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REVIEW

The biological function of microRNA195 and its relationship with angiogenesis

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MicroRNA participates in multiple biological activities by combining with target genes, degrading target mRNA or suppressing its translation which regulates the expression of genes. MicroRNA-195 is an important member of microRNA-15/161/195/424/497 family. miRNA-195 exerts its significant biological function in regulating cell cycle, apoptosis, cell metabolism, cell proliferation and metastasis by targetedly modulating MYB, CCND1, CCND3, CCNE1, E2F3, CDK6, Bcl-2, APP, BACE1, GLUT, SRC-3, Vav2, and CDC42. Furthermore, miRNA-195 can regulate angiogenic factors such as FGF1, VEGF and signaling pathways such as TGF-β1/ Smads and participate in the restoration of intima, progress of tumour, and the remodling of angiocarpy.

Keywords: micro RNA-195; angiogenesis; cell cycle, apoptosis; cell metabolism; cell proliferation; metastasis

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Introduction

MicroRNA (miRNA), consisting of 21~23 nucleotides, is a kind of noncoding, single stranded RNA molecules. Usually, it combines with the site in the 3' untranslated region (UTR) and mediates the cleavage or the suppression of translation of the target mRNA [1]. A single miRNA is capable of regulating thousands of target genes simultaneously, thus widely participating in various physiological and pathological process such as embryonic development, cell proliferation, differentiation and apoptosis, substance metabolism, wound healing, the occurence and development of tumour [2].

Angiogenesis refers to the process, during which the original vessels produce new vessels by the proliferation and differentiation of endothelial cells in or not in the form of blastogenesis. This process is regulated by both angiogenic factors and antiangiogenic factors [3]. Recent studies have found that miRNA plays a key role in the physiological and pathological process closely related to angiogenesis such as wound healing, tumour, and scar proliferation. There have already been studies indicating that miRNA-195 affects angiogenesis and participates in the occurence and development of maglinancies and the remodeling of heart by regulating the signaling pathway in which the target genes are involved. This article is an overview about the biological function of miRNA-195 and its role in angiogenesis.

The introduction to miRNA-195

Lagos-Quintana [4] is the first to have discovered that the sequence of miRNA-195 exists on mice genes. Subsequently, by using homologous sequence prediction, Landgraf [5] has

demonstrated that miRNA-195 exists on human genes as well. The genes of has-miRNA-195 has been found to be located at the region of 17p13.1 on the chromosome by Flavin [6]. The mature sequence of miRNA-195 is UAGCAGCACCAHAAAUAUUGGC, which belongs to miRNA-15/16/195/497 family and possesses the same 5' core sequence as mi-RNA-15, miRNA-16, miRNA-497: CGACGA[7]. miRNA-15A/16-1, miRNA-15b/16-2, miRNA-195/497 are respectively located at the region of 13p14.3, 3q26.1 and 17p13.1 in the form of gene clusters[8].

The mechanism of action of miRNA-195

MiRNA-195 exerts its function by base-pairing with the silence complex and combining with the target mRNA, thus regulating the expression of the target mRNA and protein. In recent years, Bioinformatics and experimental studies have found that miRNA-195 exerts its biological function of regulating cell cycle, apoptosis, cell metabolism, cell proliferation and metastasis by targetedly regulating MYB, CCND1, CCND3, CCNE1, E2F3, CDK6, Bcl-2, APP, BACE1, GLUT, SRC-3, Vav2, CDC42, and FAFN.

MiRNA-195 inhibits cell cycle

Cell cycle is the process during which a series of biochemistry reactions and structural changes take place and cell growth and proliferation are achieved. This process is mainly regulated by cell cycle regulatory protein. Cell cycle regulatory protein includes cell cycle protein, CDK, CDKI. MYB transcription factor family, which plays an important role in the regulation of cell cycle, is a kind of transcription factors containing MYB domain. Studies have discovered that miRNA-195 can act on 3' untranslated region of MYB miRN-A and inhibits the expression of MYB miRNA so that cell proliferation is reduced [9]. Furthermore, miRNA-195 down-regulates the expression of CCND1, CCND3, CCNE1, and E2F3 by acting on 3'UTR region of miRNA which codes for CCN1, CCN3, CCNE1, E2F3, blocking the G1/S transition[10-14]. Additionally, Deng [15] has suggested that gastric carcinoma cells of MGC-803, AGS, are respectively blocked by miRNA-195 at G0/G1, G2/M of cell cycle. Further studies have discovered that miRNA-195 suppresses the expression of CDK6 targetedly and inhibits the progression of cell cycle.

