL-5, interleukin-5; VEGF, vascular endothelial growth factor.

of cancer, where miR-205 has been most studied, it is paradoxically considered pro or anti-oncogenic. In thyroid cancer, miR-205 was demonstrated to act as a tumor suppressor by repressing the expression of CCNB2 (54). In breast cancer it targets Küppel-like factor 12 (KLF12) (55) and angiomotin (AMOT) (56) reducing cell invasion. Focusing on angiogenesis, it similarly demonstrates contradictory functions, which will be discussed in further detail.

3. miR-205 in angiogenesis

Angiogenesis is essential in physiological processes to provide oxygen and nutrients to tissues for their maintenance and repair. However, angiogenesis can be associated with the onset or progression of pathological processes. Angiogenesis is guided by complex pathways that primarily affect EC, the main cells involved, which undergo several steps for the formation of blood vessels: Matrix degradation, migration, proliferation and survival (20). The angiogenesis switch depends on the resultant molecular balance between pro-angiogenic and anti-angiogenic factors (57). Among the pro-angiogenic factors that act directly on EC, VEGF (58) and fibroblast growth factor (FGF) (59) stand out. VEGFA (a member of VEGF family) binds to VEGF receptor 2 (VEGFR2) inducing dimerization and transautophosphorylation of cell cytoplasmatic tyrosine residues, activating EC migration, survival and vascular permeability through the PI3K/Akt pathway (60). Therefore, the p38 mitogen-activated protein kinase (MAPK) is activated after VEGFA-VEGFR2 interaction and promotes actin remodeling, cell migration and stress response (61). FGF plays a crucial role in angiogenesis and works synergically with VEGF inducing EC proliferation, migration and increase vascular permeability via PI3K/Akt and MAPK (62,63). Also, TGFβ in EC can signal via ALK1 which leads to phosphorylation of R-Smad1/5/8 with the consequent activation of cell migration, proliferation and angiogenesis (64,65). Studies confirm that some pro-angiogenic pathways involved Janus kinases/Signal Transducer and Activators of Transcription (JAK/STAT) which are stimulated by VEGFA-VEGFR2 interaction (66,67). This interaction induces the JAK activation, which phosphorylates STAT proteins, acting as a transcriptional factor of proangiogenic genes such as VEGF (68) (Fig. 2).

Some of the factors involved in the aforementioned pathways, are regulated by miR-205. miR-205 plays a significant

Table I. miR-205 targets and related angiogenic pathways.

Authors, year	Role	miR-205 targets	Related pathway	Pathology	(Refs.)
Xue *et al*, 2020	Anti-angiogenic	VEGFA and ANG-2	MAPK	Psoriasis	(23)
Zhu *et al*, 2019		VEGF	VEGF	Diabetic foot	(79)
Tan *et al*, 2021		VEGFA	VEGFA	High glucose conditions	(69)
Oltra *et al*, 2020		VEGFA	VEGF	Retinal epithelial cell disorder	(22)
Gao *et al*, 2020		VEGFA	VEGFA	Cerebral Ischemic stroke	(80)
Salajegheh *et al*, 2015		VEGFA	VEGF	Thyroid cancer	(75)
Vosgha *et al*, 2018		VEGFA	VEGFA	Thyroid cancer	(76)
Zhang *et al*, 2021		VEGFA and FGF1	ERK1/2	Gastric cancer	(77)
Ouyang *et al*, 2020		VEGF and CDH11	-	Osteogenesis	(82)
Tabruyn *et al*, 2013		SMAD1/SMAD4	TGF-β pathway	Hereditary hemorrhagic telangiectasia	(65)
Tao *et al*, 2019		MICAL2	ERK1/2	Pulmonary arterial hypertension	(99)
Jiang *et al*, 2021		NOTCH2	VEGF	Mandibular distraction osteogenesis	(103)
Du *et al*, 2017		YAP1	STAT3 (IL-11 and IL-15)	Breast cancer	(72)
Sun *et al*, 2019	Pro-angiogenic	PTEN	PI3K/AKT	Thrombosis	(24)
Yao *et al*, 2019		PTEN	PI3K/AKT	Gastric cancer	(74)
Cai *et al*, 2013		PTEN	AKT/FOCO3A and AKT/mTOR	Lung cancer	(73)
Wang *et al*, 2020		HITT	HIF-1α	Colon cancer	(25)

VEGF/VEGFA, vascular endothelial growth factor A; ANG-2, angiopoietin-2; FGF1, fibroblast growth factor 1; CDH11, cadherin-11; SMAD, mothers against decapentaplegic homolog; MICAL2, microtubule-associated monooxygenase, calponin and LIM domain-containing 2; NOTCH2, neurogenic locus notch homolog protein 2; YAP1, yes-associated protein 1; PTEN, phosphatase and tensin homolog; HITT, HIF-1α inhibitor at the transcriptional level; TGF-β, transforming growth factor-β; ERK1/2, extracellular signal-regulated kinase 1/2; AKT, protein kinase B; mTOR, mechanistic target of rapamycin.

role in the regulation of vascular processes, which, depending on the context including cell type, stimulation and regulated target, can be considered pro-angiogenic or anti-angiogenic (Table I and Fig. 3). The present review aimed to elucidate its dual role as a regulator of angiogenic processes.

The present review performed an enrichment analysis that revealed that miR-205-associated genes are markedly over-represented in several canonical signaling pathways implicated in angiogenesis, vascular remodeling and diabetic complications (Fig. 4) (24,40,41,65,69-74). Among the most enriched pathways were the Hippo signaling pathway, AGE-RAGE signaling in diabetic complications (69,70), PI3K-Akt (24,73,74), TGF-β (65,71), and p53/EGFR-related cancer pathways (40,41,72), as well as processes linked to cell cycle control, cellular senescence and FoxO signaling (73). These findings suggest that miR-205-5p exerts a broad regulatory influence across interconnected angiogenic and stress-response pathways. Notably, the Hippo/YAP1 and PI3K-Akt/PTEN axes, both central regulators of endothelial proliferation and migration, were among the top enriched categories. In addition, the identification of the AGE-RAGE signaling pathway underscores the potential role of miR-205-5p in hyperglycemia-induced vascular dysfunction (69,70).

miR-205 as anti-angiogenic regulator. One of the most studied implications of miR-205 is its regulation of angiogenesis, where it is mostly considered to play an anti-angiogenic role, making miR-205 a protective agent against a number of conditions involving blood vessel formation, such as cancer and ocular diseases, among which DR and macular degeneration are conspicuous (22,23,69,70,75-78). This anti-angiogenic role is due to the post-transcriptional regulation of pro-angiogenic genes (22,69,77). The following section explains how miR-205 regulates angiogenesis depending on the targeted gene.

miR-205 and VEGF. VEGF, as already mentioned, is one of the most studied and relevant pro-angiogenic factors; it activates the migration, survival and vascular permeability of EC, thereby inducing angiogenesis (59-61). Different studies have shown that miR-205 has affinity, through base complementarity, with the 3'UTR region of mRNA that encodes for VEGF (22,69,77).

