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Review

Umbilical cord mesenchymal stem cells: A novel approach to intervention of ovarian ageing

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ABSTRACT

Ovarian aging leads to endocrine disorders and systemic degeneration of tissue and organ structure and function, seriously affecting women's physical and mental health. Safe and effective treatments for this condition are lacking. Umbilical cord mesenchymal stem cells (UCMSCs), which have multidirectional differentiation potential, show strong self-renewal, secrete bioactive factors and release exosomes, can undergo homing, colonization, integration and differentiation into supporting and functional cells in tissues and organs through direct manipulation and can also improve the tissue microenvironment through paracrine action, promoting cell division, proliferation and microangiogenesis, inhibiting inflammation and apoptosis, reducing oxidative stress, and mediating two-way immune regulation. These processes activate dormant cells, repaired damaged cells, replace necrotic cells, and regenerate fresh cells, restoring the structure and function of the ageing ovary. Furthermore, with the increasing development of UCMSC research and technology, the therapeutic use of UCMSCs is expected to become an effective means for the treatment of ovarian ageing caused by tissue cell ageing, degeneration, and necrosis.

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1. Introduction

1.1. Pathobiology of ovarian ageing

Ovarian ageing is a complex biological process that accumulates gradually with the interaction of many factors. Decreases in follicle quantity and quality are notable characteristics of ovarian ageing. In addition to age, DNA damage, oxidative stress, inflammation, fibrosis, apoptosis and metabolite accumulation are considered important causes of ovarian ageing. Single-cell transcriptome sequencing revealed that the ovary was mainly composed of oocytes, granulosa cells, thecal cells, stromal cells, immune cells, endothelial cells and epidermal cells, and with ovarian ageing, the proportion of oocytes, granulosa cells and membrane cells decreased, while the proportion of lymphocytes and fibroblasts increased significantly [1]. At the spatial level, the analysis of age-related gene expression showed that the DNA damage response may be the key biological pathway of oocyte senescence [2]. Ovarian aging can cause endocrine disorders, lead to systemic degeneration of tissue and organ structure and function, reduce fertility, and increase the occurrence and development of chronic diseases such as osteoporosis, metabolic syndrome and diabetes. Safe and effective treatments for this condition are lacking, and this issue should be addressed.

1.2. A new medical model of UCMSCs in the treatment of ovarian ageing

Umbilical cord mesenchymal stem cells (UCMSCs) have become one of the most respected new type of cell biotherapy technology in recent years, and the main biological characteristics of UCMSCs have been revealed [3]. At present, a number of research and development institutions and stem cell clinical research hospitals have conducted clinical research projects on UCMSCs [4–6], and the technical system for large-scale preparation, quality control and long-term storage of UCMSCs has been established [7], providing the basis for clinical application. In animal models of human disease, UCMSC treatment was shown to be safe and effective for tissue injury [8], inflammation [9], autoimmune diseases [10], metabolic diseases [11], coagulation disorders [11,12], and formulated clinical therapy strategies [13,14]. Importantly, UCMSC products already meet the technical conditions for clinical application and are in the transitional stage from the laboratory to the clinic.

One umbilical cord can produce standardized UCMSC products for hundreds of treatments and is associated with ease of use and low cost; these products have been widely studied by researchers [15]. No notable acute immune rejection response was observed when UCMSCs were transplanted through intravenous infusion, vascular administration or local administration. Many studies have found that UCMSCs differentiate into mature cells under the induction of the tissue microenvironment and participate in injury repair [10,16,17], and these cells can also secrete cytokines and exosomes to promote tissue repair [18], regulate immunity and inflammation, and improve the balance and stability of tissue microenvironment [19] to promote structural and functional regeneration. Thus, UCMSCs have good potential in the treatment of ovarian aging.

2. Development of UCMSCs in vivo

2.1. In vivo pathways and biological processes

UCMSCs can home to injured and inflamed tissue, migrate out of blood vessels through the space between endothelial cells and then migrate to and colonize inflamed or injured target tissue [20–23]. Homing to inflamed, ischaemic, and injured tissue is one of the important characteristics of UCMSCs and is a multistep coordinated process involving cytokines, chemical factors, adhesion factors, and extracellular matrix-degrading proteases [22–25]. UCMSCs first identify the microvascular endothelial cells in the target tissue and roll along the vascular endothelium, pass through the blood vessels through the intercellular space, and then enter the target tissue in response to specific tissue microenvironmental factors. During tissue injury, a variety of chemokines, adhesion factors and growth factors are released locally, and this series of microenvironmental changes are the initial factors that attract UCMSCs [24,26]. The interaction between a variety of chemical factors and their receptors in the internal environment guides UCMSCs to diseased tissue [21,22,25,26].

