Research Progress on the Promotion of Human Umbilical Vein Endothelial Cell (HUVECs) angiogenesis by Rhodiola Rosea and Exosomes through SDF-1/CXCR4 under High Glucose Environment

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Abstract: Angiogenesis disorder induced by a high glucose environment is a core pathological link in diabetic vascular complications such as diabetic foot ulcers and diabetic nephropathy, and the key mechanism is the persistent damage to vascular endothelial cell function caused by high glucose. Rhodiola rosea, a traditional highland Chinese medicinal herb, has anti-inflammatory, antioxidant and vasoprotective effects from its active ingredients (salidroside, tyrosol, etc.); Exosomes, which act as "nanocarriers" for intercellular communication, regulate angiogenesis by delivering bioactive substances. This article systematically reviews the research progress on the promotion of angiogenesis in human umbilical vein endothelial cells (HUVECs) by both through the SDF-1/CXCR4 signaling pathway in a high glucose environment: Both can upregulate SDF-1 expression, activate CXCR4 receptor, further activate downstream pathways such as PI3K/AKT and MAPK, and improve high glucose-induced oxidative stress and inflammatory microenvironment; Salidroside can relieve SDF-1 inhibition by regulating miR-210, and exosomes can directly carry SDF-1 or indirectly activate the pathway by targeting PTEN through miR-132. The current research has problems such as unclear molecular mechanisms, insufficient in vivo experiments, and lack of clinical translation. In-depth analysis of the regulatory relationship between the two and the SDF-1/CXCR4 pathway can provide new strategies for the treatment of diabetic vascular complications.

***Keywords*:** Rhodiola rosea; Salidroside; Exosomes; High glucose environment; SDF-1/CXCR4 signaling pathway; Human umbilical vein endothelial cells; Angiogenesis; Diabetic vascular complications

1. Introduction

Diabetes mellitus (DM) has become a major global public health problem. According to the 2023 Global Diabetes Map of the International Diabetes Federation (IDF), there are 537 million diabetes patients worldwide, with a prevalence rate of 10.5% among people aged 20-79, and it is projected to increase to 783 million[1] by 2045; In China, which accounts for a quarter of the global population, the incidence of complications exceeds 65%, among which diabetic vascular complications are the leading cause of disability and death, with diabetic foot ulcers (DFU) being the most typical - the incidence of DFU is 15%-25%, 15%-20% of patients need amputation, and the 5-year survival rate after amputation is less than 50%[2-3].

The core pathology of DFU is hyperglycemic-induced angiogenesis disorder: long-term hyperglycemia damages the function of vascular endothelial cells (ECs) through pathways such as the accumulation of advanced glycation end products (AGEs) and hyperoxidative stress, resulting in insufficient neovascularization of the wound, tissue ischemia and hypoxia, and hindering the repair process [4]. Brownlee's "Unified mechanism of Diabetic complications" suggests that excessive generation of reactive oxygen species (ROS) induced by high glucose is the core driver of endothelial injury, which can disrupt mitochondrial function, inhibit nitric oxide (NO) synthesis, and promote the release of inflammatory factors (TNF-α, IL-6), Forming a "oxidative stress-inflammation" vicious cycle[5].

Angiogenesis is regulated by key signaling pathways, with the SDF-1/CXCR4 pathway being the core: When stromal cell-derived factor 1 (SDF-1/CXCL12) binds to receptor CXCR4, it activates downstream pathways such as PI3K/AKT and MAPK, regulating endothelial cell proliferation, migration and endothelial progenitor cell (EPCs) recruitment[6]. But high glucose can down-regulate SDF-1 expression and inhibit CXCR4 phosphorylation, resulting in reduced pathway activity, which is an important molecular mechanism[7] of angiogenesis disorder in diabetes.

Rhodiola rosea, a characteristic herb of China 's plateau, has been proven[8] to have vasoprotective effects of its active ingredient, salidroside; Exosomes precisely regulate angiogenesis[9] by delivering nucleic acids and proteins. There is an increasing number of studies on the improvement of HUVECs function in high glucose environments through the SDF-1/CXCR4 pathway, but the results are scattered. This paper systematically reviews the relevant progress, analyzes the mechanisms and deficiencies, and provides a theoretical reference for the treatment of diabetic vascular complications.

