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A Review of the Studies on Placental Mesenchymal Stem Cells and Their Exosomes Applied to Preeclampsia

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Abstract: Preeclampsia (PE) is a complex complication of pregnancy, which is a major cause of maternal and neonatal mortality. Its pathogenesis is closely associated with placental defects, although the specific mechanisms remain unknown, and specific targeted therapeutic interventions are currently unavailable. This article reviews recent domestic and international literature on PE and reveals the differences in placental mesenchymal stem cells (PMSCs) between PE and normal pregnancy groups. PMSCs play a crucial role in intercellular communication, regulating the normal functions of cells and organs, including maintaining a healthy pregnancy. The pathogenesis of PE is intricately linked to PMSCs, and abnormalities in these cells are associated with oxidative stress, inflammation, vascular endothelial damage and placental anomalies. Recent research on exosomes offers the potential for treatment strategies for PE. This article provides a comprehensive overview of the role of PMSCs and their exosomes in the pathogenesis of PE, while also delving into their potential utility in the prognosis and management of this distinctive pregnancy-related ailment presenting invaluable perspectives for forthcoming investigations within this domain of scholarly inquiry.

1. Introduction

Preeclampsia is a complex pregnancy disorder characterized by new-onset hypertension after 20 weeks. The diagnosis includes new-onset hypertension (systolic blood pressure≥140 mmHg or diastolic blood pressure≥90 mmHg) accompanied by one or more other clinical features: proteinuria. In the world, the incidence of preeclampsia is about 2%-8%[1], which includes maternal multi-system functional impairment (including liver function impairment, renal function impairment, blood system impairment, etc.) and fetal and its appendages dysfunction. Preeclampsia is a complex multifactor and multisystem disease, which can be accompanied by diseases such as fetal growth restriction in utero, premature delivery and placental abruption. It can seriously affect the prognosis of pregnant women and fetuses, and even lead to long-term complications in women and newborns[2], and its pathophysiological mechanism remains unclear. Current studies suggest that abnormal placental growth caused by trophoblastic dysfunction. And vascular endothelial injury are closely related to the onset of preeclampsia [3]. For the treatment of preeclampsia, there is no radical treatment, most of them are symptomatic treatment and timely termination of pregnancy. We hope to fundamentally

treat preeclampsia through the study of placental mesenchymal stem cells.

2. Placenta and preeclampsia

Placenta is an important organ during pregnancy, which plays an important role in transporting nutrients, exchanging wastes, and maintaining the immune balance of mother and fetus[4]. The placenta is composed of a large number of villi, which are composed of epithelial cells, trophoblast cells and stromal cells[5]. The villous mesenchymal cells include endothelial cells, placenta-derived mesenchymal stem cells, Hofbauer cell and so on. There are three main types of trophoblastic cells, including syncytiotrophoblastic cells, cytotrophoblastic cells and extrvillous trophoblastic cells. The normal communication and interaction between the above cells are closely related to the successful completion of the pregnancy process, and once the relationship between these cells is unbalanced, it will lead to adverse pregnancy outcomes, such as recurrent abortion, stillbirth and preeclampsia[6].

Studies have shown that the placental villous interstitium of preeclampsia patients has fibrosis accompanied by necrosis, the infiltration of placental leukocytes is significantly higher than that of normal pregnancy group, and the endometrial macrophages of placental blood vessels have fibrinoid necrosis and lipid accumulation[7]. At present, as is well-known that the pathogenesis of eclampsia is the two-stage theory proposed by Redman. In the first stage, the erosion ability of trophoblastic cells decreased, resulting in insufficient infiltration of the placental bed, accompanied by failure of spiral artery transformation and placental ischemia and hypoxia. In the second stage, after the imbalance of circulating angiogenesis factors and renin-angiotensin system, accompanied by multiple organ and system injuries, appear a variety of clinical manifestations[8].

Oxidative stress damage and inflammation existed in the above stages. The two-stage theory emphasizes that placental hypoplasia leads to shallow placental implantation and reduced effective exchange area, resulting in decreased placental function. At the same time, the changes of endocrine hormones in maternal serum and many oxidative products aggravate the damage of vascular endothelial cells, and such a vicious cycle ultimately leads to the formation of preeclampsia. However, regardless of the pathogenesis, we believe that the formation of preeclampsia is closely related to placental dysfunction, and the placental development defect is the basis of preeclampsia.