The fate of UCMSCs that are injected intravenously in vivo is not completely clear and involves internal pathways and biological processes. The internal pathways include internal circulation, migration, distribution, colonization, and survival, and biological processes include differentiation, integration, repair of injury, secretion of cytokines and exocrine processes [27,28]. According to the in vivo tracking results of UCMSCs labeled with green fluorescent protein, the red luciferase gene, chemicals labeled and chromosomes labeled [29–31], the basic processes of UCMSCs in vivo are as follows (see Fig. 1): (1) cells flow through various tissues and organs through the blood circulation; (2) some cells enter the lung, spleen, liver, bone marrow and other tissues; (3) the cells nest in inflamed tissue and ischaemic tissue; (4) the cells colonize the tissue, differentiate, integrate and repair injured tissue; and (5) some UCMSCs die and are degraded. The main biological processes are (1) the release of growth factors, inflammatory and immunomodulatory factors, and exosomes into the blood circulation, which remotely regulate related biological responses; (2) homing to the target tissue to participate in injury repair; (3) the secretion of growth factors, inflammatory and immunoregulatory factors, exosomes

and other regulators of the surrounding tissue environment to promote injury repair (these factors can also remotely regulate other tissues in the body); (4) the cells proliferate and differentiate into mature functional cells induced by the tissue microenvironment, and their phenotype and function change as they become functional cells of the tissue type, repairing and replacing injured cells; (5) these cells directly contact or secrete factors that regulate the balance of inflammation and immunity, save tissue from cell death and promote in situ cell growth; and (6) they indirectly promote metabolic, endocrine and antioxidant functions.

2.2. The ultimate destination

The fate of UCMSCs after transplantation in vivo is not only a scientific question but also a common concern of doctors and patients. UCMSC homing is relatively targeted, as these cells generally reach the injured tissue to participate in and promote injury repair, and these cells are induced by the tissue microenvironment to differentiate into mature cells of the corresponding tissue type; they will not differentiate into other types of cells in the tissue [32,33]. Ultimately, UCMSCs exhibit the following fates (see Fig. 1): (1) a small number of UCMSC colonize, differentiate, integrate and survive in the injured tissues; (2) some are distributed in liver, bone marrow and other tissues, and a small number may survive for a long time; (3) the cells may be rejected due to the expression of certain antigens after differentiation or disappear due to apoptosis, scorching and death; and (4) macrophages may be eliminated by phagocytosis and decomposition, but the evidence of this outcome is not sufficient.

2.3. The effects of UCMSCs in treating ovarian ageing

Ovarian ageing is a progressive and dynamic process of ovarian function decline until exhaustion, and this process is closely related to patient age; it is regulated by multiple factors, including hereditary factors, the nervous system, the endocrine system, the immune system, oxidative stress, genetic susceptibility, and mitochondrial damage [32,34]. This condition mainly manifests as tissue atrophy, structural destruction and functional decline, oocyte quantity and quality decline, and decreased sex hormone secretion and regulation ability [33,35]; the corresponding induction of oocyte maturation disorders and follicular atresia result in a decline in female fertility and affect the structure and function of whole-body tissues and organs. According to animal models in which UCMSCs have been used to treat human diseases and in clinical trials, UCMSC therapy is mainly suitable for diseases caused by degeneration, necrosis, and the loss of tissue cells due to mechanical, physical, chemical, and biological factors [34,36]. As a complex biological process with multifactor interactions and gradual accumulation, a decrease in follicle quantity and quality are the key factors leading to ovarian ageing [35]. Studies have shown that exogenous supplementation of mesenchymal stem cells is the most promising way to treat ovarian ageing, and UCMSCs play an important role in promoting structural and functional regeneration of ageing ovaries [34,36–38]. UCMSCs secrete hepatocyte growth factor (HGF) to activate the PI3K-AKT pathway to improve ovarian structure and function [37,39]. UCMSCs regulate the AMPK/NR4A1 signalling axis to significantly improve the ovarian tissue structure, restore ovarian function, and reduce fibrosis [38,40]. UCMSCs regulate NR4A1-mediated mitochondrial mechanisms and inhibit