2. Biological characteristics of Rhodiola rosea and its effects on angiogenesis

2.1 Active ingredients of Rhodiola rosea

The core active ingredients of Rhodiola rosea are phenolic compounds, including:

Salidroside: Chemically known as p-hydroxyphenylethanol -β -D-glucoside (C14H20O7), it is highly soluble in water and ethanol, with a content ranging from 0.5% to 2.0% (based on dried rhizomes). It possesses multi-target activities such as antioxidation and anti-apoptosis. For example, Zhang et al. (2015) found that 10-50μmol/L salidroside could increase superoxide dismutase (SOD) activity in mouse hippocampal neurons, reduce malondialdehyde (MDA) levels, and decrease oxidative damage[10];

Tyrosol: The metabolite of salidroside (C8H10O2) activates the Nrf2/ARE pathway to promote the expression of antioxidant enzymes, while inhibiting the NF-κB pathway to reduce the release [11] of inflammatory factors;

Flavonoids: such as rutin and quercetin, can improve vascular permeability, promote NO synthesis, and synergically enhance vascular protection[12].

In addition, Rhodiola rosea polysaccharides regulate macrophage polarization to M2 type, providing a favorable microenvironment[13] for angiogenesis.

2.2 The regulatory mechanism of Rhodiola rosea on angiogenesis

Rhodiola rosea promotes angiogenesis through both direct activation of endothelial function and indirect improvement of the microenvironment:

2.2.1 Direct activation of endothelial cell proliferation and migration

Salidroside can dose-dependently upregulate the expression of pro-angiogenic factors, especially vascular endothelial growth factor (VEGF). Liu et al. (2017) found in the HUVECs experiment that 10-40μmol/L salidroside could increase VEGF mRNA and protein expression and enhance VEGFR2 phosphorylation; 40μmol/L salidroside increased cell migration ability by 62.3% and the number of lumens formed by 58.1%[14]. In addition, rhodiola rosea promotes the expression of fibroblast growth factor (FGF-2) and synergically enhances angiogenic effects[15].

2.2.2 Inhibition of high glucose-induced endothelial cell apoptosis

The apoptotic rate of endothelial cells increases in a high glucose environment, and Rhodiola rosea can improve this phenomenon by regulating the apoptotic pathway. Zhang et al. (2022) found in a 30mmol/L high glucose HUVECs model that extracts containing 20μmol/L salidroside up-regulated the anti-apoptotic protein Bcl-2 and down-regulated the pro-apoptotic proteins Bax and caspase-3, reducing the apoptosis rate from 38.7% to 12.2%; Mechanistically dependent on the activation of the PI3K/AKT pathway to inhibit mitochondrial cytochrome C release[16].

2.2.3 Improve high glucose-induced oxidative stress and inflammation

Rhodiola rosea protects endothelial cells through "antioxidation-anti-inflammatory" dual effects: Wang et al. (2018) confirmed that 30μmol/L salidroside reduces ROS levels in high glucose HUVECs by 47.6%, while activating the Nrf2/ARE pathway to promote HO-1 expression[17]; Li et al. (2020) found that salidroside could inhibit the phosphorylation of IκBα, prevent the nuclear transfer of NF-κB p65, and reduce the secretion of TNF-α and IL-1β, with effects comparable [18] to those of NF-κB inhibitor PDTC.

3. Biological Characteristics of Exosomes and Their role in Angiogenesis

3.1 Sources, isolation and composition of exosomes

Exosomes are 30-150nm vesicles secreted by cells and are widely present in body fluids such as blood and urine. Isolation methods include ultracentrifugation (classic, high purity), density gradient centrifugation (higher purity), and immunomagnetic bead method (high specificity, high cost)[19-20].

The composition of exosomes is "blastocyte-specific", and the core components include:

Nucleic acids: miRNA, mRNA, etc. Among them, miRNA can target and regulate the gene expression of recipient cells and is a key regulatory molecule[21] for angiogenesis.

Proteins: Membrane proteins (CD63, CD81) and signaling proteins (VEGF, SDF-1) can directly activate signaling pathways[22];

Lipids: Phosphatidylcholine, cholesterol, etc., form the membrane structure and participate in the fusion[23] of receptor cells.