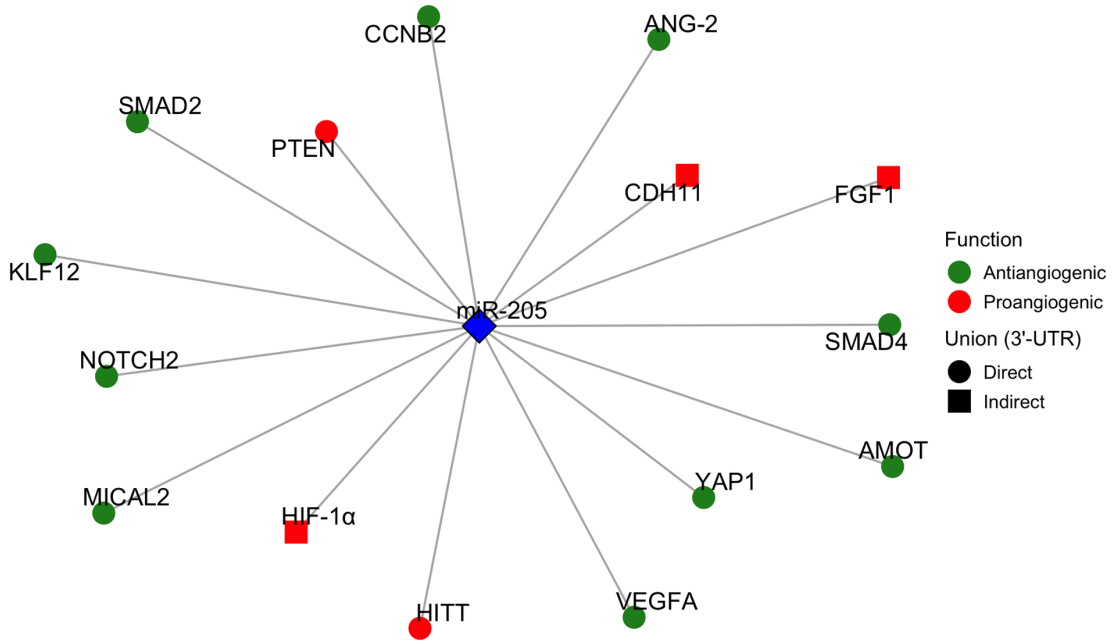

Figure 3. Representation of the 3'UTR targets of miR-205. Targets acting as anti-angiogenic factors are shown in green, and pro-angiogenic ones in red. Direct targets, defined by miR-205 binding to the 3'UTR region, are depicted as circles, while indirect targets of miR-205 are depicted as squares. miR-205, microRNA-205; ANG-2, angiopoietin-2; AMOT, angiomotin; CCNB2, cyclin B2; CDH11, cadherin-11; FGF1, fibroblast growth factor 1; HIF-1α, hypoxia-inducible factor 1-alpha; HiTT, HIF-1α inhibitor at the transcriptional level; KLF12, Krüppel-like factor 12; MiCAL2, microtubule-associated monooxygenase, calponin and LIM domain-containing 2; NOTCH2, neurogenic locus notch homolog protein 2; PTEN, phosphatase and tensin homolog; SMAD2, mothers against decapentaplegic homolog 2; SMAD4, mothers against decapentaplegic homolog 4; VEGFA, vascular endothelial growth factor A; YAP1, yes-associated protein 1; 3'-UTR, 3'-untranslated region.

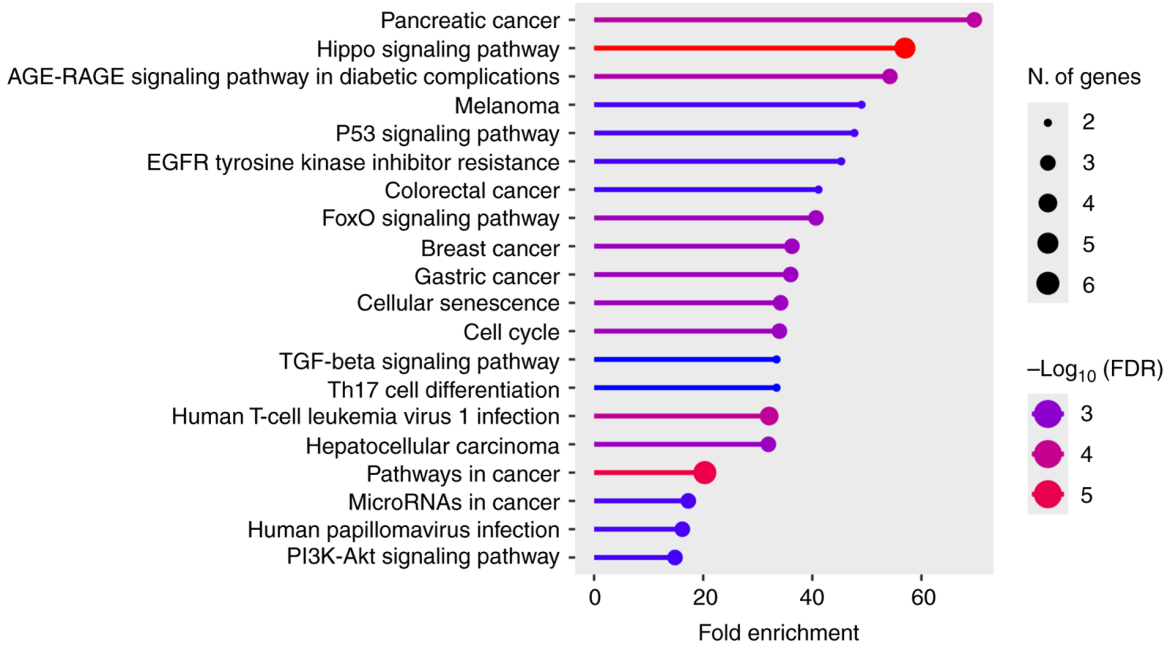

Figure 4. KEGG pathway enrichment of miR-205-regulated genes. Dots represent enriched pathways; x-axis: Fold Enrichment; dot size: number of genes; dot color: -$\log_{10}$(FDR). The top pathways (Hippo/YAP1, PI3K-Akt/PTEN, TGF-β/SMAD, p53/EGFR resistance, AGE-RAGE in diabetic complications) highlight canonical mechanisms by which miR-205 can exert anti- or pro-angiogenic effects depending on the targeted nodes and context. KEGG Kyoto Encyclopedia of Genes and Genomes; FDR, false discovery rate; miR-205, microRNA-205; PI3K-Akt, phosphoinositide 3-kinase-protein kinase B; TGF-β, transforming growth factor-β; EGFR, epidermal growth factor receptor; HPV, human papillomavirus; AGE-RAGE, advanced glycation end products-receptor for advanced glycation end products.