MiRNA-195 regulates apoptosis

Apoptosis is the natural death of cells, controlled by a series of genes and is regulated by the internal and external environment. Apoptosis is a significant balance factor in cell proliferation, differentiation and various pathologicial processes. miRNA-195 participates in multiple intracellular processes that promotes apoptosis. Latest studies have shown that the overexpression of miRNA-195 in hESC-NPCs has induced a number of cells to apoptosis [16]. The mechanism is that miRNA-195 regulates the small molecule GTP binding protein ARL2, which leads to apoptosis. The reduction of the number of cells caused by the overexpression of miRNA-195 is antagonized by the overexpression of ARL2. Qu [17] has explored the function of miRNA in colon cancer cells and its adriamycin-resistant strains. The substantial down-regulation of the expression of miRNA-195 has been verified in HT29/DOX and LOVO/DOX drug-resistant strains of colon cancer by using miRNA microarray and PT-PCR. Drug-resistant strains which overexpress miRNA-195 are more sensitive to adri-amycin and more susceptible to apoptosis. miRNA-195 acts on 3'UTR region of Bcl-2mi-RNA, especially the first combing site of it. The suppression of the expression of Bcl-2L2 has been shown to promote apoptosis by further studies. Chen [18] has also discovered that miRNA-195 contributes to the down-regulation of Bcl-2, thus promoting apoptosis and participating in the progression of diabetic renal damage. Zhu [19] has disclosed that the apoptosis of myocardial cell is promoted when miRNA-195 down-regulates Sirt1, ROS. He [20] has also disclosed that miRNA-195 affects the apoptosis of neurons and participates in the pathogenesis of Alzheimer Disease. miRNA-195 has been demonstrated to act on various target genes and to regulate the apoptosis of multiple kinds of cells.

MiRNA-195 inhibits cell metabolism

Substance metabolism and energy metabolism are included in cell metabolism. Energy metabolism occurs together with substance metabolism and takes substance metabolism as its vector. Biological activities are based on cell metabolism. miRNA-195 has already been verified to play a significant role in the metabolism of glucose, lipids and protein. GLUT, which plays a part in transporting glucose into tissues and cells, is a kind of carrier protein, inserted in cell membrane. GLUT3 is characterized by its low value of Km, indicating that GLUT3 possesses great affinity to glucose and a higher efficiency in delivering than other carrier proteins. Therefore, the cells, at which GLUT3 is located, are characterized to metabolize vigorously. Fei [21] has discovered the high expression of GLUT3 in T24 of human bladder cancer cells. It has been revealed that miRNA-195-5p targetedly suppresses the expression of GLUT3 in T24 cells, thereby reducing the glucose delivering in human bladder cancer cells and affecting cell growth. FASN is the key enzyme to catalyze the synthesis of endogenous long-chain fatty acids and the key factor to participate in lipids metabolism. Mao [22] has disclosed that miRNA-195 is capable of down-regulating the expression of

fatty acid synthase, therefore inhibiting the metastasis of osteosarcoma cells.

MiRNA-195 inhibits cell proliferation and migration

The biological activities of cells are importantly characterized by cell proliferation, which is the process of cell growth and splitting thus increasing the number of cells. To make up for the senescent and dead cells, the process of proliferation during which new cells are produced, is still needed after the organism has become mature. Cell migration refers to cells' movement after receiving migratory signals and plays an important part in embryogenesis, cell foraging, wound healing, immunization, infection and the metastasis of cancer.miRNA-195 has been proved by several studies to inhibit cell proliferation and migration. SR-C-3 up-regulates and promotes the proliferation of cancer cells during the occurrence of human tumours (breast cancer, lung cancer, prostatic cancer). In liver cancer cells, miRNA-195 down-regulates the expression of SRC-3 protein by combining with 3' UTR region of SRC-3 gene, therefore inhibiting cell proliferation [23]. Vav2, a kind of important intracellular signal transduction protein, plays a key role in the formation of flat pseudopodia and cell migration. Vav2 is also the activator of Rho/Rac metabolism pathway which regulates blood pressure. This pathway modulates the cytoskeleton of vascular smooth muscle cells to promote vasoconstriction. Studies [24] have shown that the expression of migratory factors, Vav2 and CDC42 can be down-regulated by miRNA-195. After the silence of miRNA-195 is induced, the expression of Vav2 and CDC42 has increased, thus stimulating the signal of V-av2/Rac1/CDC42 and the formation of lamellipodia, which promotes cell migration.