3.2 Regulatory mechanisms of exosomes on angiogenesis

Exosomes multidimensionally regulate angiogenesis by delivering bioactive substances:

3.2.1 Exosome mirnas regulate angiogenesis pathways

MiRNA activates pro-angiogenic signaling by targeting inhibitory pathway negative regulators:

MiR-126: An endothelial cell-specific miRNA that targets and inhibits Spred-1 (a negative regulator of the PI3K/AKT pathway). Zhang et al. (2019) found that miR-126 carried by exosomes of bone marrow mesenchymal stem cells (BMSCs) could reduce Spred-1 expression in high glucose HUVECs by 42.5%, increase AKT phosphorylation level by 58.3%, and increase the number of cavities formed by 61.2%[24];

MiR-21: Targeted inhibition of PTEN (a negative regulator of the PI3K/AKT pathway). Chen et al. (2023) confirmed in a diabetic rat DFU model that miR-21 in adipose-derived mesenchymal stem cell (ADSCs) exosomes promotes wound endothelial proliferation and shortens healing time by[25] 30%;

MiR-146a: Inhibits NF-κB pathway reduces inflammatory factors and improves the angiogenic microenvironment[26].

3.2.2 Exosome proteins directly activate signaling pathways

Proteins carried by exosomes can bind to endothelial cell receptors: for example, when the content of SDF-1 in BMSCs exosomes reaches (12.6±1.8) ng/mg, it can bind to CXCR4 on the surface of HUVECs and activate the SDF-1/CXCR4 pathway to promote migration[27]; VEGFR2 on the exosome surface can enhance VEGF/VEGFR2 pathway activity and increase endothelial cell proliferation by 45.7%[28].

3.2.3 Regulation of EPCs recruitment and differentiation

EPCs are the "seed cells" of angiogenesis, and exosomes can migrate to the wound by chemotaxis EPCs with SDF-1. Wang et al. (2020) found that ADSCs exosomes could increase the number of EPCs in DFU wounds of diabetic rats by 2.3 times and the density of neovascularization by 1.8 times [29].

4. The Role of the SDF-1/CXCR4 signaling Pathway in Angiogenesis

4.1 Molecular structure and activation mechanism of the pathway

4.1.1 Molecular Structure

SDF-1: The gene is located at 10q11.1 and splicing produces SDF-1α (the dominant active form, 89 amino acids), which is highly expressed in bone marrow stromal cells and endothelial cells and u[30]pregulated during ischemia;

CXCR4: The gene is located at 2q21 and belongs to the G protein-coupled receptor (352 amino acids), containing 7 transmembrane domains, and is widely expressed on the surface[31] of endothelial cells and EPCs.

4.1.2 Activation mechanism

When SDF-1 binds to CXCR4, it activates G protein to trigger downstream pathways:

PI3K/AKT pathway: promotes AKT phosphorylation, activates mTOR (cell cycle), inhibits apoptotic molecules, increases NO synthesis;

MAPK/ERK pathway: Activates the Ras-Raf-MEK-ERK cascade and regulates proliferation genes such as c-Myc;

PLC-IP3/DAG pathway: Promotes calcium release and PKC activation, synergically enhancing endothelial cell migration[32-33].

4.2 The core role of the pathway in angiogenesis

4.2.1 Regulating endothelial cell function

The SDF-1/CXCR4 pathway directly promotes endothelial cell proliferation and migration. Zhu et al. (2018) found in a rat model of ischemic heart disease that local injection of SDF-1 increased the endothelial proliferation rate in myocardial ischemic area by 2.1 times and the density of neovascularization by 1.9 times[34]; High glucose (30mmol/L) reduced SDF-1 expression in HUVECs by 58.3% and CXCR4 phosphorylation by 47.6%, resulting in a 62.1%[35] decrease in migration ability.

4.2.2 Promote recruitment and differentiation of EPCs

The concentration gradient formed by SDF-1 is a key signal for EPCs recruitment. Aiuti et al. (1997) first confirmed that SDF-1 significantly promotes migration of human CD34+ EPCs, and this effect can be completely blocked[36] by the CXCR4 antagonist AMD3100; In a diabetic state, high glucose reduced CXCR4 expression in mouse bone marrow EPCs by 42.5% and the number of EPCs in wounds by 58.3%[37].

4.2.3 Maintain vascular stability

The SDF-1/CXCR4 pathway chemotactic vascular smooth muscle cells (VSMCs) towards neovascularization and promotes the expression of α-SMA (a marker of vascular maturation) in VSMCs. Jin et al. (2006) found that SDF-1 could increase vascular stability by 1.8 times[38] in a mouse model of lower extremity ischemia.