Thus, VEGF is one of the most studied angiogenic factors due to its involvement in various diseases. In this regard, the present study will focus on the VEGF-miR-205 relationship. One of the diseases in which the regulatory role of miR-205-VEGF has been studied is psoriasis (23). Psoriasis is characterized by excessive neovascularization in dermis and epidermal hyperproliferation,

in fact angiogenic factors such as VEGF and ANG-2 are elevated in plasma from patients. Xue *et al* (23) observed a negative correlation between the expression of miR-205, VEGF and ANG-2 in skin samples. After the subcutaneous injection of a miR-205 mimetic, the authors observed a decrease in inflammation and tissue damage. These improvements were due to the overexpression of miR-205, which reduced the levels of VEGF and ANG-2, thus blocking the MAPK pathway. Therefore, the authors concluded that miR-205 administration reduces the severity of psoriasis in mice.

On the protective role of miR-205, different authors agree that the state of hyperglycemia modifies the expression levels of miR-205, specifically decreasing them. It is hypothesized that MALAT1 sponges miR-205, facilitating the transcription of mRNA encoding VEGF (69,79). This regulatory mechanism can be considered protective or not, depending on the alteration. Under hyperglycemic conditions, an increase in proliferation, migration and endothelial tube formation is observed, which are pathophysiological processes associated with conditions such as DR, due to overexpression of miR-205 (69). However, in diabetic foot ulcer proliferation, migration and tube formation processes are considered essential for optimal recovery. So, both studies highlight the importance of MALAT1 and miR-205 in the regulation of VEGF and angiogenesis, but from opposing perspectives: One focuses on the positive therapeutic effects for diabetic foot due to the underexpression of miR-205, while the other addresses how reducing MALAT1 and increasing miR-205, can alleviate pathological angiogenesis induced by high glucose levels. In any case, miR-205 is considered to have anti-angiogenic capacity. In a similar context, under conditions of oxidative stress, such as hyperglycemia, the expression levels of miR-205 are also found to be reduced, while VEGF levels are elevated in retinal pigment epithelium cells (RPE) (22,70). This suggests that miR-205 acts as a regulatory agent of processes such as migration, proliferation and cellular apoptosis, emphasizing its potential as an anti-angiogenic factor in proliferative ocular diseases such as DR and age-related macular degeneration. Building on the MALAT1-miR-205-VEGF relationship, Gao *et al* (80) determined that MALAT1 serves as a protective agent for the angiogenic function of human brain microvascular endothelial cells under oxygen-glucose deprivation/reoxygenation conditions. The authors' findings align with the role of MALAT1 as a ceRNA for miR-205, sequestering it and thereby enhancing VEGF expression. This interaction protects and promotes angiogenesis, highlighting its potential protective role against ischemic injury.

The role of VEGF-miR-205 relationship has also been studied in cancer, one of the most extensively researched fields in every aspect. Thyroid cancer is a well-studied cancer type (75,76). Authors agree on the role of miR-205 as a tumor suppressor in thyroid cancer. Notably, the authors observed that miR-205 overexpression reduced angiogenesis by decreasing VEGF expression. Additionally, miR-205 inhibited EMT, invasion, migration and tumor growth. In gastric cancer, the miR-205-VEGF axis has also been studied, revealing that miR-205 is underexpressed in gastric cancer tissues (77). In renal cell carcinoma, miR-205 exerts a protective role by regulating VEGF expression, while metformin, a common antidiabetic drug, modulates miR-205 levels (81). These findings demonstrate the protective effect of metformin through its regulatory action on miR-205. Its overexpression markedly reduces cancer cell proliferation and angiogenesis *in vivo*. miR-205 achieves this effect by regulating not only VEGF but also FGF1 via ERK pathway, both of which are critical factors in the formation of new blood vessels. Therefore, the miR-205-VEGF axis in cancer is considered a tumor suppressor due to its inhibitory role in angiogenesis. Consistent with the regulatory function of miR-205 on VEGF, it has been observed that during osteogenesis, the biological process responsible for bone tissue formation and closely linked to vascular development, miR-205 expression levels were low, while VEGF expression was elevated (82). These expression levels are attributed to the lncRNA ENST00000563492, which acts as a ceRNA, sequestering miR-205. This sequestration increases VEGF expression, promoting angiogenesis during bone formation and facilitating bone healing.

Hereditary hemorrhagic telangiectasia (HHT) is a genetically heterogeneous disorder characterized by abnormal vascular structures. In this disease elevated VEGF plasma levels are considered HHT biological markers. By contrast, miR-205 in plasma levels are reduced (83). Although the authors of the present study do not mention the specific VEGF/miR-205 relationship or inter-regulation, their findings align with previously discussed studies: Low miR-205 levels lead to increased VEGF, which, in some cases results in abnormal vessel formation.