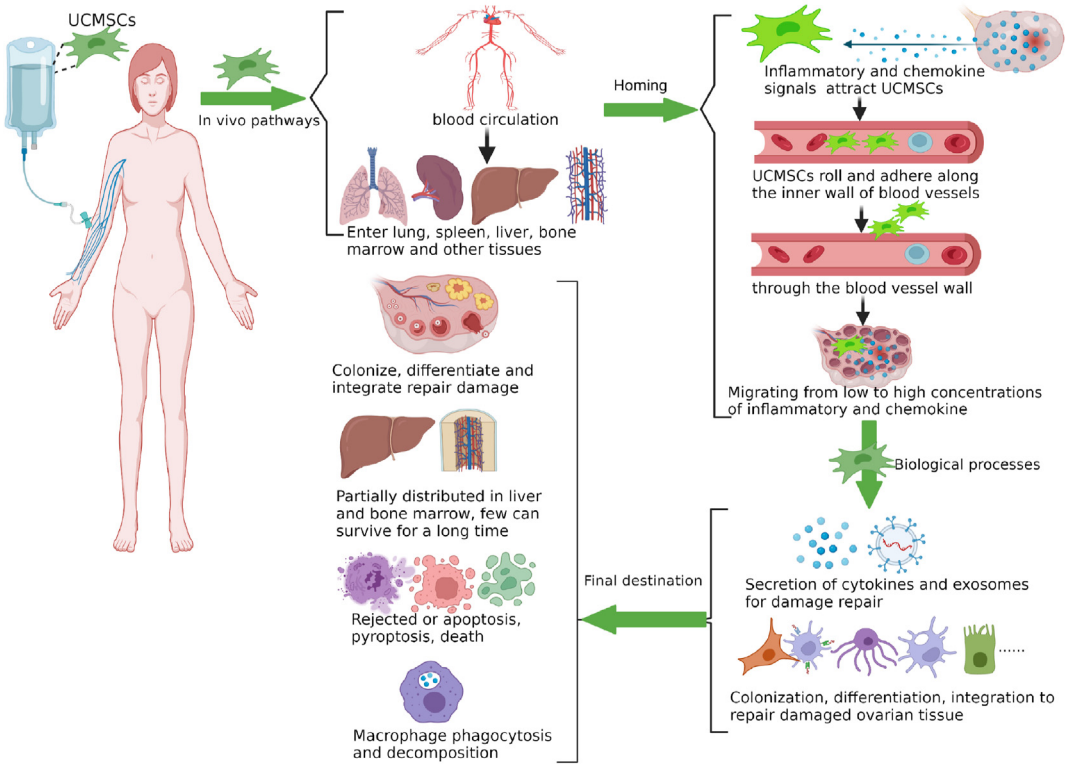

Fig. 1. Fate of UCMSCs in vivo. UCMSCs enter the lung, spleen, liver, bone marrow and other tissues through the blood circulation. The injured ovarian tissues release inflammatory and chemokine signals to attract UCMSCs, and UCMSCs identify the microvascular endothelial cells in the target tissue and roll along the vascular endothelium, pass through the blood vessels through the intercellular space, and then enter the target tissue in response to specific tissue microenvironmental factors. UCMSCs secrete cytokines and exosomes for injury repair and colonization, differentiation, and integration to repair damaged tissue. Finally, a small number of UCMSC colonize, differentiate, integrate and survive in the injured tissues; some are distributed in the liver, bone marrow and other tissues and are partly rejected, where they undergo apoptosis, cell death, and elimination by macrophage-mediated phagocytosis and degradation.

theca interstitial cell apoptosis to recover ovarian function [39,41]. However, research on the use of UCMSC therapy to reconstruct reproductive function has not been reported at home or abroad, indicating that there are still many scientific and technical problems to be solved in UCMSC therapy.

2.4. Adjuvant therapy and drugs and food to avoid during UCMSC treatment

The main function of UCMSC therapy is to promote the growth, differentiation, and proliferation of tissue cells and to regenerate the structure and function of damaged tissue [42,43]. Thus, appropriate adjuvant therapy for patients receiving UCMSC therapy is helpful for ensuring and improving the efficacy of UCMSCs. The following adjuvant treatment measures are suggested (see Fig. 2): (1) proper exercise is recommended, and some fatigue or symptoms similar to those in the early stage of a cold may be felt within a short period of time after the infusion of UCMSCs, which can gradually disappear after a brisk walk of 2–3 km; maintaining proper exercise is helpful to promote blood circulation and improve the curative effect, but strong irritating exercise and strong physical labour should be avoided; (2) proper ingestion of nutritious food, especially food with high levels of vitamins and trace elements, which provides the necessary nutrients for UCMSC renewal; (3) prioritizing a light diet, reducing the intake of high-fat and high-energy foods; and (4) some drugs that promote blood circulation contribute to the secretion and homing of UCMSCs.

