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# A Review of the Research Progress on Stem Cell Therapy for Moyamoya Disease

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## Abstract

Moyamoya disease (MMD) is a chronic cerebrovascular disease characterized by progressive stenosis and occlusion of major intracranial vessels and the formation of abnormal vascular networks at the base of the brain. Existing surgical revascularization procedures are ineffective in fundamentally halting the disease progression. Stem cell therapy, with its multiple biological functions, including promoting angiogenesis, immunomodulation, and neuroprotection, offers a novel treatment strategy for MMD. This article provides a comprehensive narrative review of the research progress on stem cell therapy for MMD, focusing on the mechanisms by which mesenchymal stem cells (MSC), induced pluripotent stem cells (iPSC), and hematopoietic stem cells (HSC) improve neurological function by paracrine secretion of vascular endothelial growth factor (VEGF) and other factors, promoting therapeutic angiogenesis, inhibiting the release of proinflammatory cytokines such as TNF-$\alpha$ and IL-6, and modulating connexin 43 (Cx43) expression. Preclinical studies have shown that stem cell transplantation can increase microvascular density and improve cerebral blood flow in MMD models. Preliminary clinical evidence suggests that autologous bone marrow stem cell mobilization combined with surgery can significantly reduce inflammatory cytokines and enhance cerebral blood flow reserve in patients. However, this field still faces challenges, including standardized stem cell preparation, long-term safety validation, and the lack of large-scale randomized controlled trials. At present, stem cell-based interventions for MMD remain investigational and should be considered adjunctive experimental approaches rather than established treatments. Future research can further explore aspects such as stem cell sources and quality control, survival efficiency, mechanism complexity, clinical research limitations, and safety to promote the clinical translation of stem cell therapy.

**Keywords**

Moyamoya Disease, Stem Cell Therapy, Mesenchymal Stem Cells (MSC), Induced Pluripotent Stem Cells (iPSC), Hematopoietic Stem Cells (HSC), Angiogenesis, Immunomodulation, Neuroprotection, Combination Therapy

## 1. Introduction

Moyamoya disease (MMD) is a chronic progressive cerebrovascular disease of unknown etiology, characterized by progressive stenosis or occlusion of the distal ends of the bilateral internal carotid arteries and the origins of the anterior and middle cerebral arteries, accompanied by the formation of an abnormal vascular network at the base of the brain. Because the abnormal vascular network appears to be smoke-like during cerebral angiography, it is named "moyamoya" (meaning "smoke" in Japanese) [1]. Currently, surgical treatment is the main treatment for MMD. Although surgical treatment can improve the patient's clinical symptoms to a certain extent, it still has many limitations [2]. In recent years, stem cell therapy has shown good prospects in the treatment of various diseases and has provided new ideas for the treatment of MMD [3]. This article presents a narrative review of the current literature on stem cell-based approaches for MMD, summarizing preclinical evidence, clinical experiences, and key translational challenges.

## 2. Mechanism and Types of Stem Cell Treatment for MMD

Stem cells can self-renew through multiple processes of cell growth and cell division while maintaining an undifferentiated state; and can differentiate into various specific types of cells during life, playing an important role in tissue repair and regeneration. Currently, various stem cell types, such as mesenchymal stem cells (MSC), induced pluripotent stem cells (iPSC) and hematopoietic stem cells (HSC), have been applied to basic and clinical research on MMD. Their potential advantages include: promoting angiogenesis in ischemic brain tissue and improving cerebral blood flow; regulating local immune inflammatory responses and reducing brain damage; exerting neuroprotective effects and promoting neurological function recovery [4]. It should be noted, however, that much of the mechanistic evidence discussed below is derived from studies on stroke, cerebral ischemia, and other neurodegenerative conditions, and direct evidence from MMD-specific studies remains limited. Where MMD-specific data are available, they are explicitly indicated.

### 2.1. Types and Characteristics of Stem Cells Used for MMD Treatment

#### 2.1.1. Mesenchymal Stem Cells (MSC)

Mesenchymal stem cells (MSC) are currently the most widely used stem cell type in research on the treatment of MMD. They are widely available, easy to isolate

and culture, have strong proliferation capacity, low immunogenicity, and are not subject to ethical controversy [5] [6]. These characteristics make MSC ideal for cell therapy of MMD. The therapeutic efficacy, safety, and efficacy of MSC have been demonstrated in both basic research and clinical applications of MMD.

#### 2.1.2. Induced Pluripotent Stem Cells (iPSC)

Induced pluripotent stem cells (iPSC) are cells that, through genetic reprogramming, induce adult cells (such as skin fibroblasts and peripheral blood lymphocytes) to possess embryonic stem cell-like pluripotency. iPSC possess similar differentiation potential to embryonic stem cells, allowing them to differentiate into various cell types while avoiding the ethical and immune rejection issues associated with embryonic stem cells. These cells provide a new source of cells for the treatment of MMD [7] [8]. In the study of MMD, the application of iPSC in studying the pathogenesis of the disease and screening therapeutic drugs has also been preliminarily verified [8].

