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Research Progress of Mesenchymal Stem Cells in the Treatment of Chemotherapy-induced Premature Ovarian Failure

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Abstract: Nowadays, the incidence of cancer in women is increasing. As the main treatment of most tumors, chemotherapy often damages the ovarian function of women, causes premature ovarian failure (chemotherapy-induced premature ovarian failure, CIPOF) induced by chemotherapy, and results in loss of fertility. It has caused great harm to women's physical and mental health and caused a series of social problems. Therefore, the effective treatment of CIPOF has become the focus of medical research. Stem cells have become the focus of research because of their ability of multi-differentiation and self-replication. Scholars at home and abroad have applied dry and fine stem cells. Preliminary results have been obtained in the animal experiment of restoring ovarian function, which brings hope to the recovery of ovarian function and reproductive function in patients with CIPOF. The progress of mesenchymal stem cell therapy for CIPOF is reviewed.

1. Introduction

In contemporary society, the incidence of cancer among women is on the rise and occurring at younger ages. Chemotherapy, a critical treatment modality, induces a range of side effects, particularly significant damage to the reproductive systems of young women. This includes apoptosis of ovarian granulosa cells (GC), a reduction in antral follicle count (AFC), follicular damage, and diminished ovarian function. These factors contribute to chemotherapy-induced premature ovarian failure (CIPOF). Patients may experience abnormal menstrual cycles (amenorrhea or irregular menstruation), hot flashes due to decreased estrogen levels, facial flushing, reduced libido, decreased fertility or even infertility—seriously impacting their quality of life as well as physical and mental health. Currently, hormone replacement therapy (HRT) remains the primary intervention for CIPOF; however, it primarily alleviates symptoms associated with estrogen deficiency resulting from impaired ovarian function while posing risks for complications. Its efficacy in restoring ovarian function and fertility is limited; moreover, prolonged HRT can elevate

the risk of thrombosis, coronary heart disease, and breast cancer [1-2]. Consequently, there is an increasing clinical focus on more effective prevention strategies and treatments for CIPOF that aim to restore fertility.

Stem cells are primitive undifferentiated cells characterized by their multi-directional differentiation potential and self-replication capabilities—fundamental properties necessary for forming various tissues and organs within the human body. They are classified into two categories based on developmental stages: embryonic stem cells and adult stem cells. Due to ethical concerns surrounding their use, research involving embryonic stem cells faces restrictions. In contrast, adult stem cells have emerged as a prominent area of investigation owing to their abundant availability without ethical constraints. Research indicates that stem cell therapy has protective effects on ovaries by preventing further functional decline while also restructuring ovarian architecture—thereby restoring functionality [3] and enhancing fertility prospects.

Mesenchymal stem cells (MSC), which are derived from mesodermal tissue predominantly found in connective tissues across various organs are easily sourced along with being straightforward to isolate, culture, expand, and purify. With attributes such as self-renewal capacity, pluripotency, and immunomodulatory functions, MSCs find extensive applications in cell therapy, tissue engineering, and regenerative medicine. Presently MSCs are regarded as promising candidates for treating CIPOF—a topic explored further within this article.

2. Research on Mesenchymal Stem Cells in CIPOF

2.1. Investigation of Bone Marrow Mesenchymal Stem Cells in CIPOF

Bone marrow mesenchymal stem cells (BMSCs) are the earliest identified adult stem cells, originating from bone marrow, and currently represent the most extensively utilized type of mesenchymal stem cells. Research indicates that chemotherapy can induce apoptosis in follicular granulosa cells, reduce ovarian volume, and lead to a decline in ovarian function; however, BMSCs have been shown to mitigate chemotherapy-induced granulosa cell apoptosis in rats, delay follicular atresia, promote follicular development and growth, increase ovarian volume, enhance serum estradiol levels along with other hormonal changes, thereby protecting and restoring ovarian function as well as preserving reproductive capacity [4-5].

2.2. Examination of Adipose-Derived Mesenchymal Stem Cells in CIPOF

Adipose-derived mesenchymal stem cells (AdMSCs) are pluripotent stem cells isolated and cultured from adipose tissue suspension. Studies demonstrate that AdMSCs significantly augment both the number of follicles and ovulation volume post-chemotherapy across various time points in mice; they also elevate follicle counts at all stages within rat ovaries while increasing stromal cell density concurrently with enhanced expression of ovarian cytokines and luteum count—accompanied by a significant reduction in serum FSH and LH levels. Notably, no adverse reactions such as deformities or tumors were observed following treatment with next-generation AdMSCs administered to rats. In conclusion, AdMSCs markedly improve and restore ovarian function among rats and mice afflicted by CIPOF thus enhancing their fertility [6-7].