Cytotoxic drugs are not suitable for the use in combination with UCMSCs because these drugs are cytotoxic and interfere with or block cell proliferation; these drugs will affect the biological activity and reduce the curative effect of UCMSCs [44,45]. Alcohol consumption, especially excessive alcohol consumption, should be avoided as much as possible after treatment with UCMSCs, as a high alcohol concentration in the blood may weaken the therapeutic effect. In addition to drinking, patients should also try to reduce the consumption of food with cytotoxicity and strong stimulation to the human body, such as spicy food and fried or barbecued food.

2.5. Timing, optimal dose, and course of UCMSC treatment

Based on the biological characteristics of UCMSCs, clinical treatment needs to consider ways that are conducive to the entry of UCMSCs into tissue, the appropriate tissue microenvironment and the in vivo environment that plays the most effective therapeutic role [46,47]. In clinical practice, the appropriate treatment time should be chosen according to the specific disease, different stages of the same disease and the degree of tissue injury. For inflammatory and autoimmunity resulting in ovarian ageing, it is suggested that UCMSC treatment should be performed in the early and middle stages of the disease because during the acute reaction or progressive stage of tissue injury, the injured tissue can release more inflammatory factors and factors that attract UCMSCs to the injured tissue, microvascular injury is also conducive to the entry of UCMSCs into tissue, and the tissue microenvironment is also conducive to the colonization and differentiation of UCMSCs [48–50]. When ovarian ageing enters the chronic stage, treatment mainly depends on paracrine effects or remote secretion by UCMSCs, and the number of UCMSCs that enter the injured tissue is relatively low [51,52]. It is necessary to increase the dose and the number of treatment times to exert therapeutic effects. For natural ovarian ageing and degeneration [53–55], the timing of UCMSC treatment is unrestricted because the development of the disease is slow, the inflammatory reaction in the diseased tissue fades, the concentration of factors that attract UCMSCs is relatively low, and there is little difference in the therapeutic effect at different time points.

At present, there is no unified accepted standard for the optimal dose of UCMSCs for treating diseases, and the dose-effect relationship for different diseases is not fully understood. Most of the reports calculate a single treatment dose of UCMSCs based on body weight, and doses in animal model experiments and clinical studies are calculated as 1×10^6 cells/kg [56]. A dose of 5×10^7 cells has been used by adults according to age, and the range of single treatment is approximately 3×10^7–1×10^8 cells per dose [57]. To ensure safety, it is recommended to use a dose of 1×10^6–1×10^7 cells/kg [10], the volume should not be too large, and the density of UCMSCs should not be too high to avoid microvascular embolism caused by the accumulation of UCMSCs, which can be injected several times at regular intervals.

The course of UCMSC treatment depends on the type and severity of the disease. The course of treatment in the author's research centre is 1×10^6 cells/kg body weight, once per week for 3 consecutive doses; for some chronic diseases, 5 consecutive doses may be administered, or within a safe range, the dose can be shortened to once per day for 3 consecutive times [58–60]. UCMSCs can regulate inflammation and immunity, and the continuous effect after a single treatment is approximately 2 weeks. Generally, three consecutive treatments can show obvious curative effects. After that, increasing the number of treatments may be helpful in improving and consolidating the curative effect. We conducted a course of treatment on individuals with autoimmune and inflammatory diseases and some health conditions. The patients were treated with 1×10^6 cells/kg once every other day, once per week, once per month, 3 times per month and 5 times per month. The overall impression was that the effect of once every other day, 3 times per week and 5 times in a row was the best, followed by 3 times per week and 5 times per week, and there was little difference between the other two regimens. However, this was only a small batch of asynchronous therapeutic studies, and in vivo biological behaviours such as migration, distribution, colonization, differentiation and survival times of UCMSCs in vivo need to be studied. A large sample control experiment must be conducted before we can accurately explain the difference in curative effects between different treatment courses. Our suggestion is that for ovarian ageing, 5×10^6 cells/kg body weight, once every other day, 3 times in a row, is recommended.

