The biological function of microRNA195 and its relationship with angiogenesis

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Received: February 09, 2015
Published online: March 11, 2015

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, Bel-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 remodeling of angiocarpyn.

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

To cite this article: Jingjing Wang, et al. The biological function of microRNA195 and its relationship with angiogenesis. RNA Dis 2015; 2: e610. doi: 10.14800/rd.610.

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 occurrence 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 occurrence 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
MiRNA-195 inhibits cell cycle

The mechanism of action of miRNA-195

MiRNA-195 inhibits cell cycle

MiRNA-195 regulates apoptosis

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 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 of 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 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 vascular 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. ALK is the type I receptor of TGF-β. Smad which participates in the signal transduction 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 inhibiting angiogenesis. 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.

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 angiogenesis. 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.

Conflict of interest

We declare that we have no conflict of interest.

References


