Mesenchymal Stem Cell Therapy In Premature Ovarian Failure: Mechanisms And Future Prospects

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***Abstract*-** Premature Ovarian Failure (POF) is one type of ovarian dysfunction that is characterized by severe changes in the reproductive and physiological functions of females , resulting in 1percent of infertility before 40 years old. The traditional treatment options using hormonal substitute therapy (HRT) comes with numerous negative side effects, and it isn't able to repair the normal reproduction capacity and ovarian function.

With the aid of Regenerative medicine, mesenchymal cells (MSCs) therapy has opened promising new possibilities for POF, with high efficacy , especially for those suffering from infertility. They are stem cells that have multipotency that have low immunogenicity. They can be extracted from various tissues, including bone marrow, umbilical chord peripheral blood vessels, fat tissues, menstrual fluid and the placenta. This article reviews the various types of MSCs that are currently available for treatment with POF, the properties as well as their complicated mechanism of action and their therapeutic value in clinical application.

In a short period of expansion, apoptosis, vaccination autophagy, oxidative stresses and fibrosis of the Ovarian cells are controlled by paracrine actions following migration of MSCs into the ovary that has been injured. Clinical trials and preclinical studies are progressing smoothly. The latest breakthroughs in the field of engineering MSCs and their efficient components along with additional measures have made them a perfect source for the future of cell therapy in POF to ensure security in clinical use.

***Index Terms*-** premature ovarian failure, mesenchymal stem cells, regenerative medicine.

I. Introduction

Premature Ovarian Failure (POF) is a complicated hormonal disorder that develops before 40 years of age with a the prevalence of 1% worldwide and is characterized by elevated gonadotrophin levels (FSH>=40 mg/ml) and reduced hormone (E2) levels, accompanied by amenorrhea secondary or primary 1.. It is the main causes for female fertility problems. The destruction of the ovary is irreparable and the causes are autoimmunity, heredity, Iatrogenic infections, viral infections, psychological and environmental factors, with approximately 90% of cases being Idiopathic.[2,3]