#### 2.1.3. Hematopoietic Stem Cells (HSC)

Hematopoietic Stem Cells (HSC) are a type of stem cells that exist in the bone marrow and have the ability to self-renew and multidirectionally differentiate. Their main function is to differentiate into various blood cell components.

Recent studies have found that, in addition to playing a role in the blood system, HSC may also participate in angiogenesis and tissue repair processes, which provides a theoretical basis for their application in the treatment of MMD [9]. Studies have shown that in the treatment of MMD, the application of HSC is mainly achieved through the mobilization of autologous bone marrow stem cells. In addition, compared with other types of stem cells, HSC do not require *in vitro* culture and manipulation, and can achieve therapeutic purposes by mobilizing endogenous stem cells, reducing the risk of infection and immune rejection, and the operation is relatively simple [9].

### 2.2. Core Mechanism of Stem Cell Therapy for MMD

#### 2.2.1. Promoting Angiogenesis

The core pathological changes of MMD are stenosis and occlusion of major blood vessels in the brain and the formation of abnormal vascular networks. Therefore, promoting therapeutic angiogenesis and establishing effective collateral circulation are the keys to improving cerebral blood perfusion. Stem cells have a strong ability to promote angiogenesis, which mainly works through the following pathways: First, stem cells can parasecretly secrete a variety of related factors, such as VEGF, hepatocyte growth factor (HGF), insulin-like growth factor (IGF)-1, platelet-derived growth factor (PDGF), etc. These cytokines can directly act on vascular endothelial cells, promoting their proliferation, migration and lumen formation [6] [10]. In addition, some studies have suggested that stem cells may have the potential to differentiate into vascular endothelial cells under specific experimental conditions [9]. However, the *in vivo* contribution of direct differentiation

to therapeutic angiogenesis is considered limited; the prevailing view is that paracrine signaling, rather than direct cell incorporation, is the primary mechanism driving the pro-angiogenic effects of stem cell therapy. These pro-angiogenic mechanisms have been extensively characterized in models of cerebral ischemia and general regenerative medicine; their specific relevance to MMD requires further validation in MMD-specific models.

#### 2.2.2. Immunomodulatory and Anti-Inflammatory Effects

The occurrence and development of MMD is closely related to immune inflammatory reactions. Abnormal immune activation and the release of inflammatory factors are involved in the damage and stenosis of the vascular wall. Elevated levels of pro-inflammatory cytokines, including IL-6, TNF-$\alpha$, and IL-1$\beta$, have been detected in the serum and cerebrospinal fluid of patients with MMD, and inflammatory cell infiltration has been observed in affected vascular tissues in pathological studies [11]. Stem cells have unique immune regulatory functions and can inhibit excessive immune responses and reduce inflammatory damage through various mechanisms, providing new ideas for the treatment of MMD. MSC are the most studied type of stem cells with immune regulatory functions. First, MSC can inhibit the proliferation and activation of T lymphocytes and B lymphocytes and reduce the secretion of proinflammatory cytokines (such as TNF-$\alpha$ and IL-1$\beta$); secondly, they can induce the differentiation of naive T cells into regulatory T cells (Treg), thereby promoting systemic immune tolerance; in addition, they can enhance immune tolerance by secreting soluble factors such as prostaglandin E2 (PGE2) and indoleamine 2,3-dioxygenase (IDO) [5] [6] [10]. These immunomodulatory properties are well established in MSC biology; however, direct evidence demonstrating their therapeutic relevance specifically in MMD is currently limited.

#### 2.2.3. Neuroprotection and Tissue Repair

In addition to promoting angiogenesis and regulating immune inflammatory responses, stem cells also have direct neuroprotective and tissue repair effects, which are crucial for improving the neurological prognosis of patients with MMD. First, they can secrete a variety of neurotrophic factors, which can protect neurons from ischemic hypoxia damage and promote the maintenance of neuronal function [6]. Second, treatment with exosomes from MSC has been shown to promote neurogenesis, neurite growth and recovery through the transfer of miR-133b [10]. In terms of tissue repair, while early studies suggested that stem cells might differentiate into neural cells, this direct differentiation is now considered a minor contributor to therapeutic effects *in vivo*. The more widely accepted mechanism is that paracrine factors secreted by stem cells—including neurotrophins and exosomes—promote the proliferation and differentiation of endogenous neural stem cells, enhance neuronal survival, and facilitate nerve regeneration. As with angiogenesis and immunomodulation, these neuroprotective mechanisms have been primarily characterized in non-MMD models of neurological injury, and their applicability to MMD requires further investigation.

## 3. Clinical Research and Current Status

### 3.1. Clinical Research and Application

Preclinical studies in animal models have demonstrated the potential mechanisms and effectiveness of stem cell therapy for MMD, providing a theoretical basis for its clinical application. The establishment of animal models can simulate the fundamental pathological features of MMD, providing an excellent experimental platform for stem cell therapy research. With the deepening of preclinical research, the clinical application of stem cell therapy in the treatment of MMD has gradually expanded. Currently, research focuses on the application of MSC and HSC, while clinical research on iPSC is relatively limited.