In summary, considering the regulatory pair miR-205/VEGF, the presence of miR-205 is regarded as protective, as it reduces VEGF levels and consequently angiogenesis in ischemia, cancer, psoriasis, or hyperglycemia conditions. However, in cases such as diabetic foot or osteogenesis, it is the absence of miR-205 that is deemed protective, as it promotes blood vessel formation due to increased VEGF levels. Regardless, all the mentioned studies agree on the regulatory potential of the miR-205/VEGF axis in angiogenic processes, with miR-205 being recognized as anti-angiogenic.

miR-205 and angioprotein (ANG) 2. ANG-1 and ANG-2 are another type of cell growth factors having an angiogenic activity after binding its tyrosine kinase receptor Tie-2 which is expressed primarily on EC (84). ANG-2 is considered a miR-205 target (23), although its angiogenic role remains to be clarified. Some authors consider that ANG-2 may inhibit angiogenesis by promoting the shedding of pericytes (85) while others consider ANG-2 as a VEGF enhancer promoting angiogenesis (86). Apart from the previously mentioned miR-205/VEGF regulation, Xue *et al* (23) observed that ANG-2 was overexpressed in psoriasis patients' plasma while miR-205 was underexpressed. The authors concluded that miR-205 acts as a negative regulator of ANG-2, decreasing angiogenesis and cell proliferation in the context of psoriasis following the subcutaneous injection of the miRNA. Abouaitah *et al* (87) observed that both miR-205 and ANG-2 are involved in the anticancer effects of a drug delivery system based on mesoporous silica nanoparticles (MSNs) against colon cancer. This strategy is widely used to enhance drug delivery and efficacy. They found that MSN administration markedly inhibited the expression of both miR-205 and ANG-2. These results do not align with those reported by other researchers. Although the authors do not specifically address the miR-205/ANG-2

relationship, their findings suggest that, in this experimental cancer cell model and conditions, MSNs-miR-205 treatment does not regulate ANG-2 expression. However, despite not discussing this regulation, they highlight the protective role of miR-205 in suppressing migration, invasion, and EMT. Similar observations were made in HHT, where both miR-205 and ANG-2 levels were found to be low in patients' plasma (83). Under these conditions, miR-205 cannot be considered an ANG-2 regulator. Therefore, further studies are needed to clarify the regulation of ANG-2 by miR-205.

miR-205 and SMAD. SMAD proteins act as crucial transcription factors in the regulation of angiogenesis following the activation of TGFβ pathway in EC. TGFβ signaling begins when TGFβ binds to its surface receptors, leading to the phosphorylation of SMAD1/5 by activin receptor-like kinase-1. These phosphorylated SMADs then form a complex with SMAD4, which translocate to the nucleus to regulate the transcription of specific genes involved in key processes such as migration and proliferation, essential for angiogenesis (88,89). Once again, in HHT, Tabruyn *et al* (65) established that miR-205 was downregulated, affecting the TFGβ signaling pathway in ECs. Specifically, the authors observed that miR-205 negatively regulates the SMAD1 and SMAD4 genes. The reduction in miR-205 expression leads to an increase in SMAD1 and SMAD4 activity, shifting the TGFβ balance toward a pro-angiogenic state, thereby promoting migration, proliferation and tube formation in ECs. In this context, miR-205 acts as an anti-angiogenic factor by downregulating the TGFβ pathway through the regulation of SMAD1 and SMAD4 (65). Similar results were observed in an *in vivo* cellular model of human lung adenocarcinoma, where miR-205 represses SMAD4 expression by directly binding to 3'UTR region of its mRNA. This leads to a reduction in TGFβ signaling, thereby decreasing cancer cell invasion and migration, key processes for angiogenesis (71). Other authors state that in glioma, miR-205 can regulate the expression of SMAD2 (90), another member of the SMAD transcription factor family and a critical protein in tumor proliferation regulation (91). Duan *et al* (90) report that miR-205 is underexpressed in glioma cells, leading to increased SMAD2 expression, which promotes TGFβ signaling and contributes to glioma cell proliferation and migration, thereby enhancing tumor malignancy. Moreover, studies confirm these results concretely in hyperplastic scars, characterized by excessive growth of fibrous tissue, where miR-205 negatively regulates SMAD2 (65,71,90). The authors observed that miR-205 levels were reduced, while SMAD2 levels were elevated. The restoration of miR-205 was able to suppress cell proliferation and promote apoptosis, in addition to inhibiting the expression of key extracellular matrix components, such as collagen I and II (92). Although the authors' results do not specifically address angiogenesis, they align with previous findings underlining the protective role of miR-205 in suppressing cell proliferation and migration; both essential processes for blood vessel formation.

miR-205 and molecule interacting with CasL 2 (MICAL2). MICAL2 is an enzyme that catalyzes actin oxidation-reduction destabilizing F-actin in cytoskeletal dynamics (93). MICAL2 is required to mediate Semaphorin3A-NRP2 response to VEGFR1 in EC, being Semaphorin3A-NRP2 essential in the modulation of cell proliferation and migration (94). Furthermore, VEGF promotes the assembly of p130Cas interactome that contains, among others, the MICAL2 protein. This interactome is responsible for driving chemotactic signaling and angiogenic properties of ECs (95). Different authors have linked MICAL2 overexpression in EC to chemoresistance and increased mortality in various types of cancer, including breast (96), bladder (97) and gastric cancer (93). One of the key processes influencing tumor progression is neoangiogenesis. Specifically, Barravecchia *et al* (98) observed that MICAL2 is expressed in ECs of pathological neoangiogenic capillaries but not in normal capillaries. Consequently, MICAL2 inhibition reduces EC viability and functional performance by impairing their ability to respond to VEGF stimulation, the authors point to MICAL2 as a possible new target for anti-angiogenic therapy. Tao *et al* (99) were the first and only ones to establish that the 3'UTR region of MICAL2 is a target of miR-205. The authors observed that in pulmonary arterial smooth muscle cells affected by pulmonary arterial hypertension, miR-205 is downregulated, while MICAL2 expression levels are elevated, promoting pulmonary arterial smooth muscle cell proliferation through the ERK-1/2 pathway. Therefore, the authors further propose miR-205 as an antiangiogenic agent, as it reduces MICAL2 expression, inhibits ERK-1/2 pathway activation, and consequently diminishes the cellular response to VEGF signaling.

miR-205 and NOTCH2. The Notch pathway is a highly conserved intercellular signaling system activated by the interaction of transmembrane ligands with Notch receptors (Notch1-4). Ligand binding induces cleavage of the Notch receptors and subsequent nuclear translocation of the Notch intracellular domains binding to multiple DNA-binding proteins. Notch, at initial angiogenesis stages, is suppressed to allow EC to proliferate in response to VEGF stimulation and its expression is subsequently upregulated when EC stop proliferating and the vessels begin to stabilize (100,101). Therefore, the Notch signaling pathway is considered a negative regulator of angiogenesis in most physiological contexts (101). However, in the skeletal system, the role of Notch signaling pathway is the opposite, being pro-angiogenic (102). There are few studies linking miR-205 to NOTCH2. Jiang *et al* (103) identified NOTCH2 as a direct target of miR-205 in the context of mandibular distraction osteogenesis, a surgical procedure used for controlled bone regeneration following fractures. In this setting, the NOTCH2 pathway plays a pro-angiogenic role. The authors' findings demonstrated that miR-205 regulates osteogenesis by modulating NOTCH2 expression, a key factor in bone angiogenesis. Inhibiting miR-205 markedly enhanced angiogenesis, whereas its overexpression had the opposite effect. Moreover, transduction with a lentiviral miR-205 inhibitor successfully restored angiogenic activity, accelerated bone regeneration and promoted local remodeling. Once again, miR-205 emerges as an anti-angiogenic factor, which, in this case, is considered detrimental to osteogenesis. Further studies are needed to clarify the relationship between miR-205/NOTCH and angiogenic processes, as well as their potential use as therapeutic targets.