3. Placental mesenchymal stem cells and pregnancy

In the past, our understanding of placental lesions in preeclampsia was largely based on histological slides. With the development of stem cell technology, we have deepened our understanding of the pathogenesis, diagnosis and treatment of preeclampsia from the perspective of placental mesenchymal stem cells. Placental mesenchymal stem cells are a group of fibroblast-like cells with multipotential differentiation and paracrine function. The source of placental mesenchymal stem cells is abundant and exists in the placenta and its fetal membrane in large quantities. The placenta can be obtained as medical waste after delivery without invasive surgery, and amniotic mesenchymal stem cells and chorionic mesenchymal stem cells can be isolated and cultured from the placenta. Compared with bone marrow mesenchymal stem cells and other mesenchymal stem cells, placental mesenchymal stem cells show stronger endothelial transformation ability [9]. Therefore, placental mesenchymal stem cells are considered to be the main source of early placental endothelial cells and have strong repair and regeneration ability. Placental mesenchymal stem cells can promote angiogenesis, mainly in the following aspects: (1) Differentiation: placental mesenchymal stem cells residing in placental blood vessels differentiate into vascular endothelial cells. (2) Paracrine effect: placental mesenchymal stem cells promote the formation of placental blood vessels by secreting many growth factors. (3) Immunomodulatory effect: By interacting with immune cells, excessive immune response is suppressed, immune tolerance is induced, and the immune state of the uterus and placenta

is regulated. Under normal circumstances, placental mesenchymal stem cells have a protective effect on endothelial cells. However, when placental mesenchymal stem cells are abnormal, pathological pregnancy will result. For example, placental mesenchymal stem cells of preeclampsia patients can weaken the migration and invasion ability of trophoblast cells and destroy the placental vascular system, thus showing abnormal proliferation, inhibited migration and accelerated aging [10].

4. Placental mesenchymal stem cells and their exosomes with pregnancy

4.1 Overview of exosomes

Exosomes belong to a type of extracellular vesicles, which are nanoscale vesicle-like bodies that are actively secreted and released by cells into the exocytosis. It is present in almost all eukaryotic cells and can be detected in blood, semen, cerebrospinal fluid, milk, amniotic fluid, placenta, etc. Exosomes are about 40-100 nm in diameter and can be extracted by differential ultracentrifugation, size exclusion chromatography, immunoaffinity and other methods, including proteins, messenger RNA (mRNA), DNA fragments, lipids and metabolites[11]. Exosomes can achieve material transport and information transfer between cells through paracrine, autocrine and other ways. Different cells achieve intercellular communication by secreting exosomes carrying different components. Exosomes are closely related to the occurrence and development of some diseases, and previous studies have shown that exosomes play a role in immune response, inflammation, tumor, angiogenesis and other processes [12]. Human reproduction, pregnancy, and embryonic development require dynamic intercellular communication, and exosome-mediated intercellular communication begins before implantation. Placenta formation begins after embryo implantation, and placenta-derived exosome can be detected as early as 6 weeks of gestation, and maternal circulating placental exosome levels gradually increase as gestation progresses until full term and return to non-gestational levels within 8 hours after delivery[13].

4.2 Function of exosomes derived from placental mesenchymal stem cells

Exosomes derived from placental mesenchymal stem cells are involved in the regulation of angiogenesis and immune tolerance during placenta formation and are closely related to the occurrence of obstetric complications. It mainly plays its role in the following aspects: (1) During placental formation, exosomes promote trophoblast cells to invade deciduate and myometrium, reshape uterine spiral artery, promote vascular smooth muscle cell migration and stimulate endothelial cell generation[14]. The specific mechanism of exosomes promoting angiogenesis is still unclear. (2) Throughout the pregnancy, the fetus is an allograft of the mother, and exosomes play a key regulatory role in immune activation[15]. As a regulator of inflammatory response, exosomes play a dual role by promoting the in situ release of exosomes and inhibiting the pro-inflammatory response of immune cells. Exosomes regulate various inflammatory responses through signaling pathways such as PI3K/AKT/mTOR, JAK/STAT and Notch[16]. NK cells, macrophages and T cells are the three most important cell types, accounting for more than 90% of the immune cells at the maternal and fetal interface after implantation. Mesenchymal stem cell-derived exosomes can induce macrophages to polarization toward M2 phenotype, and M2 macrophages can inhibit the function of T cells and NK cells, induce regulatory T cells, and inhibit the release of pro-inflammatory factors, such as tumor necrosis factor α (TNF-α) and interleukin-1α (IL-1α). Mesenchymal stem cell-derived exosomes can make helper T cell type 2 (Th2) cytokines dominate [17]. When the proportion of helper T cell 1 (Th1) cells is higher than Th2, implantation failure, abortion and preeclampsia will occur.

