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Review article

Challenges and research progress of the use of mesenchymal stem cells in the treatment of ischemic stroke

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Abstract

Cerebral Ischemic Stroke (CIS) has become a hot issue in medical research because of the diversity of risk factors and the uncertainty of prognosis. In the field of regenerative medicine, mesenchymal stem cells (MSCs) have an increasingly prominent position due to their advantages of multiple differentiation, low immunogenicity and wide application. In the basic and clinical research of CIS, there are still some problems to be solved in the treatment of CIS. This paper will discuss the progresses and some obstacles of current MSCs for the treatment of CIS.

Keywords: Ischemic stroke; Stem cells; Mesenchymal stem cells; Transplantation

1. Introduction

As one of the three most lethal diseases in the world today, 3/4 of stroke survivors have lost their working capacity to varying degrees, bringing great financial burden to families and society. Its high morbidity, high disability, and high mortality have made it a global health problem and a focus of human concerns and modern medical research. There is still no exact and effective therapy to cure CIS. In recent years we have found that MSCs may have great potential in CIS therapy. As early as 1968, Friedenstein et al. found MSCs in the bone marrow, and Lazarus et al. used them for the earliest clinical studies by 1995. Globally, MSC products have been on the market in Australia, South Korea, Italy and other countries for the treatment of diseases including bone injury, acute necrotic heart disease, acute child hormone resistance, GVHD (graft-versus host reaction), and traumatic corneal injury. It has been more than ten years since clinical trials of MSCs have been applied to CIS, but their safety and efficacy are still uncertain due

Abbreviations: CIS, cerebral ischemic stroke; MSCs, mesenchymal stem cells; GVHD, graft-versus host reaction; BDNF, brain-derived neurotrophic factor; NGF, nerve growth factor; FGF, fibroblast growth factor; VEGF, vascular endothelial growth factor; Evs, extracellular vesicles; iPS, induced pluripotent stem cell; VCAM-1^{+}, vascular cell adhesion molecule 1; SPION, ultrasmall superparamagnetic iron oxide nanoparticle; ELS, exosome-like silica

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to the lack of normative clinical data support. In the field of regenerative medicine, the therapeutic mode of MSCs transplantation has broad prospects, but it also faces great challenges. Regarding the mechanism of MSCs' action, transplantation strategy, and efficacy evaluation, some controversies still exist. This paper mainly discusses the research progresses and bottlenecks of MSCs.

2. The potential mechanisms of MSCs in the CIS therapy

The mechanisms of MSCs are complicated. In addition to the mechanism of neurotransmitter supplementation, institutional integration and cell mobilization, this paper mainly discusses the following three possible mechanisms (Fig. 1).

2.1. Replacement after differentiation

The initial view was that MSCs can differentiate and replace damaged nerve cells after transplantation [1,2]. Tomohiro et al. transplanted a Muse cell, a subtype of BMSCs into the brains of mice with CIS, and found the expression of the neuron-specific markers Tuj-1 and NeuN, which further supported the possible effects of differentiation and substitution [3]. Wakao S and Kuroda Y also supported this view by detecting the expression of neuronal-specific markers such as nestin, Musashi-1, NeuroD, and MAP-2 [4,5]. However, other researchers suggest that there is no direct evidence to prove that MSCs can differentiate into substitutable cells adapted to target tissues [6].

2.2. MSCs regulate local microenvironment

Inflammation may be the central factor that mediates secondary injury and poor prognosis after CIS [6]. After the occurrence of CIS, inflammatory cells and factors from the peripheral organ cycle to the brain tissue and secondary damage occurs afterwards, and after transplantation, MSCs can modulate microglia and macrophages, particularly promoting M2 type macrophages [6,7], and effectively clearing the inflammatory mediators, thereby reducing the local harmful inflammatory process. MSCs therefore play a role in stabilizing the micro-environment and neuroprotection [7,8]. However, it has also been suggested that in the acute phase of CIS, the survival rate of MSCs after transplantation is low in the local microenvironment with hypoxia and inflammation, and their anti-inflammatory effect remains to be seen.

2.3. Neurotrophic effects of MSCs

The secretion mechanism of MSCs has been the focus of many studies. Ruud et al. showed that MSCs can play a biological role indirectly through nutrient secretion and other endocrine or paracrine pathways [9]. Some studies have also suggested that MSCs can be quickly mobilized, especially in ischemic brain tissue. Excreting brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), and other bioactive factors, respectively, promoting vascular regeneration and synaptic formation [10]. In stem cell research, extracellular vesicles (EVs) have been found. EVs are cell secretions shed from the cell surface and are 0.1–1 μm in size. In recent years some studies have found that EVs derived from MSCs play an important biological role in a variety of diseases. They facilitate angiogenesis, neurotization and synaptic formation [11].

3. Research technology and progress relevant to MSCs

3.1. In vitro culture and expansion of stem cells

3.1.1. Culture medium and material for MSCs

The stem cell subsets vary with the changes in the culture media [12], the current mainstream culture media can be divided into two types: serum and serum-free.

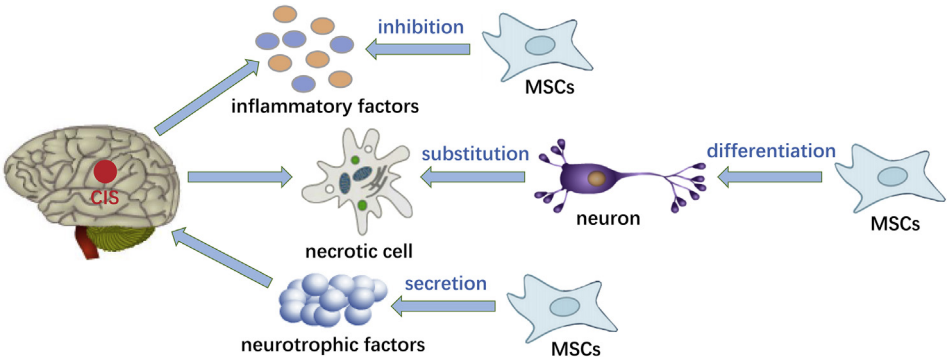

Fig. 1. The common mechanisms of MSCs in ischemic stroke therapy including cell replacement, local microenvironment regulation and neurotrophic effect.

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