An open-label, single-arm clinical study investigated the safety and efficacy of local transplantation of autologous bone marrow-derived mononuclear cells (BM-MNCs) for the treatment of MMD. The study included 52 patients with MMD. Through hematoxylin-eosin (HE) staining, immunohistochemistry staining and other methods, it was observed that after Cx43 protein expression treatment, the levels of inflammatory factors such as IL-6 and TNF-$\alpha$ in the patients' peripheral blood decreased, and the level of IL-1$\beta$ (a pro-inflammatory cytokine) also increased. Compared with traditional surgery, autologous bone marrow stem cell (ABMSC) treatment helps to balance the inflammatory response of the disease, reduce damage to cerebral vascular tissue, and regulate tissue repair by acting together with various inflammatory factors [4]. However, it should be noted that BM-MNC is a heterogeneous cell population containing hematopoietic stem cells, mesenchymal stem cells, and other progenitor cells, rather than a purified stem cell product. Moreover, this study lacked a control group receiving surgery alone, limiting the ability to attribute the observed changes specifically to the cell therapy component.

Another study enrolled 54 patients with MMD who received pharmacological mobilization of bone marrow stem cells with G-CSF, combined with dexamethasone and anti-infective therapy, following surgical revascularization [12]. This was also a single-arm study without a control group. Neurological outcomes were assessed using the Barthel Index for activities of daily living, the Chinese Stroke Scale (CSS), and the National Institutes of Health Stroke Scale (NIHSS). The authors reported improvements in these scores post-treatment. However, because all patients received multimodal therapy (surgery + G-CSF + dexamethasone + anti-infectives), the specific contribution of stem cell mobilization to the observed neurological improvements cannot be isolated. This approach relies on endogenous stem cell mobilization rather than transplantation of ex vivo expanded cells, and the mobilized cell population includes hematopoietic stem/progenitor cells as well as other bone marrow-derived cells.

### 3.2. Current Research Status

Although stem cell therapy has shown great promise in the treatment of MMD, it

still faces many challenges, including the following: First, there is the issue of stem cell source and quality control. Stem cells from different sources (such as bone marrow, fat, umbilical cord, etc.) may have different biological characteristics and therapeutic effects. How to choose the optimal stem cell source is a problem that needs to be solved [5] [6]. In addition, during the *in vitro* culture and expansion of stem cells, problems such as cell aging and decreased differentiation potential may occur. How to ensure the quality and activity of stem cells is also a challenge. For induced pluripotent stem cells, there are also issues with the safety and differentiation efficiency of gene editing [7] [8]. Secondly, there is the issue of stem cell survival. Whether stem cells can survive long-term after transplantation is one of the key factors determining the therapeutic effect. Studies have shown that the survival efficiency of intravenously infused stem cells is low, and most cells will be cleared by organs such as the liver and spleen after infusion [5] [10]. How to improve the survival efficiency of stem cells and prolong their survival time in the body is an important issue that needs to be solved. Third, the complexity of the therapeutic mechanism. Although the potential mechanisms of stem cell therapy for MMD have been preliminarily elucidated, the interactions between these mechanisms and the specific characteristics of their effects at different stages of the disease are still not fully understood [6] [10]. For example, whether there is a synergistic or antagonistic relationship between the angiogenic and immunomodulatory effects of stem cells requires further investigation. Fourth, the limitations of clinical research. As mentioned above, current clinical studies on stem cell therapy for MMD have small sample sizes, lack randomized controlled trials, and have low levels of evidence [12]. In addition, the lack of unified efficacy evaluation standards makes it difficult to compare different studies, which also limits the clinical translation of stem cell therapy. Finally, there is the issue of safety. The long-term safety of stem cell therapy has not been fully verified, including the risk of tumorigenesis and immune rejection [5] [13]. For induced pluripotent stem cells, there is also the risk of gene mutation caused by gene editing, which requires thorough evaluation before clinical application.

## 4. Future Outlook

Given the current challenges facing stem cell therapy for MMD, future research can further explore aspects such as stem cell sources and quality control, survival efficiency, mechanism complexity, clinical research limitations, and safety. This will promote the clinical application of stem cell therapy in the treatment of MMD and bring new hope to patients with MMD. Although stem cell therapy for MMD is still in the research stage, its demonstrated therapeutic potential cannot be ignored. With continued in-depth research and technological advancements, stem cell therapy is expected to become an important means of treating MMD and make a significant contribution to improving patients' prognosis and quality of life.

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## Availability of Data and Materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## Author Contributions

**Hanying Gu:** Writing—original draft, Writing—review & editing, Software, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Xiuxia Shi:** Writing—original draft, Writing—review & editing, Supervision, Project administration, Data curation, Conceptualization. **Jiangtao Zhang:** Writing—original draft, Writing—review & editing, Supervision, Project administration, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization.

## Conflicts of Interest

The authors declare no competing interests.

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