miR-205 and Yes-associated protein 1 (YAP1). YAP1 is a key transcriptional coactivator in the Hippo signaling pathway,

which is involved in cell proliferation, migration and cancer invasion. Overexpression of YAP1 has been observed in several carcinomas, including lung, prostate, and colon cancer, among others, promoting tumor growth, proliferation and metastasis (104). Several studies have demonstrated that YAP1 is a target of miR-205 in different types of cancer, such as thyroid cancer (105), breast cancer (72), colon cancer (52) and gastric cancer (106). All these studies agree on the role of miR-205 as a tumor suppressor by inhibiting YAP1. However, YAP1 is widely recognized as an oncogene. Notably, YAP1 is not only regulated by miR-205 but also indirectly by ZEB1-AS1, a lncRNA that stimulates its expression on colorectal cancer tissues by acting as a post-transcriptional regulator of miR-205 (52). Although multiple studies have confirmed the miR-205/YAP1 axis in the regulation of cell proliferation and migration (52,72,105,106), few have explored its connection to angiogenic processes. Du *et al* (72) demonstrated that the miR-205/YAP1 axis promotes angiogenesis in breast cancer through the STAT3 pathway, independently of VEGF. In cancer-associated fibroblasts (CAFs) from breast cancer stroma, miR-205 is downregulated, suggesting a regulatory role. The authors' findings showed that restoring miR-205 expression attenuates angiogenic processes. Specifically, miR-205/YAP1 signaling activates normal breast fibroblasts, converting them into CAFs, which in turn promote tube formation by EC (HUVECs). However, this YAP1-driven increase in angiogenesis was not mediated by VEGF. Instead, it enhanced the expression of IL-11 and IL-5, maintaining the angiogenic environment even in the presence of VEGF-neutralizing drugs. More specifically, IL-11 and IL-5 activated the STAT3 pathway, promoting angiogenesis. In this context, miR-205 emerges as a potential anti-angiogenic agent, whose overexpression could reduce blood vessel formation. There are additional studies bringing to light the relationship between YAP1 and angiogenic processes. For instance, in DR, YAP1 was found to play an essential role (107). MALAT1, a lncRNA that also regulates miR-205, negatively regulates miR-200b-3a under high-glucose conditions. The downregulation of miR-200b-3p led to the de-repression of YAP1, increasing its expression and pro-angiogenic activity. Although this study did not specifically investigate the involvement of miR-205, it suggested that the regulation of YAP1 via MALAT1 may not be limited to miR-200b-3p but could also involve miR-205.

miR-205 as pro-angiogenic regulator. Although most studies examining miR-205 and its implication in angiogenesis consider it to be anti-angiogenic, there are some that document the opposite. miR-205 acts as a pro-angiogenic by blocking the transcription of factors with anti-angiogenic capacity, among which PTEN and HITT are prominent.

miR-205 and PTEN. As aforementioned, miR-205 exhibits a dual pro- and anti-angiogenic profile, potentially acting as either protective or an inducer of pathological processes. PTEN is a widely studied target of miR-205 due to base complementarity. In fact, different studies demonstrate that the sequence of miR-205 is complementary to 3'UTR of PTEN (24). One of the contexts in which the regulation role of miR-205/PTEN has been studied is in deep vein thrombosis (DVT). DVT refers to the formation of blood clots, inducing blood flow disorders and complications such as pulmonary embolism with fatal consequences (108). Angiogenesis is essential for thrombus recanalization and DVT resolution (109). Sun *et al* (24) demonstrated that the intravenous administration of miR-205 mimics reduced thrombus size and weight, increasing recanalization and DVT resolution. This effect was due to the enhanced migration and angiogenic capacity and suppressed apoptosis of EC. This pro-angiogenic effect of miR-205 was due to the regulation of PTEN, a negative regulator of PI3K/Akt pathway. The overexpression of miR-205 under thrombosis conditions represses the expression of PTEN, stimulating the PI3K/Akt pathway, which as a result induces, among others, the expression of MMP2. MMPs are considered important proteases for matrix degradation, activated by pro-angiogenic factors, necessary for EC migration (110). Therefore, the blockade of PTEN in ECs by miR-205 promotes the activation of migration and cell survival and reduces apoptosis through the PI3K/Akt pathway, suggesting miR-205 as a protective agent against thrombosis (24). However, other studies show the pro-angiogenic role of miR-205/PTEN axis but with potential pathological implications, especially in cancer contexts. In different tumor processes AKT signaling is constitutively activated in part because of PTEN loss of function (111,112). Lung cancer cell lines show an upregulation of miR-205 expression repressing PTEN expression activating AKT/FOXO3a and AKT/mTOR signaling pathways accelerating tumor cell proliferation and blood vessel formation, both *in vivo* and *in vitro* (73). Therefore, in tissues from patients with gastric cancer, it was observed that the expression of miR-205 was higher compared with healthy tissue, while the expression of PTEN was inversely proportional to that of miR-205. In Yao *et al* (74), *in vitro* analyses were performed in gastric cancer cell lines, showing that the administration of miR-205 inhibitors increased apoptosis and reduce cell proliferation and migration by PTEN overexpression (74). In endometrial cancer, the regulation of PTEN by miR-205 is also observed, suggesting miR-205 as a biomarker for endometrial cancer; however, its functional implication in angiogenic processes was not studied (113). These studies concluded that miR-205 can be considered an oncogene by reducing PTEN expression, promoting cell migration, proliferation, angiogenesis and mitochondrial damage contributing to the malignant phenotype of tumor processes.

miR-205 and HITT. The HIF-1α inhibitor at translational level (HITT) is a lncRNA whose expression is typically reduced in cancer and is associated with an advanced stage of the disease (25). As aforementioned, HIF-1α acts as a transcriptional factor for genes involved in angiogenesis, metastasis and EMT among others. One of the well-established HIF-1α targets is VEGF, promoting angiogenesis, allowing the cells to adapt to the hypoxic environment characteristic of tumor processes (43,114). HITT inhibits HIF-1α translation by blocking YB-1 (a transcriptional factor for HIF-1α), increasing tumor growth and angiogenesis processes (115). Indeed, high HIF-1 levels and low HTT levels are associated with poor cancer prognosis since they increase metastatic potential and angiogenesis (116). Wang *et al* (25) demonstrated, for the first time, the implication of miR-205 in HIF-1α/HITT axis in colorectal and cervical cancers. The authors determined that HITT is a direct target of miR-205, but at the same time, the miR-205 expression is also dependent on HIF-1α

Table II. miR-205-EVs targets and related angiogenic pathways.