4.3 Exosomes derived from placental mesenchymal stem cells and preeclampsia

There were significant differences in the concentration and composition of exosomes between normal pregnancy and pathological pregnancy. Kuria et al. compared the serum total exosomes and placental exosomes of pregnant women in normal pregnancy and preeclampsia pregnancy group, and the concentration and average diameter of total exosomes and placental exosomes in maternal plasma were higher than those of pregnant women in normal pregnancy[18]. MiRNAs are small non-coding RNA molecules that regulate gene expression and are critical in cell development, proliferation, and apoptosis, with each miRNA controlling hundreds of target genes. Exosomes are the main carriers of miRNA and the bridge of information exchange between cells. The occurrence of preeclampsia may be related to the alteration of miRNA expression in placental tissue and maternal circulation[19]. miR-16 is highly expressed in preeclampsia exosomes, which inhibits the vasogenic ability of placental mesenchymal stem cells and the migration ability of endothelial cells. These functional changes are closely related to the occurrence of preeclampsia. In addition, high expression of miR-16 can further exacerbate apoptosis and inflammatory response of cells. The expression of miR-29 was significantly increased in placental sections of preeclampsia group, and miR-29 could induce apoptosis of trophoblast cells and inhibit trophoblast invasion and angiogenesis[20]. Salomon et al. [21] found 12 differentially expressed exosome miRNAs between normal pregnancy and preeclampsia pregnancy, among which the increased expression levels of miR-486-1-5p and miR-486-2-5p were most significant in the preeclampsia group. To sum up, changes in miRNA content in exosomes lead to abnormal cell growth, adhesion, migration and invasion, and ultimately affect endothelial cells, resulting in systemic endothelial dysfunction and impaired angiogenesis [22]. The current study is still limited, and more studies are needed to further clarify the differences in expression and mechanism of action of these miRNAs in preeclampsia. With our understanding of exosomes, the pathogenesis of preeclampsia will continue to be clarified, and specific ways will be found to change the expression of miRNA, providing a strong basis for miRNA targeted therapy and early diagnosis of preeclampsia.

5. Advances in the use of placental mesenchymal stem cells and their exosomes in preeclampsia

Exosomes, as a new type of non-cellular therapy, have the advantages of more stable biological activity, easy storage, low immunogenicity, ability to pass the blood-brain barrier, and accurate delivery to target cells[23]. The exosomes derived from mesenchymal stem cells retain the biological activity of the parent mesenchymal stem cells. It has been shown that exosomes show similar therapeutic effects to mesenchymal stem cells in selected animal models [24]. Therefore, exosomes will be an important alternative treatment option in the future. At present, there have been many relevant reports on the study of exosomes from different sources in preeclampsia.

5.1 Exosomes of other mesenchymal stem cell origin

Huang et al.[25]found that the exosome derived from umbilical cord mesenchymal stem cells could inhibit the content of inflammatory factors in the placental tissues of preeclampsia rats and reduce the apoptosis rate by upregulation of miR-18b-3p and targeted reduction of leptin levels, thereby reducing the systolic blood pressure and 24-hour proteinuria of rats, and increasing the weight of the placenta. Zheng et al.[26] demonstrated that exosomes derived from decidual mesenchymal stem cells can improve serum endothelial dysfunction in LPS and preeclampsia patients, reduce the levels of inflammatory factor IL-6 and malondialdehyde related to lipid peroxidation, promote cell proliferation, and alleviate cellular inflammation and oxidative stress. Chen et al. [27] demonstrated that long non-coding RNA (lncRNA) H19 of exosomes derived from bone marrow mesenchymal stem cells increased the expression of FOXO1 and activated the AKT pathway, thereby promoting

the migration and invasion of trophoblast cells and inhibiting cell apoptosis. It is suggested that it may be possible to treat preeclampsia by the above mechanism. In addition, zhu et al. [28] confirmed that exosomes derived from human adipose stem cells can promote angiogenesis by targeting the let-7 / AGO1 / VEGF signaling pathway and can decrease the degradation of vascular endothelial growth factor. Chu et al. [29] used hypoxia-induced human amniotic mesenchymal stem cells to improve the survival rate of trophoblast cells exposed to adverse conditions by activating the mTOR pathway. The above related reports all confirm that exosomes from different sources have great potential in the treatment of preeclampsia.