2.3. Exploration of Umbilical Cord Mesenchymal Stem Cells in CIPOF

Umbilical cord mesenchymal stem cells (UC-MSCs), first isolated from human umbilical cord Wharton's jelly for culture purposes possess multi-dimensional differentiation potential due to their non-invasive nature compared to BMSC isolation methods which are clean yet tumorigenic risks

remain minimal given their low immunogenicity—a topic garnering considerable interest within the field of stem cell research. Investigations reveal that UC-MSCs can localize within the ovarian tissues of CIPOF-afflicted rats exhibiting directed chemotactic migration towards damaged areas where they repair granulosa cells while restoring overall ovarian functionality alongside increased serum INHB and AMH concentrations leading to higher live birth rates [8-10]. Furthermore, UC-MSC treatments applied to CIPOF mice resulted not only in significant restoration of both ovarian morphology but also an increase in follicle counts thereby substantially improving fertility outcomes [11].

2.4. Analysis on Placental Mesenchymal Stem Cells Regarding CIPOF

Placental mesenchymal stem cells (PMSCs) extracted from placental tissue, exhibit robust proliferation capabilities coupled with strong differentiation potential. According to recent studies, indicating PMSC administration leads toward elevated cytokine secretion fostering, improved local microenvironments, and conducive for repairing damaged follicles across all developmental stages, resulting ultimately into substantial increases regarding total follicle numbers, whilst effectively restoring overall ovarian functionality [12-13].

Placental mesenchymal stem cells (PMSC) were isolated and cultured from placental tissue, and their cell proliferation and differentiation ability were strong. Studies have shown that in rats with CIPOF, PMSC can increase cytokine secretion, improve the local ovarian microenvironment, repair damaged follicles at all levels, significantly increase the number of follicles at all levels, and improve and restore ovarian function

Additionally noteworthy is evidence suggesting endometrial MSCs derived from menstrual blood alongside chorionic MSCs (CP-MSCs) plus human amniotic fluid MSCs collectively contribute positively towards reinstating normalcy concerning compromised ovaries affected by chemotherapy-induced premature failure conditions [14-16].

3. Mechanistic Insights into MSC Functionality within Contextual Framework Pertaining To CIPOF

The mechanism of MSC treatment of CEPOF may involve migration, anti-apoptotic effects, anti-fibrotic activity, anti-inflammatory, immunomodulation, and antioxidant stress, among which anti-apoptotic and antioxidant have been well studied.

3.1. Antioxidant Activity

Oxidative stress is the cause of pathological ovarian senescence. Increased levels of reactive oxygen species (ROS) can directly oxidize proteins and DNA, or indirectly activate intracellular signaling pathways that induce cell damage [17-18]. MSC reduces the activities of ROS, malondialdehyde polyunsaturated fatty acid peroxide degradation products (MDA), lactate dehydrogenase (LDH), and superoxide dismutase (SOD), improve the activities of catalase (CAT), glutathione peroxidase (GPX), and glutathione reductase (GR), play an antioxidant role, reduce oxidative damage, increase oxidative protection, and inhibit ovarian aging [19].

In addition, studies have shown that MT (melatonin) is mainly secreted by vertebrate pineal gland, placenta, ovary and other organs to reduce ovarian oxidative stress induced by chemotherapy through melatonin receptor type 1 (MT1)/AMP-activated protein kinase (AMPK) pathway. MSC can increase the expression of MT1 and AMPK in the ovaries of CIPOF mice [19], delay ovarian aging, regulate ovarian biological rhythm, promote follicle formation, and improve oocyte quality and fertilization rate [20]. These findings suggest that the multi-target antioxidant properties of

MSC can protect against the damage of oxygen free radicals to the ovaries.

3.2. Anti-Apoptotic Effects

Cellular apoptotic fates hinge fundamentally upon equilibrium maintained between pro-apoptosis versus anti-apoptosis gene expressions wherein alterations induced via MCS favorably shift balances favoring survival pathways mediated through upregulated survivin/BCL2 mRNA transcripts concomitantly down-regulating caspases three/nine facilitating inhibition apoptotic cascades initiated previously noted contexts[19].