Authors, year	Role	miR-205 targets	Related pathway	Pathology	(Refs.)
Zhang *et al*, 2025	Anti-angiogenic	VEGFA and ANG-2	VEGF	Ocular neovascularization	(78)
Liu *et al*, 2021				Diabetic foot	(127)
Zhuang *et al*, 2022				Oral squamous carcinoma	(128)
Yang *et al*, 2022	Pro-angiogenic	DSC-2	EGRF/ERK	Nasopharyngeal carcinoma	(124)
He *et al*, 2019		PTEN	PI3K/AKT	Ovarian cancer	(125)

VEGF/VEGFA, vascular endothelial growth factor A; ANG-2, angiopoietin-2; DSC-2, desmocollin-2; PTEN, phosphatase and tensin homolog; PI3K, phosphoinositide-3-kinase; AKT, protein kinase B; ERK, extracellular signal-regulated kinase; EGFR, epidermal growth factor receptor.

under hypoxic conditions. Specifically, the authors showed that under normoxic conditions, HITT does not undergo HIF-1α/miR-205-mediated destabilization. Under these conditions, HITT binds to YB-1, preventing YB-1 from associating with the 5'-UTR region of HIF-1α, thereby inhibiting its translation and reducing HIF-1α levels. However, under hypoxic conditions, HITT levels are regulated by miR-205 (in a HIF-1α-dependent manner). Elevated miR-205 levels are induced by HIF-1α acting as a transcription factor for miR-205. In hypoxia, miR-205 destabilizes HITT, reducing its inhibitory effect on HIF-1α transcription, which promotes angiogenesis and tumor growth. Therefore, miR-205 is considered a pro-angiogenic and oncogenic agent by regulating the HITT/HIF-1α axis.

4. miR-205 in extracellular vesicles as regulators of angiogenesis

EVs and exosomes are spherical lipid membranes released by different cell types containing proteins, lipids and nucleic acids, such as miRNAs. Among the miRNAs contained in EVs, miR-205 has been observed (26). EVs play crucial role in modulating biological responses, especially in the development, growth and maturation of blood vessels. An increasing number of studies emphasize the marked potential of EVs to revolutionize drug delivery systems (80). Compared with traditional methods, EVs, particularly, exosomes, offer significant advantages, including low immunogenicity, exceptional biocompatibility and high biosafety. They can efficiently cross challenging barriers, such as the blood-brain barrier, while enhancing the stability of encapsulated nucleic acid drugs and facilitating their transport through biological barriers (77,117). EVs have shown great promise as drug delivery systems, particularly in small interfering RNA delivery for pancreatic cancer treatment, with encouraging results in mice leading to ongoing clinical trials (118-120). Research emphasizes that EVs play an active role by influencing key stages of vascular development through different mechanisms. In fact, among the functional proteins present in EVs, VEGF emerges as a key mediator of angiogenesis (121). Their well-documented involvement in these processes has sparked growing interest in their potential therapeutic applications for regenerative medicine and angiogenesis-related diseases (Table II) (121,122)

One of the clinical applications that promises to have therapeutic potential effects as a regulator of angiogenesis is the use of EVs containing miR-205. EVs carrying miR-205 can promote EC proliferation and migration, facilitating angiogenesis. Moreover, the injection of exosomes loaded with miR-205, obtained from adipose-derived stem cells, reduces cardiac fibrosis and decreases cardiomyocyte apoptosis in myocardial infarction animal model (123). In line with previous findings, elevated levels of miR-205 in serum nasopharyngeal carcinoma subjects, have been associated with disease progression and poorer survival outcomes. This association was attributed to the regulation of desmocollin-2 (DSC2) by miR-205. miR-205 modulates DSC2, promoting EGFR/ERK pathway and the expression of MMP2/MMP9, thereby enhancing angiogenesis and metastasis (124). In ovarian cancer, it was found that the overexpression of miR-205 was associated with metastatic progression. This miRNA could reach EC from ovarian cancer cells through EVs, promoting angiogenesis both *in vivo* and *in vitro*. In this case, miR-205-EVs induce angiogenesis by regulating *PTEN*, thereby stimulating the PI3K/AKT pathway and enhancing angiogenesis (125,126). In these contexts, miR-205-EVs exhibits a pro-angiogenic role.

As reviewed in the present review, miR-205 directly targets *VEGF* and *ANG-2*, two key drivers of neovascularization. Research by Zhang *et al* (78) explored the use of EVs as delivery vehicles for miR-205. Concretely, in an ocular neovascularization mouse model the authors observed a significant reduction of both neovascularization and vascular leakage by miR-205 administration negatively regulating VEGF and ANG-2. On the other hand, it was observed that miR-205, along with miR-195, within EVs derived from wound fluid of diabetic foot ulcers, was able to inhibit angiogenesis by reducing VEGF expression, negatively affecting wound healing in patients with diabetic foot ulcers (127). These authors suggested that both miR-205 and miR-195 could be potential therapeutic targets to improve wound healing in diabetic foot ulcers. In the same direction, Zhuang *et al* (128) observed that the anti-diabetic drug phenformin upregulated the expression levels of miRNAs in EVs derived from oral squamous carcinoma cells. Among the altered miRNAs, the authors identified miR-1246 and miR-205, highlighting their role in blocking angiogenic processes in EC due to VEGF repression. These authors proposed phenformin as a useful tool to modify the tumor microenvironment by reducing carcinoma growth through changes in miRNA encapsulated in EVs. *In vitro* assays using RPE cells demonstrated that miR-205 EVs-cargo was lower under hyperglycemic conditions. Increasing the number of

miR-205 copies in EVs by using mimetics inhibited EC migration and tube formation (26). Given these findings, miR-205 emerges as a potent anti-angiogenic regulator that holds promise as a therapeutic option. Its delivery via EVs represents an innovative and effective strategy for treating conditions such as DR and cancer.