5.2 Placental mesenchymal stem cells and their exosomes

Yan Li et al. [30] reported that exosomes derived from placental chorionic mesenchymal stem cells can up-regulate the expression of TRIM72 contained in trophoblastic cells and down-regulate the expression of tumor protein P53, which interact with each other to promote P53 ubiquitination and proteasome degradation, reduce the apoptosis rate of trophoblastic cells and promote proliferation and migration of trophoblast and improve placental function. The placental manifestations of preeclampsia are associated with a decrease in proliferation and erosion of trophoblast cells. Therefore, the authors suggest that exosomes derived from placental chorionic mesenchymal stem cells could serve as a potential strategy for the treatment of preeclampsia. Di Wu et al. [31]co-cultured placental mesenchymal stem cells modified by heme oxygenase-1 (HO-1) with human umbilical cord endothelial cells and decidua villi, and the results showed that vascular endothelial growth factor (VEGF) levels were increased in the conditioned medium of placental mesenchymal stem cells. The level of soluble FMS-like tyrosine kinase-1 (sFlt-1) was decreased. HO-1 modified placental mesenchymal stem cells improve placental angiogenesis by promoting the balance of pro-angiogenic factors and anti-angiogenic factors and are worthy of further study as an alternative treatment for preeclampsia to improve placental angiogenesis. In addition, Zhang[32] et al co-cultured conditioned media prepared from human placental mesenchymal stem cells with cytotrophoblast of hypertensive diseases during pregnancy, reducing the apoptosis of trophoblast cells. Du W et al.[33] demonstrated the pro-angiogenic effect of exosomes in a mouse model by using exosomes derived from placental mesenchymal stem cells to promote the expression of vascular endothelial growth factor receptor 2. At present, there are few reports LP on the treatment of preeclampsia by exosomes derived from placental mesenchymal stem cells. However, the feasibility of exosomes derived from placental mesenchymal stem cells in the treatment of other diseases has been reported. For example, Milton D. Chiang et al.[34] demonstrated that the exosomes of human placental mesenchymal stem cells could improve the LPS-induced lung injury model of obese mice, and that the exosomes of placental mesenchymal stem cells could reduce the polarization of macrophages to M1 type and reduce the phosphorylation of PI3K and Akt. Inflammation and apoptosis were inhibited by down-regulation of apoptotic protein BCL2-associated X (Bax) and Cleaved Caspase3, and up-regulation of anti-apoptotic protein B-cell lymphomato-2 (Bcl2). The authors suggest that exosomes of placental mesenchymal stem cells can ameliorate lung injury in mice by this mechanism. The pathogenesis of preeclampsia is also characterized by excessive inflammatory response. Therefore, it can be inferred that the application of exosomes from placental mesenchymal stem cells to preeclampsia will have certain therapeutic effects based on the pathological mechanism of inflammation.

Exosome therapy with autologous mesenchymal stem cells can reduce the immune rejection of transplanted organs and improve the effectiveness and safety of drug administration. This protocol promotes possibilities for modulating the immune response, inducing tissue regeneration and improving pregnancy outcomes. At present, the exosome of placental mesenchymal stem cells for the treatment of complex perianal fistula has been tested in phase I clinical trials, and a six-month follow-

up has been conducted [35]. We confirm that exosomes are an effective alternative and safer than direct use of placental mesenchymal stem cells without causing serious adverse reactions. Exosomes of placental mesenchymal stem cells have good immunomodulatory, regenerative and neuroprotective properties, and have also been used as drug candidates for the treatment of multiple sclerosis [36]. Compared with other mesenchymal stem cells, placental mesenchymal stem cells have more abundant sources and exist in the placenta and its fetal membrane in large numbers. As previously reviewed, the occurrence of preeclampsia is closely related to the abnormal function of the placenta, and the placenta-derived exosomal body of preeclampsia patients can cause preeclampsia like symptoms in mice. Therefore, placental mesenchymal stem cell exosomes can be targeted to improve placental function, which has great potential in the treatment of preeclampsia, and deserves further study.

6. Summary and Prospect

Placental mesenchymal stem cells and their exosomes are expected to be a new method for the treatment of preeclampsia, but the practical application still faces a lot of challenges. First, it is currently difficult to extract and manufacture exosomes on a large scale and with high purity, so it is crucial to develop a technology that can produce a large number of exosomes quickly and cost-effectively and ensure the quality of exosomes for clinical application in the future. Secondly, when exosomes are used for treatment, the way of administration is also worth discussing. The more traditional ways of administration include oral administration, intravenous or intraperitoneal injection, etc. Bioactive materials can also be used as scaffolds for administration at a single site to increase the residence time and concentration of exosomes at the target site and reduce systemic adverse reactions. More research is also needed to select the right delivery method for different diseases. In addition, the long-term toxicity and immunogenicity of repeated administration of exosomes should also be studied through hematological examination, histopathological analysis and other tests to find out whether it may trigger immune or toxic reactions and ensure its safety and effectiveness. In summary, there is still a long way to go to promote the subsequent placental mesenchymal stem cells and their exosomes in clinical application.

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