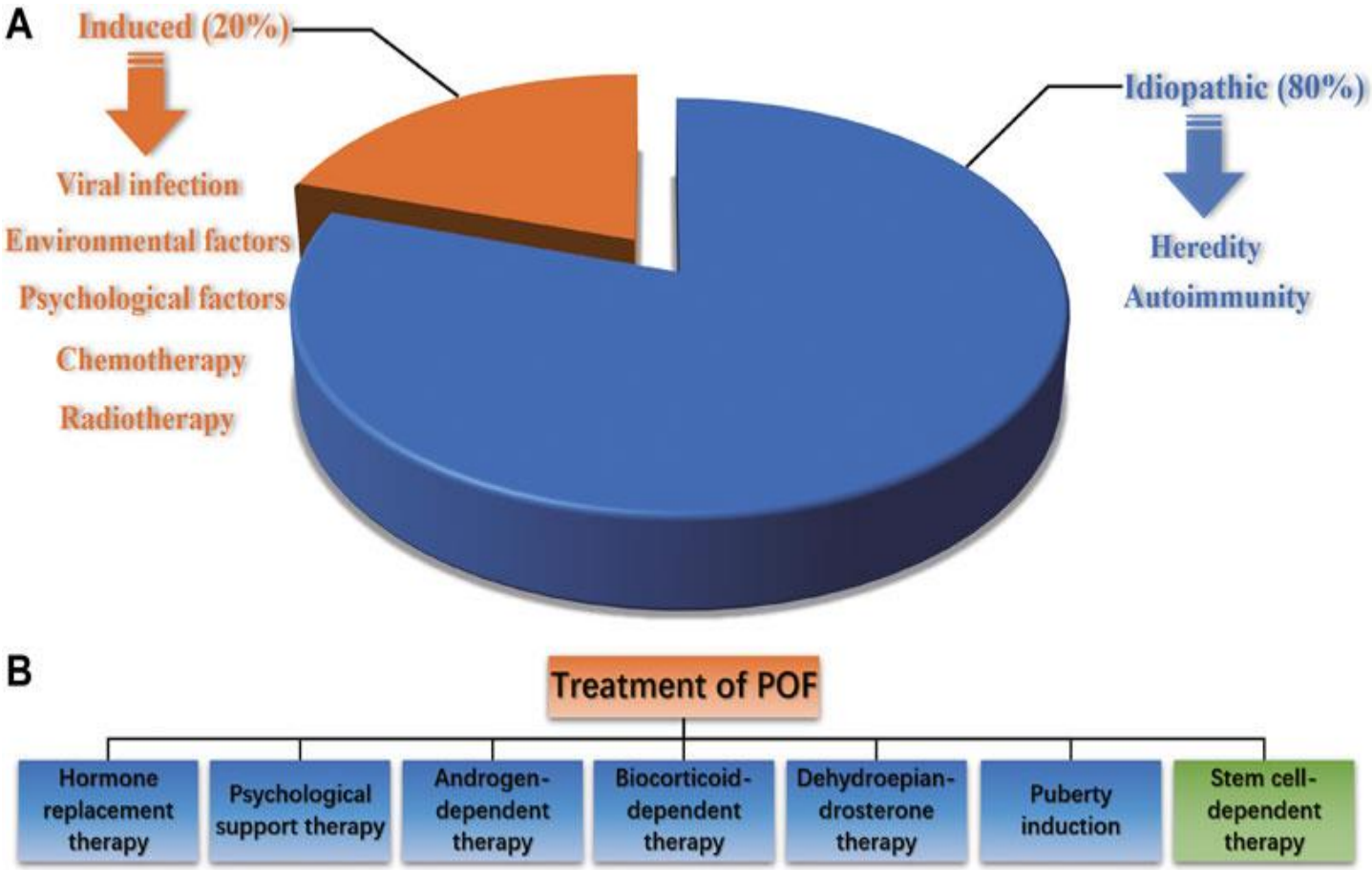

Figure1 Pathogenic factors and treatment of POF [4]

II. PATHOPHSIOLOGY

Granulosa cell (GC's) and Oocytes are vital components of the the ovarian system of functioning. They play a significant function in maintaining the follicular development and the release of growth and hormones which regulate the growth of oocytes. The hormone receptors that are expressed in GC's , such as estrogen receptor as well as the follicle stimulating hormone receptor (FSHR) are essential for folliculogenesis as well as the ovulation process. 5 Although the exact cause is unknown, the possible molecular causes of POF include accelerated apoptosis the GC's and Oocytes, and blocking maturation of follicles and other abnormalities of follicular functions, which result in the depletion or dysfunction of the follicles of the ovarian.

III. MSCs IN POF

Mesenchymal Stem Cells (MSCs) comprise a collection of stromal cells that can differentiate into a variety of embryonic lineages, including mesodermal. MSC-based treatments are an ideal alternative for POF because of their lack of immunogenicity, the wide range of sources, and accessibility 6.. This treatment has made significant advancements as it develops into a technologies for regenerative and cell therapy. Their efficacy in treating reproductive disorders is proven through clinical and preclinical research. [7]

MSCs used for treatment of POF are

BMMSCs	Bone marrow
UCMSCs	Umbilical cord
PMSCs	Placental
AMSCs	Amnion
AFMSCs	Amniotic fluid
MBMSCs	Menstrual blood
ADMSCs	Adipose tissue
PeMSCs	Peritoneum
SMSCs	Skin

The sources mentioned above of stem cells share similar characteristics, and following treatment, they have seen the number of hair follicles present in each stage of development including dormant, antral and mature follicles significantly increased. The treatment improves the hormone secretion capacity as well as improves the growth of follicular cells and the survival of GCs and also restores function of the ovary. 8 MSCs in the form of IV infusions is simple, fast and efficient method. A meta-analysis of POF revealed that MSCs may reduce the levels of FSH and raise E2 levels, and encourage the growth of follicles.[9]