3. The mechanism of UCMSCs in the treatment of ovarian ageing

3.1. Paracrine effects

3.1.1. Cytokines

Cytokines are characterized by low expression levels but have a robust effect on the initiation and amplification of outcomes. Both in vitro and in vivo, UCMSCs secrete growth factors, interleukins, colony stimulating factors, chemokines, interferon and tumour necrosis factors, neurotrophic factors, metalloproteinases, plasmin and superoxide dismutase, which promote the in situ growth of injured tissue through paracrine or other regulatory mechanisms and play an important role in cell growth, inflammation and immune regulation [27,61,62] (see Fig. 3). UCMSCs can be injected into animals or patients with ovarian tissue and organ injury and secrete a variety of bioactive factors that play important roles in promoting in situ cell growth and injury repair in injured tissues, and these are important mechanisms for inhibiting the inflammatory response and regulating the immune balance [63,64]. Based on the comparative analysis of the secretory functions of MSCs from different sources, UCMSCs secreted stem cell growth factor, vascular endothelial growth factor and nerve growth factor more robustly than MSCs from other sources [65,66], suggesting that

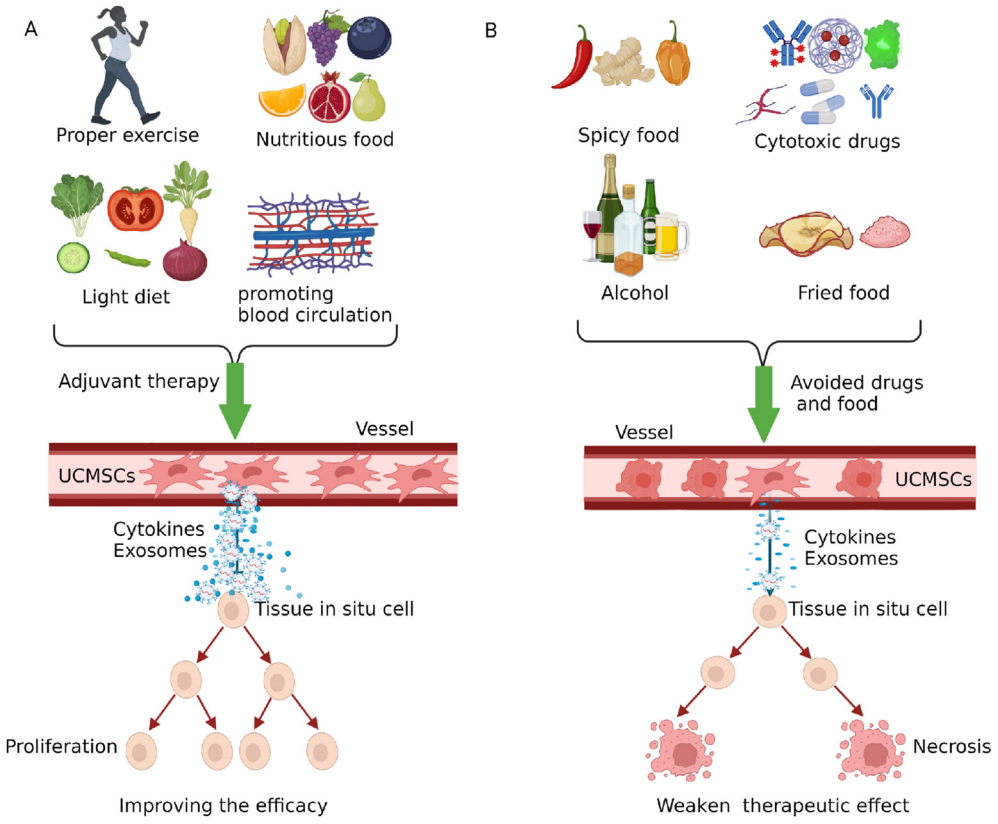

Fig. 2. Adjuvant therapy, drugs and food should be avoided during UCMSC treatment. Appropriate adjuvant therapy includes proper exercise, nutritious food, light diet, and promotion of blood circulation, while cytotoxic drugs, alcohol, and spicy and fried food are not suitable for use in combination with UCMSCs.

UCMSCs may play a more powerful role in promoting cell growth than other types of MSCs.