Gadd45 family members comprising Gadd45a/b/g localized cytoplasm/nucleus exert pro-apoptotic influences mediated interactions proliferating nuclear antigen p21 CDC2/CyclinB kinases involved regulatory cycles responding external stimuli respectively. Binding dynamics established between Gadd45a/Gadd45b proteins CDC2/CyclinB complexes yield dissociation events inhibiting respective kinase activities subsequently retarding progression phases experienced during G/M transitions underlined herein[21]. Chemotherapeutic agents incite elevations regarding Gadd45b expressions granulosas impairing CDC/cyclins' functional integrity inducing blocks preventing proliferation henceforth MCS facilitate transitions enabling recovery promoting healthy growth trajectories resuming normative functioning states[22].

Intercellular channels are composed of connexins and membrane proteins. Studies have found that connexin 43 (Cx43) and connexin 37 (Cx37) are the most abundant gap connexins in the ovary. Cx37 is expressed in oocytes and is responsible for the connection between oocytes and granulosa cells, and Cx43 is expressed in granulosa cells and is responsible for the connection between granulosa cells [23]. These proteins are associated with follicular formation, ovulation, meiosis, steroidogenesis, and apoptosis. Studies have shown that Cx43 is inversely proportional to apoptosis and is necessary for cell survival [24]. The membrane protein family includes membrane protein 1 (Panx1), membrane protein 2 (Panx2), and membrane protein 3 (Panx3). Panx1 is considered to be part of the P2X7 receptor complex necessary for ATP release and is involved in many physiological and pathological processes, mediating apoptosis. Studies have reported that Panx1 is also involved in mediating cell apoptosis in the ovary. It was mentioned in the report that chemotherapy drugs can inhibit or destroy these linkers and membrane proteins, leading to cell apoptosis, and MSC can produce anti-apoptotic effects by regulating these proteins, thus restoring ovarian function.

Chemotherapy caused interstitial fibrosis of the ovarian tissue and decreased follicles at all stages, especially sinus and secondary follicles. Studies have shown that after transplantation, MSC only appears in the mesenchymal and plays an important supporting role in the ovarian microenvironment. It is not found in follicles and does not differentiate into oocytes or GCs [25]. The TrkA receptor secreted by MSC activates phosphatidylinositol -3 kinase (PI3K) and mitogen-activated protein kinase (MAPK) in oocytes and GC to promote cell survival and proliferation [26], that is, it can regulate follicle growth, maturation and periodic ovulation through the PI3K/Akt signaling pathway [27]. It regulates oocyte growth and survival and development of original follicles, promotes proliferation and differentiation of GCs, and inhibits apoptosis [28], while MSC protects GCS by secreting NGF to prevent apoptosis of GC cells [27].

MSCS are mainly located in the ovarian stroma and are not differentiated into follicular cells or granulosa cells, which may be produced by growth factors such as TGF-β, HGF, IGF-1, VEGF, EGF, HB-EGF and bFGF. FSHR, TNF-α and IL-1β proteins and FOXL2, Oct4, GDF-9, LIF and SCF mRNA improve the local ovarian microenvironment, promote follicle development, granulosa cell proliferation and secretion function, and inhibit granulosa cell apoptosis [24].

In addition, MSCS have been shown to be located in the stroma of the ovary, but cannot differentiate into follicular cells, and play a role through the paracrine mechanism, that is,

MSC-derived extracellular vesicles have been found to be carriers of intercellular communication, participating in the paracrine effect to protect GCs from chemotherapy-induced apoptosis in vitro and restore ovarian function [29].

3.3. Anti-inflammatory Propertiest

Studies have shown that chemotherapy drugs can cause the imbalance of ovarian inflammatory response [30], MSCs can reduce the production of inflammatory cytokines in damaged ovaries, play an anti-inflammatory role by activating AKT and P38 pathways, and restore the ovarian microenvironment and ovarian function.

4. Future Directions

With the increase of tumor incidence, chemotherapy-induced premature ovarian failure has become a major threat to female reproductive health, and there is no clear and effective treatment. MSC has a wide range of sources, convenient materials, multi-differentiation potential, tissue damage repair and immune regulation capabilities, and can be derived from the self, without immune rejection and other problems, which brings hope for the treatment of chemotherapy-induced premature ovarian failure. At present, the research of MSC in chemotherapeutic premature ovarian failure is still in the preliminary stage, and further research on MSC is needed to find a better and more effective treatment plan for chemotherapeutic premature ovarian failure and clarify its therapeutic mechanism.

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