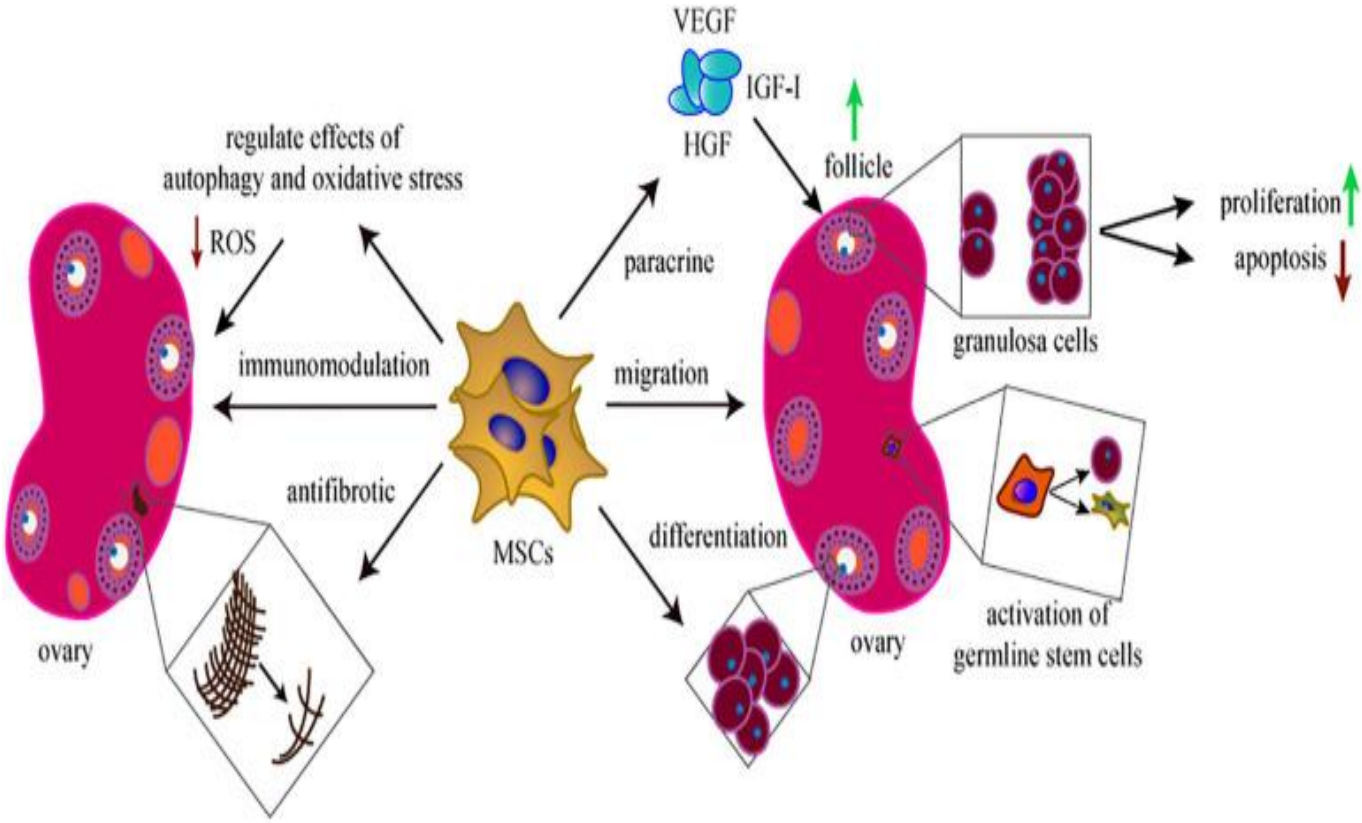

Figure 2 Mechanisms of MSCs in treating POF[10]

IV. MECHANISMS OF MSCs

The therapeutic effect of MSCs cannot be controlled by one factor, but is a complex system of biological regulation and mechanisms. Immunisation, proliferation, apoptosis angiogenesis, oxidative stress and the fibrosis of ovarian cells is affected by paracrine reactions following the migration of MSCs into the ovary that has been injured.

1)Migration and hosting of MSCs

Homing is the process of delivering stem cells to the damaged location. MSCs can migrate into the an ovary via intravenous transfer and, once they moving to the organ of choice it can have a long therapeutic effects. Migration is therefore an essential to the therapeutic efficacy. MSCs are not able to directly differentiate into oocytes however they do reside in the an ovarian matrix, and release various hormones and enhance the function of the ovarian reserve via paracrine pathways. Homing factors include TNF- (Tumor Necrosis Factor), (Tumor Necrosis Factor), HGF (Hepatocyte Growth Factor) and FGF (Fibroblast Growth Factor). 11