5. miR-205, angiogenesis and ocular disorders

miR-205-5p plays a crucial role in regulating gene expression in different tissues, including the eye. In ocular biology, it is involved in several essential processes, particularly in the development and maintenance of the cornea. Studies have shown that miR-205 is expressed in corneal epithelial cells and plays a role in their differentiation and function (33,129,130). Dysregulation of this miRNA has been linked to corneal diseases such as keratoconus, highlighting its importance in maintaining corneal homeostasis (131). In addition, miR-205 modulates lacrimal gland development (32,132). Beyond the cornea, miR-205 has also been studied in relation to retinal biology. Research indicates its involvement in retinal development and function, including the regulation of genes critical for photoreceptor survival and function (133).

Angiogenesis is a prime sign of corneal and retinal diseases including, DR, age related macular degeneration (AMD), neovascular glaucoma and corneal neovascularization. Although ocular angiogenesis is essential for tissue repair and maintenance, its dysregulation can lead to severe pathologies. Currently, the available treatments for these ocular disorders focus on blocking VEGF through use of anti-VEGF antibodies (ranibizumab and bevacizumab) (134). Although these drugs can control the disease and slow the progression of blindness in some patients, they are not completely effective, making their overall success questionable. miRNAs have been extensively studied as potential candidates for new therapeutic strategies. Given their regulatory role, their use as biomarkers or therapeutic tools in cancer and pulmonary diseases is already a reality (18,19). Focusing on the relationship between miR-205, angiogenesis and ocular disorders, some studies have been conducted, with most of them agreeing on the anti-angiogenic role of miR-205 in the ocular context. Understanding the precise mechanisms by which mR-205 influences these conditions could provide insights into new therapeutic approaches for treating retinal disorders.

In patients with uveitis, an inflammatory disease of the vascular layer of the eye (uvea), lower levels of miR-205 were detected compared with control patients (18). Even though the authors did not establish a direct connection with vascular processes, it is well known that the acute or chronic inflammation caused by uveitis can induce the production of VEGF, IL-6 and TNF-β, all of which are factors capable of promoting angiogenesis (135,136). Additionally, one of the potential complications of uveitis that can lead to vision loss is macular edema (137). The absence of miR-205 in these patients could trigger an increase in VEGF, one of the targets of miR-205, enhancing vascular processes and highlighting the anti-angiogenic role of miR-205. However, in patients with primary pterygium, a benign fibrovascular lesion of the conjunctiva, miR-205 expression levels showed no significant differences between patients and controls, reducing its relevance in this disease (138). This suggests that the anti-angiogenic role of miR-205 is context-dependent, varying according to the specific cellular environment and disease.

As previously mentioned, among the ocular diseases that lead to blindness due to the formation of aberrant blood vessels, AMD stands out. One of the miRNAs found to be downregulated in the serum of patients with wet AMD was miR-205. Low expression levels of this miRNA were associated with increased disease severity, although no direct correlation was observed between miR-205 expression and mortality. However, the mortality of patients was indeed associated with the number of anti-VEGF injections received; a higher number of injections associated with lower survival rates, pointing out the need to develop new therapies (139). Nevertheless, miR-205 could still be considered a potential biomarker for AMD.

Several *in vivo* studies have focused on the role of miR-205 in angiogenesis processes, using RPE cells as a model. This layer is a key component of the blood-retina barrier, playing a crucial role between the bloodstream and retinal photoreceptors. Due to its functions in light regulation, metabolic rate and photoreceptor renewal, the RPE is constantly exposed to oxidative stress, a major risk factor for the progression of AMD and RD. Oltra *et al* (22) used an RPE cell model exposed to high doses of H_2O_2 to stimulate the oxidative stress conditions that RPE experience. Under these stress conditions, miR-205 expression levels were low, while VEGF levels were high, indicating a negative correlation between them. The authors observed that after administering miR-205 mimics, tube formation was markedly reduced. The study concluded that under normal conditions, miR-205 inhibits VEGF and suppresses blood vessel formation by blocking PI3K/Akt pathway, underscoring the anti-angiogenic role of miR-205.

Using the same cellular model but exposed to high glucose concentrations to simulate the DR model, members of the same research group reaffirmed the role of miR-205 in regulating angiogenesis and cell migration through VEGF (70). Additionally, Ybarra *et al* (70) were the first to administer a miR-205 mimic via intravitreal injections in diabetic mice, observing a significant reduction in VEGF levels. This reduction could be linked to the improvement of aberrant vascular processes characteristic of RD. Based on these findings, the authors proposed miR-205 as a potential therapeutic agent against angiogenesis through intravitreal injections. Other researchers have included the lncRNA MALAT1 in the miR-205/VEGF axis, indicating that under hyperglycemic conditions, high MALAT1 levels reduce miR-205 expression, which in turn increases VEGF expression and consequently promotes angiogenesis (69). In any case, there is a consensus on the therapeutic potential of the miR-205/VEGF axis for pathological angiogenesis-related conditions.

In addition, using the RPE model exposed to high glucose levels, it was observed that miR-205, this time encapsuled within EVs, induced changes in recipient cells that internalized these EVs. Specifically, EVs released under control conditions contained a higher number of miR-205 copies. After loading EVs with synthetic miR-205 copies, tube formation and cell migration *in vitro* were markedly reduced (26). These findings not only confirm the anti-angiogenic role of miR-205 in RPE but also highlight its potential therapeutic use when encapsulated within EVs. In fact, Zhang *et al* (78) administered EVs

loaded with sufficient miR-205 copies via intravitreal injections in a mouse model of retinal and choroidal neovascularization. These EVs effectively strengthened the endothelial barrier, reduced vascular leakage and, most importantly, markedly inhibited the formation of abnormal blood vessels (78). In this case, the therapeutic effect of miR-205 is thought to be mediated not only by the negative regulation of VEGF but also by the downregulation of ANG-2.

Therefore, different studies agree on the usefulness of miR-205 as a therapeutic strategy against the formation of aberrant blood vessels in ocular diseases. Furthermore, miR-205 has potential implications as a biomarker in ocular diseases. Its expression levels in ocular tissues or biofluids could serve as indicators of disease progression or response to treatment. This biomarker and therapeutical potential underscore the importance of further research into miR-205 in ophthalmology, aiming to harness its diagnostic and therapeutic benefits for improving eye health outcomes.

6. Integrative view: Explaining the dual role of miR-205 in angiogenesis

The seemingly contradictory effect of miR-205 on angiogenesis is increasingly understood as context-dependent, influenced by a wide range of biological variables rather than representing true inconsistencies. Several mechanisms may explain this dual behavior, including cell-specific targets, disease stare, tissue type, and microenvironmental cues, such as glucose concentration, oxygen levels, or inflammatory mediators.