3.1.2. Exosomes

Exosomes are nanoscale membranous vesicles that are released into the extracellular environment after the fusion of eukaryotic polyvesicular endosomes and cell membranes, and these factors contain different kinds of proteins, lipids, mRNAs, microRNAs, signalling molecules and other biologically active substances and easily fuse with the cell membranes of neighbouring cells [67]. Biologically active substances are selectively delivered to recipient cells to transmit information, regulate signal transduction, and play a variety of biological roles [68]. The role of exosomes in tissue repair mainly involves (1) promoting cell proliferation and inhibiting apoptosis [69]; (2) regulating inflammation and immunity, improving the microenvironment of injured tissue, and preventing secondary inflammatory injury [70]; (3) promoting angiogenesis, improving nutrient supply and the secretion of metabolites [71]; and (4) delivering and releasing mRNA, miRNA and proteins to regulate gene transcription and expression, cell growth and proliferation, inflammation and immunity [72,73]. In summary, exosomes, which are a transmission medium, transmit specific cargo such as proteins, mRNAs, miRNAs and lncRNAs to injured ovarian tissue to activate or inhibit certain signalling pathways or signalling proteins and promote the repair of tissue injury by regulating cell proliferation, apoptosis, angiogenesis and immunity (see Fig. 3).

3.2. Direct participation

During the treatment of some diseases involving tissue and cell degeneration, necrosis and loss, it was found that some MSCs migrated and homed to the injured tissue after superficial intravenous infusion, vascular administration, lacunar injection or localized transplantation [74]. MSCs colonize injured tissue, differentiate into functional cells of the corresponding tissue types and integrate into the tissue under the induction of the tissue microenvironment [75]. However, there was almost no distribution of MSCs in healthy control animals without tissue damage, indicating that transplanted MSCs were involved in the structural remodelling of injured tissue. During the treatment of systemic radiation injury with UCMSCs, the distribution of MSCs in intestinal tissue was highest; a proportion of transplanted cells was also found in the liver, kidney, lung, thymus and skin, but no GFP-labeled MSCs were found in unirradiated control animals [16,76]. In UCMSC-treated systemic lupus erythematosus, UCMSCs were distributed in liver, kidney, skin, and other autoimmune injured tissues, and the structure and function of corresponding tissues were improved [77,78], indicating that UCMSCs transferred in vitro were not only distributed in injured tissues but also played a role in repairing the damage. In summary, there have been many reports about the migration, distribution and colonization of UCMSCs in injured tissue and their differentiation into functional cells of the injured tissue type to promote injury repair. There is sufficient in vivo evidence to indicate that exogenous MSCs directly participate in injury repair. However, the distribution and colonization of UCMSCs infused in vivo are limited, the direction of differentiation is determined by the components of the tissue microenvironment, and the survival time is relatively short. The fate of UCMSCs in injured tissue is not very clear, and their role in promoting injury repair needs to be further confirmed.