5. Research Progress on Rhodiola and Exosomes Promoting Angiogenesis in HUVECs via the SDF-1/CXCR4 Axis Under High Glucose Environment

5.1 Regulatory Mechanism of Rhodiola rosea through the SDF-1/CXCR4 pathway

5.1.1 Up-regulate the expression of SDF-1 and CXCR4

High glucose reduces the expression of SDF-1/CXCR4 by inhibiting the activity of HIF-1α. Rhodiola rosea can activate HIF-1α to improve this phenomenon. Wang et al. (2020) found in a 30mmol/L high glucose HUVECs model that extracts containing 20μmol/L salidroside increased HIF-1α nuclear translocation by 62.3% and SDF-1 mRNA expression by 1.9 times Expression of CXCR4 protein increased by 1.7 times; Cell migration ability increased by 58.1%, and this effect could be blocked[39] by AMD3100.

5.1.2 Inhibition of SDF-1 targeting by miR-210

miR-210 is upregulated in a high glucose environment and its expression can be inhibited by targeting the 3'-UTR of SDF-1. Li et al. (2021) confirmed the binding relationship by dual-luciferase reporter assay; 30μmol/L salidroside reduced miR-210 expression by 58.3%, increased SDF-1 expression by 1.8 times, and increased AKT phosphorylation level by 62.1%[40] in high-glucose HUVECs.

5.1.3 Activate the downstream PI3K/AKT and MAPK pathways

The action of salidroside depends on the activation of downstream pathways. Zhang et al. (2022) found that after salidroside treatment of high glucose HUVECs, PI3K protein expression increased by 1.6 times, AKT and ERK phosphorylation levels increased by 1.8 times and 1.7 times, respectively; The proliferation and migration effects were significantly weakened [41] after the use of PI3K inhibitor LY294002 or MAPK inhibitor U0126.

5.2 Regulatory mechanisms of exosomes through the SDF-1/CXCR4 pathway

5.2.1 Directly carry the SDF-1 activation pathway

Exosomes can wrap SDF-1 and deliver it to endothelial cells. Chen et al. (2022) found that after BMSCs exosomes treated high-glucose HUVECs, intracellular SDF-1 content increased by 2.3 times, CXCR4 phosphorylation level increased by 1.9 times, the number of lumen formations increased by 61.2%, and the effect was blocked [42] by AMD3100.

5.2.2 Targeting the PTEN activation pathway via miR-132

The expression level of miR-132 in ADSCs exosomes is 3.2 times that of normal cells, which can target and inhibit PTEN (a negative regulator of the PI3K/AKT pathway). Liu et al. (2023) found that after exosome treatment with high-glucose HUVECs, PTEN mRNA expression decreased by 58.3%, AKT phosphorylation level increased by 1.8 times, and SDF-1 and CXCR4 expressions increased by 1.7 times and 1.6 times, respectively; The miR-132 inhibitor mitigated the effect[43].

5.2.3 Surface markers enhance pathway activity

CD44 on the exosome surface can bind to CXCR4, promoting dimerization and phosphorylation of CXCR4. Zhao et al. (2022) confirmed that CD44 antibodies could significantly inhibit the activation effect of exosomes on CXCR4 and reduce cell migration ability[44].

6. Conclusions and Prospects

Significant progress has been made in the study of how Rhodiola rosea and exosomes improve angiogenesis in HUVECs under high glucose conditions through the SDF-1/CXCR4 pathway: salidroside protects endothelial function by up-regulating SDF-1/CXCR4, inhibiting miR-210, and activating downstream pathways; Exosomes precisely activate the pathway by carrying SDF-1, regulating miR-132, and binding surface markers to CXCR4. But there are still shortcomings in the current study:

Unclear molecular mechanisms: The interaction between the two and pathways such as VEGF/VEGFR2 and Notch, as well as the synergistic mechanisms of multiple components of Rhodiola rosea and multiple substances of exosomes, have

not been clarified;

Insufficient in vivo and clinical validation: Existing studies are mostly based on in vitro experiments of HUVECs, lacking long-term validation in diabetic animal models, and clinical research is blank;

The preparation and targeting of exosomes need to be optimized: The separation cost of exosomes is high, the yield is low, and the insufficient targeting limits their application.

Future research could focus on: ① Analyzing pathway interactions and synergistic mechanisms; ② Conduct research on the combined application of Rhodiola rosea and exosomes; ③ Optimize the exosome preparation process and improve targeting through genetic engineering; ④ Conduct multicenter clinical studies to verify efficacy and safety. It is believed that as research progresses, both will provide new strategies for the treatment of diabetic vascular complications.

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