2.) Effects of paracrine activity MSCs

The improvement in ovarian function through MSCs is due to the release of the cytokines. Some of the most significant cytokines that influence different phases of follicular development include TGF-b, IFN -a, AMH, IFN-a, IL-1, Activin, Inhibin and BMP (Bone Morphogenic Protein). These cytokines can alter the ovarian microenvironment that aids in follicular development and selection, while also controlling cell development and the process of differentiation and follicular longevity/atresia as well as maturation of oocytes. 12,13

3)Proliferation as well as antiapoptotic actions

MSC transplantation can lower apoptosis levels and increase GC growth through the release of VEGF (Vascular Endothelial growth factor), HGF, IGF2(Insulin growth Factor 2) and FGF. 14 It blocks its expression PTEN (Phosphatase and the tensin homolog that is deleted from the chromosome 10) in addition to PDCD4 (Recombinant Human Programmed Cell Death) by enhancing the expression in miR-21(microRNA) and blocks the process of apoptosis. miR-144-5p, derived from MSC exosomes can influence p53 signaling, and may also inhibit GC cell apoptosis.[15]

4)Promotes angiogenesis as well as antifibrotic effects

Angiogenesis-related substances secreted by MSCs include VEGF HGF, IGF as well as FGF. VEGF and HGF exhibit an interplay effect that promotes length, size and branches of induced vessels , as well as increase in the size of the vascular surface. 16 These factors promote neovascularisation and enhance the perfusion of blood of transplanted ovarian tissue. The antifibrotic effect of MSCs following transplantation are due to controlling the TGF-b/SmaD-3 signaling.

5)Anti inflammation as well as Immunomodulatory effect of MSCs

MSCs have immunomodulatory effects through moving to tissues affected to reduce local inflammation, without suppressing the immune system in general. 17.. MSCs control the proliferation and functions of T cells. Restoring the function of the ovaries is accomplished by regulation of TGF-b interferon g(IFN-g) T-helper 1, T-helper 2 cells (Th1/Th2) cell cytokine ratio as well as the modulation of the numbers of naturally killer (NK) cells. The

PI3/Akt signal pathway regulates the balance between Th17/Tc17 as well as Treg and Th17 cell. 18

6.) Stress regulation and autophagy

ROS (Reactive Oxygen Species) is an immediate precursor of the process of oxidative stress as well as an early trigger of autophagy. Thus, reduction of ROS is essential to decrease the rate of apoptosis as well as damage caused by oxidative stress the Ovarian. 19 MSCs reverse the damaging effect of H 2 O 2 treated endothelial cells , which in turn enhance cell proliferation and migration. This is accomplished through the secretion of HGF and IL-6, IL-8 and VEGF, as well as activation of the FOXO, PI3K/Akt pathways.

V. NEW APPROACH AND FUTURE PROSPECTS

The combination of tissue engineering materials and MSCs for transplantation is an innovative and promising approach to POF treatment that has excellent potential for therapeutic benefits.