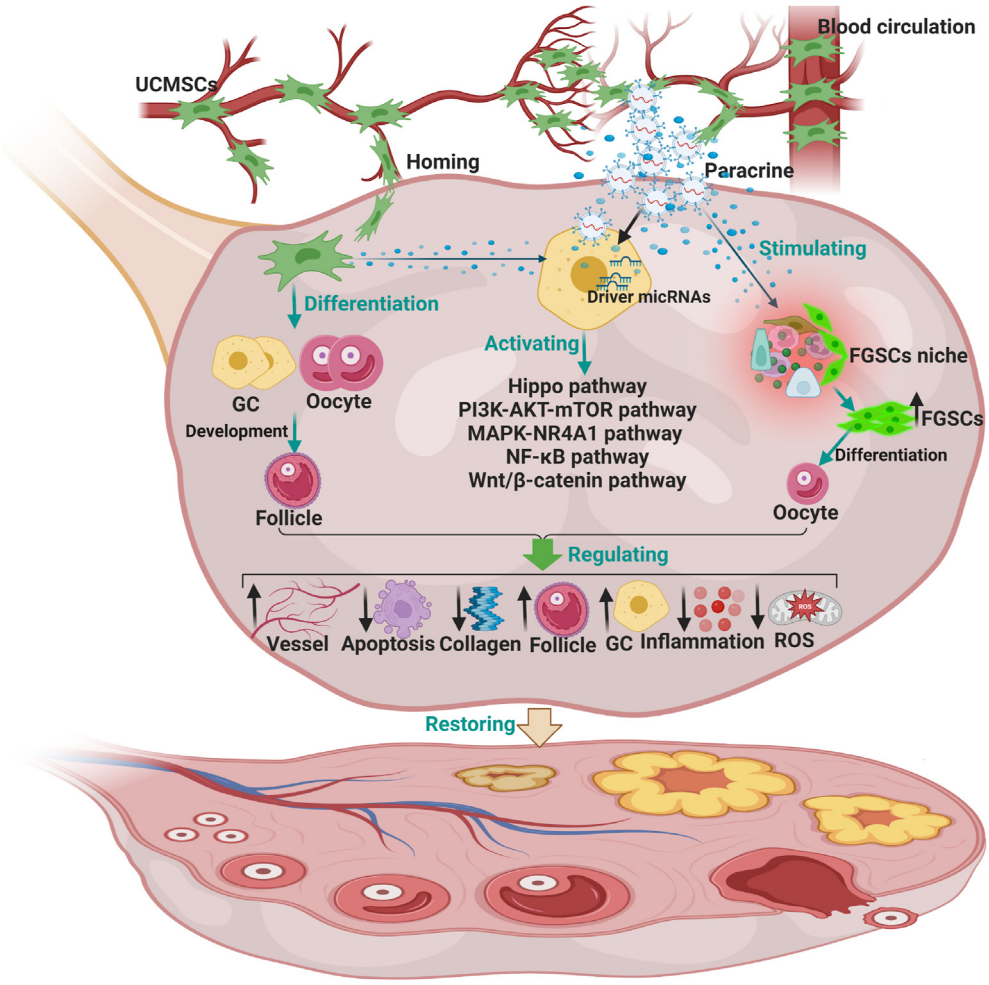

Fig. 3. The mechanism underlying the effects of UCMSC treatment of ovarian ageing. UCMSCs promote division and proliferation of in situ cell, inhibit apoptosis, suppress collagen, reduce inflammation, induce angiogenesis, decrease ROS, and increase the quantity and quality of follicles through paracrine mechanisms, direct participation, regulation of signalling pathway, and stimulation of endogenous FGSCs to restore the structure and function of aged ovaries.

3.3. Regulating key signalling pathways to promote cell division and proliferation in situ

UCMSCs interfere with ovarian senescence by secreting cytokines or releasing exocrine factors, and they play a therapeutic role in repairing damaged ovaries with multiple targets and multiple mechanisms. The effect of human umbilical cord mesenchymal stem cell exosomes (HucMSC-exos) on ovarian senescence has been a research hotspot in recent years. HucMSC-exos activate the PI3K/AKT/mTOR signalling pathway of oocytes by carrying functional microRNAs such as miR-146a-5p, miR-21-5p and miR-126-3p, which promote follicular development and maturation, enhance the division and proliferation of ovarian granulosa cells, induce microvascular network neovascularization, inhibit apoptosis, increase the levels of E2 and AMH in peripheral blood, decrease FSH levels, and increase the number of follicles [79,80]. In addition, miR-29a carried by HucMSC-exos can activate Wnt/β-catenin by targeting HMG-box transcription factor (HBP1), promote the division and proliferation of granulosa cells(GC), inhibit apoptosis, and restore ovarian function [81]. UCMSCs release exosomes to regulate the Hippo pathway, promote the division and proliferation of granulosa cells, and improve the structure and function of the ovary [82]. HucMSC-exos can inhibit the NF-κB signalling pathway, increase the expression of the anti-inflammatory factor IL-10, decrease the expression of the inflammatory factors TNF-α and IFN-γ and inhibit apoptosis in ovarian granulosa cells [83]. In a rat model of premature senility induced by chemotherapy, UCMSC transplantation was found to regulate the NGF/TrkA signalling pathway, restore the disturbance of hormone secretion and follicular development in premature ovarian failure, and increase the pregnancy rate of POF rats [84]. UCMSC transplantation can regulate the phospho-NR4A1 and AMP-activated protein kinase (AMPK/NR4A1) signalling axes, inhibit tissue fibrosis and restore ovarian function [85]. UCMSCs can secrete hepatocyte growth factor (HGF) to activate the PI3K-AKT pathway, promote follicular development and maturation, and improve ovarian function [86]. UCMSCs mainly regulate related signalling pathways through the paracrine pathway, promote cell division and proliferation in situ, inhibit cell apoptosis, reduce the inflammatory response, and then interfere with ovarian senescence.