Importantly, the primary determinant of the angiogenic role of miR-205 lies in its molecular 3'UTR target (Fig. 3). When miR-205 represses pro-angiogenic factors such as VEGFA (22), SMAD1/4 (65), ANG-2 (23), or MICAL2 (99), it exerts anti-angiogenic effects by downregulating key signaling cascades that promote endothelial proliferation and migration. This pattern has been observed in diseases such as diabetic retinopathy, psoriasis, and thyroid carcinoma. As shown by the enrichment analysis (Fig. 4), among the most notable pathways were the TGF-β and Hippo/YAP-1 signaling pathways, both associated with some of the previously mentioned anti-angiogenic targets (SMAD1/4 and YAP1, respectively) (65,72). These findings further support the anti-angiogenic role of miR-205 in this context.

Conversely, pro-angiogenic functions of miR-205 are generally associated with its repression of anti-angiogenic or tumor-suppressor genes, such as PTEN and HITT (25,73,74) (Fig. 3), which leads to the activation of pathways such as PI3K/AKT or HIF-1α. Specifically, the PI3K/Akt signaling pathway was among those represented in the enrichment analysis (Fig. 4). These effects have been documented in ovarian cancer, nasopharyngeal carcinoma and myocardial infarction, where angiogenesis is enhanced as part of pathological or compensatory tissue remodeling.

Studies illustrate how the same miRNA can exert opposing effects in different tissues. For instance, inhibiting miR-205 in diabetic foot ulcers (79) enhances VEGF expression and promotes wound healing, while in the diabetic retina (70), the inhibition of miR-205 leads to increased VEGF levels and the formation of aberrant blood vessels that drive disease progression. Similarly, in gastric cancer, miR-205 has been shown to act as an anti-angiogenic factor by targeting VEGF in some contexts (77) and as a pro-angiogenic regulator by repressing PTEN in others (74). These findings reinforce that the functional outcome of miR-205 is primarily determined by the target it regulates, rather than the miRNA sequence itself.

In summary, the dual behavior of miR-205 is not contradictory but rather reflects a highly dynamic and target-dependent regulatory network, modulated by tissue type, disease context and environmental conditions. Recognizing this complexity is crucial for developing targeted and safe therapeutic strategies that leverage the angiogenic potential of miR-205.

7. Preclinical and clinical evidence on miR-205

Emerging evidence supports the potential of miR-205, particularly its levels in circulating EVs, as a biomarker of angiogeneic activity and tumor aggressiveness in several cancers. For instance, elevated levels of exosomal mir-205 in peripheral blood have been associated with increased risk of metastasis in patients with ovarian cancer (125). A comprehensive meta-analysis evaluating miR-205 in non-small cell lung cancer patients identified it as a promising biomarker for disease detection. The diagnostic accuracy of miR-205 was high, with a pooled area under the ROC curve (AUC) of 0.90 (95% CI: 0.87-0.92), suggesting strong potential for both ruling in and ruling out the disease. In clinical terms, a positive test result for miR-205 markedly increases the post-test probability of lung cancer diagnosis (from 25-57% in hypothetical screening scenarios) (140). Moreover, in gastric cancer, circulating mir-205 has been shown to serve as a predictive biomarker, with higher baseline levels correlating with improved progression-free and overall survival in patients treated with Ramucirumab-Paclitaxel (141). The clinical association between high miR-205 expression and improved prognosis aligns with its canonical anti-angiogenic mechanism; particularly its ability to suppress VEGFA and inhibit the PI3K/AKT signaling pathway. In primary tumor environments, where vascular control is critical, elevated miR-205 levels may reflect a less angiogenic and less proliferative phenotype, acting predominantly as a tumor and angiogenesis suppressor.

From a preclinical standpoint, one of the main challenges in miR-205-based nanotherapies lies in achieving targeted delivery to ensure the desired angiogeneic effect. Delivery systems must be specifically designed to direct miR-205 mimic toward proliferation pathological endothelial cells (to suppress VEGFA) or tumor cells (to inhibit proliferation or migration), while avoiding unintended delivery to metastatic niches, where miR-205 may promote angiogenesis through activation EGFR/ERK pathways (70). Surface engineering strategies, such as biomimetic coating or targeting peptides, are being developed to improve tissue specificity and minimize off-target activation of pro-metastatic routes. These approaches are crucial for translating miR-205-based therapies into safe and effective clinical interventions.

Although no clinical trials specifically targeting miR-205 have been published to date, the feasibility of miRNA-based pro-angiogenic therapies is supported by data from other candidates. A notable example is miR-92a, a well-characterized anti-angiogenic miRNA whose inhibition has shown significant benefits in preclinical models of ischemia and diabetic

wound healing. In particular, the synthetic inhibitor MRG-110 (an antagomir targeting miR-92a) was shown to enhance angiogenesis and accelerate tissue repair, outperforming pro-angiogenic growth factors used as positive controls (142). MRG-110 advanced to Phase I clinical trials, where it was proven to be safe and capable of improving perfusion and new blood vessel formation in human volunteers, as evidenced by increased CD31 markers and perfusion imaging (143). These findings provide mechanistic proof-of-concept for therapeutic angiogenesis through miRNA modulation.

By analogy, miR-205-based strategies may follow a similar trajectory toward clinical application; provided that its dual angiogenic behavior is properly controlled through context- and tissue-specific delivery systems.

8. Concluding remarks

The present review underscored the dual role of miR-205 in angiogenesis, functioning as both pro-angiogenic and anti-angiogenic factors depending on the cellular context. Its ability to regulate kay pathways, such as VEGF and PTEN among others, position it as a potential therapeutic target for various diseases. Additionally, EVs serve as an effective delivery system for miR-205, opening new possibilities for targeted treatments.

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Authors' information

MARIA OLTRA, ORCID: 000-0001-6397-2702. MIRIAM MARTÍNEZ-SANTOS, ORCID:0000-0002-9049-6174 MARIA YBARRA, ORCID: 0000-0002-5938-7209 MARIA PIRES, ORCID: 0000-0001-5461-3433 CLARA GOMIS-COLOMA,ORCID:0000-0003-3335-5767CRISTINA MEDINA-TRILLO, ORCID:0000-0003-3972-0964 FRANCISCO SANCHO, ORCID: 0000-0001-5409-5760 JORGE BARCIA, ORCID: 0000-0002-3660-7977.

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