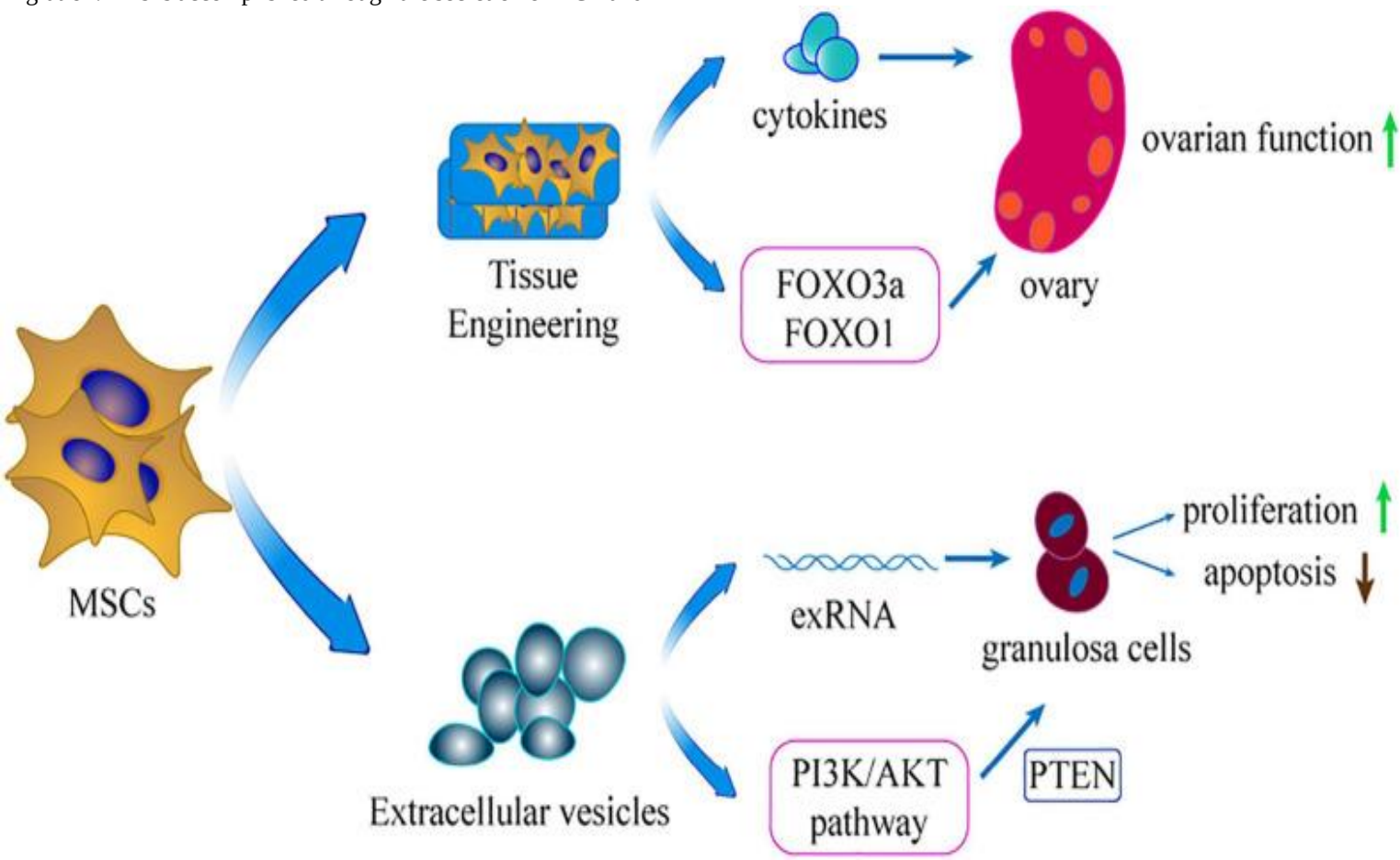

Figure 3 Extension of applicating MSCs[10]

EXTRACELLULAR VESICLES (EV's) are major paracrine effectsors that are derived from MSCs. They are more efficient than MSCs on their own. MSCs regulate the PI3/Akt signaling pathway through targeting PTEN that can help restore biological activity. There are three kinds of EVs such as Microvesicles, Exosomes, i.e ex RNA from cells (ex RNA)such such as microRNA and microRNA as well as Apoptotic body 15.. They are very stable in vivo and , being cells-free, they offer an innovative low-risk treatment for POF.

TISSUE Engineering is a rapidly developing biotechnology process that blends cells biology and material science to build tissues in vitro and in the vivo. 20 Materials like collagen scaffolds can enhance stem cell attachment to the tissue of interest, and improve proliferative and ovarian angiogenesis by phosphorylation of FOXO3a as well as FOXO1. 21

MEASURES FOR AUXILIARY USE are also utilized to boost the therapeutic value of MSCs, which includes

A) Pulsed ultrasound with low-intensity plus MSC Therapy 22

B) Preheat shock therapy + MSC treatment 23

C) MSCs combined with Estrogen therapy [24]

VI. CONCLUSION

MSCs are widely utilized stem cells that have great potential to alleviate POF in clinical and preclinical studies conducted over the last decade. Immunization, proliferation, apoptosis autophagy, oxidative stress and fibrosis are regulated through paracrine effects following the transfer of MSCs into the ovary that has been

injured. 13 Tissue engineering and extracellular vesicles are the newest methods of MSCs treatment of POF with great effectiveness. 21 The establishment of a system of standards for the culture process to the use of MSCs could increase the security of treatment while avoiding negative side negative effects. This therapy is a great potential for the fundamental restoration of the function of the ovary in patients suffering from POF.[25]

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