3.4. Stimulation of endogenous reproductive stem cells to promote oocyte differentiation

The niche of ovarian reproductive stem cells is the microenvironment around female germline stem cells (FGSCs), which can provide external signals related to nutrition supply and immune cytokine levels, maintain FGSCs homeostasis, promote FGSCs division and proliferation and initiate cell differentiation [87]. The study found that the senescence of ovarian reproductive line stem

cells in this niche may be the main cause of ovarian senescence. Germline stem cell senescence in the niche leads to the depletion of reproductive stem cells and a decrease in the number of follicles, which eventually leads to impaired female fertility [88]. At present, the specific regulatory mechanism by which UCMSCs affect the niche of reproductive stem cells and interfere with ovarian senescence is not clear. According to previous research data, we speculate that UCMSCs may stimulate and mobilize ovarian reproductive stem cells through the paracrine pathway, promote the division and proliferation of endogenous reproductive stem cells, increase the number of stem cells, and eliminate, repair or replace damaged cells to facilitate cell differentiation into oocytes in time, increasing the number of oocytes, in addition, UCMSCs can differentiate into ovarian reproductive stem cells through direct participation. Studies have shown that UCMSCs can be induced to differentiate into germ stem cell-like when the ovarian microenvironment is stimulated or key genes of reproductive stem cells are overexpressed in vitro. After induction, UCMSCs highly expressed the germ line cell-related genes Ssee4, Oct4, and Ddx4 and the oocyte-related gene GDF9 and had the potential to differentiate into female germ line cells [89]. Huc-MSCs can differentiate into oocyte-like structures, express the reproductive-like cell-specific markers Oct4, Vasa, DAZL, ZP2, ZP3 and Stra8, and secrete oestradiol [90]. It is suggested that UCMSCs themselves have the potential to differentiate into oocytes and can stimulate reproductive stem cells through the remote paracrine pathway.

3.5. Perspectives

According to the current research progress of stem cell therapy, UCMSCs are different from traditional drugs. UCMSCs are a permanent cure, while traditional medicine is a palliative strategy. The essence of UCMSC therapy involves solving the problem of injury in terms of tissue structure and function. It is a new method of ovarian ageing treatment that may completely change the current clinical medical model.

Stem cell technology will develop by leaps and bounds in the next few years, and there will be a trend towards new industries and clinical applications. In terms of stem cell sources, adult stem cells such as UCMSCs were initially used as standardized products, and many stem cell resource banks have been built. The next step is to establish standardized cell preparations to improve safety and efficacy for clinical research and treatment and to create new stem cell products and technologies that are more efficient, accurate, targeted, safe and reliable. In preclinical research on stem cells, cell imaging and tracer techniques will be further used to reveal the dynamic changes in UCMSCs in vivo and clarify their cellular and molecular regulatory mechanisms to further solve the key technical and scientific theoretical problems in the clinical transformation of new stem cells. In terms of clinical transformation and application, there are thousands of stem cell clinical research programmes in the world. Some clinical studies have entered the third phase of clinical trials, and stem cell treatments for many diseases are being confirmed by clinical trials. Some clinical research results will be popularized and used in the clinic in the next few years. With the development of stem cell technology, knowledge of UCMSCs is being popularized. The bottlenecks restricting the clinical application of UCMSC technology will be solved, and new stem cell products and technologies will continue to emerge, as will clinical transformation and application, new cells, tissues and organs and secretory products derived from stem cells; moreover, stem cell application technology management will be gradually standardized. Generally, stem cell therapy is likely to become a new technology that is widely used in the clinic, and many incurable diseases will be treated effectively.

4. Conclusions

i. UCMSC therapy improves ovarian structure and restores ovarian function. Appropriate adjuvant therapy for patients is helpful for ensuring and improving the efficacy of UCMSCs, while cytotoxic drugs are not suitable for use in combination with UCMSCs.
ii. In clinical practice, the appropriate treatment time should be chosen according to the specific disease, different stages of ovarian ageing and the degree of tissue injury. A dose of 1×10^6–1×10^7 cells/kg is recommended, and the course of UCMSC treatment depends on the severity of the disease.
iii. The fate of UCMSCs that are injected intravenously in vivo involves internal circulation, migration, distribution, colonization, survival, differentiation, integration, secretion of cytokines and exocrine processes, which promote injury repair through paracrine effects and direct participation.

Consent for publication

Not applicable.

Availability of data and materials

All data are included in this research article.

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Authors' contributions

TC and PXH wrote the manuscript, LY, ZXL and ZXQ assisted with the literature searches, XJ revised the manuscript. All authors approved the final manuscript.

Declaration of competing interest

All authors read and approved the final manuscript, and no competing interests.

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