MiRNA-195 regulates angiogenesis

The introduction to angiogenesis

Angiogenesis refers to the process, during which the original vessels produce new vessels by the proliferation and differentiation of endothelial cells in or not in the form of blastogenesis [3]. This process begins with cell chemotaxis, migration, proliferation and tube formation. Then vasular smooth muscle cells move into and adhere to the intima, which forms the complete vascular wall. Finally, the newborn vessel develops into mature vascular system by remodeling. Angiogenesis participates in the pathological process of periodical change in endometrium, embryogenesis, wound healing, diabetic retinopathy, diabetic feet, and maglinancies. Both proangiogenic factors and angiogenesis inhibitors regulate angiogenesis. VEGF, FGF, TGF-β, IL-8, Epo, heparanase, PD-ECGF, OPN, COX-2, Angs, TNF-α, HIF, LN, PLGF, Survivin and some adherence factors are proangiogenic factors. ENS and angiostatin are angiogenesis inhibitors [25]. Angiogenesis is regulated when miRNA-195 promotes or inhibits the expression and the activities of these cytokines.

MiRNA-195 affects angiogenesis by regulating cytokines

MiRNA-195 participates in various physiological processes related to angiogenesis and development of different diseases. For instance, miRNA-195 regulates the phenotype of vascular smooth muscle cell and prevents neointimal formation [26]. miRNA-195 suppresses angiogenesis of Hepatocellular carcinoma by inhibiting the expression of VEGF [24]. miRNA-195 up-regulates TGF-β1/Smads Signalling Pathway, promoting cardiac remodeling [27].

MiRNA-195 and FGF1

Fibroblast growth factor1 (FGF1) is one of the important factors which promotes angiogenesis. With stronger chemotaxis and an effect on promoting proliferation, it can promote the proliferation and migration of smooth muscle cells [28]. Wang [26] found that miRNA-195 expression was down-regulated when vascular smooth muscle cells were treated with oxidized low-density lipoprotein. They showed that the miRNA-195 could downregulate the expression level of Cdc42 and FGF1, inhibiting VSMCs proliferation and migration. Animal experiments confirmed that the miRNA-195 reduced neointimal formation in a balloon-injured carotid artery, indicating that miRNA-195 played an important role in cardiovascular disease. Further studies showed that miRNA-195 reduced the expression of Cdc42 by combining with 3'UTR region of miRNA. Cdc42 serves as an upstream signal to activate the downstream FGF1, reducing the formation of intima.

The relationship between miRNA-195 and VEGF

VEGF, which activates ERK and promotes angiogenesis by combining with VEGFR, is the most powerful proangiogenic factor that has so far been discovered. The expression of VEGF is increased in tumour cells or under the condition of anoxia, thus promoting angiogenesis. By using double luciferase test, researchers [24] have revealed that miRNA-195 can combine with 3' UTR region of VEGF. In vitro tests have further confirmed that the overexpression of miRNA-195 restrains the expression of VEGF and down-regulates VEGF/VEGFR signal pathway, thus modulating angiogenesis negatively.

The relationship between miRNA-195 and TGF-β

TGF-β is a kind of multi-functional cytokine, of which there are 2 kinds of receptors, type I and type II. AIK is the type I receptor of TGF-β. Smad which participates in the signal tranduction of TGF-β, is the cytoplasm neurotransmitter of TGF-β. Alk1 and Alk5 are two different kinds of type I receptor and participate in the regulation of angiogenesis through the signal pathway of TGF-β/Smads. After combining with its receptor, Alk1 makes Smad1/5/8 phosphorylated and induces the endothelial cells to proliferate and migrate, therefore participating in angiogenesis [29]. Smad2/3 is activated when Alk5 combines with its receptor and antagonizes the function of Alk1 signal pathway, thus inhibiting cell proliferation and the formation of network, tubular vessels and inducing apoptosis [30]. Wang [27] holds the idea that miRNA-195 promotes the remodeling of heart by up-regulating TGF-β/Smads signal pathway. However, the specific target of miRNA-195 remains unclear and needs to be further experimentally studied.

Summary and Prospect

On one hand, angiogenesis promotes the physiological process of embryogenesis, the remodeling of endometrium, wound healing. On the other hand, angiogenesis plays a key role in the development of diseases such as scar proliferation, malignancies, diabetic retinopathy. Thereby, it is of great significance to further study the mechanism of angiogenesis and to provide novel therapeutic targets for promoting or inhibiting angiogenensis. miRNA-195 regulates the translation of multiple target genes and the expression of various kinds of proteins, thus participating in the regulation of cell cycle, apoptosis, cell metabolism, cell proliferation and migration. It has been disclosed by recent studies that miRNA-195 is closely associated with the regulation of angiogenesis, indicating that miRNA-195 is likely to be the therapeutic target for promoting or inhibiting angiogenesis.

Confict of interest

We declare that we have no conflict of interest.

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