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Original Article

Potential of Stem Cells in Overcoming Infertility Problems in Women

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ABSTRACT

Stem cells are characterized as cells with undifferentiated kinds that have the ability to differentiate into a variety of various cell types in response to the environment in which they are growing and develop (niche). Stem cells are classified into three broad categories based on their origin: extra-embryonic stem cells, which are derived from the amniotic fluid, umbilical cord and placenta; adult stem cells, which are derived from adult tissues such as blood, fat, bone marrow and skin; and embryonic stem cells, which are derived from the blastocyst. Stem cells exposed to certain suitable conditions will differentiate into 3 germ layers and also primordial germ cells. This is the basis for the latest research to obtain mature haploid gametes capable of developing into normal embryos and fetuses. Somatic Nuclear Cell Transfer (SNCT) technique is used to produce mature gametes so that the resulting cells contain cell nuclei with new genetic material. Infertility is a common problem that occurs with a prevalence of 10-15% of couples of reproductive age. Causes of infertility in women include metabolic and hormonal disorders accompanied by interactions with environmental factors that reduce oocyte quality. This results in an increased rate of aneuploidy in the resultant oocytes and impairs the human implantation process. The main objective of this research is to enhance the understanding of stem cells in women's infertility. The method used in writing this review article is online literature studies obtained by accessing national and international scientific journals as well as scientific articles related to stem cells (Stem cells), infertility, women. From the results of this study, it can be seen the potential of stem cells (stem cells) in treating infertility in women. Further studies are needed, especially pre-clinical and clinical trials so that they can be widely applied.

Key words: Stem cells, Infertility therapy, Somatic cell nuclear transfer (SNCT), Health risk, Public Health.

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INTRODUCTION

Stem cells are defined as undifferentiated cells with capacity to proliferate and differentiate into a variety of various types of tissue. Some of the terminology used to describe the characteristics of different types of stem cells:[1]

Totipotent stem cells possess the capacity to differentiate into all of the cells and tissues that comprise the embryo and contribute to fetal development. such as a zygote or a fertilized ovum;

Pluripotent progenitors defined as a cells that able to self-rejuvenate by partitioning and generated further into the three significant layers of the germ cell of an early embryo and as a result, into all of the cells of the adult body, but not into extra-embryonic tissues such as the placenta;

Multipotent stem cells are those that have the capabilities to manufacture a number of specific cells that differentiate according to their location, for example somatic stem cells or adult stem cells;

Unipotent stem cells are capable of self-differentiation into a single kind of cell, for example epidermal stem cells.

The fundamental difference between pluripotent stem cells generated from blastocysts and multipotent stem cells originating in mature organisms is the quantity of differentiated cell types that can be produced by the pluripotent stem cells derived from blastocysts.[2] Numerous tissues rely on stem cells for development, homeostasis and repair. Stem cells are regulated in normal adult tissues by the integration of internal (e.g. cell nucleus factors) and extrinsic factors (through growth factors, stroma and other influences).[3]

There are many obstacles that are faced when therapy is carried out for both degenerative and congenital diseases by giving Esc. In addition to ethical, moral and religious issues, the main obstacle is the presence of immunological reactions that occur in the form of immune rejection. This reaction is mediated by the presence of MHC I and by antigen presenting cells (APCs).[4] In addition, the formation of embryoid bodies (EB) will trigger the formation of teratoma which actually threatens the life of the individual. To overcome this, the latest technology was created, namely reprogramming adult somatic cells into stem cells with the same characteristics as embryonal stem cells.[5]

Secondary infertility means that a married couple has or has had children before, but is currently unable to have another child after one year of sexual activity 2-3 times average weekly without the use of contraception or any other way.[6-9] According to the World Health Organization (WHO) it is estimated that 1 in 7 couples have problems in pregnancy, where about 50-80 million married couples from all over the world have secondary infertility problems.

Meanwhile in Indonesia, the prevalence of secondary infertility is ± 12% or about 3 million married couples. About 50% of these couples were successfully helped to treat secondary infertility problems, the rest had to adopt or live without a

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child. Secondary infertility was 40% caused by women, 20% by men and 40% by male and female factors. Meanwhile, primary infertility is 8-12%. The incidence of women with secondary infertility in Indonesia is around 15% at the age of 30-34 years, a 30% rise between the ages of 35 and 39, and a 64% increase between the ages of 40 and 44. Based on the results of the Household Health Survey (SKRT), it is estimated that there are 3.5 million couples (7 million people) who have secondary infertility while primary infection is 12-15%. The main objective of the study was to determine whether or not stem cells were involved in the treatment of infertility in women.

METHOD

The method used in writing this review article is online literature studies obtained by accessing national and international scientific journals as well as scientific articles related to stem cells (Stem cells), infertility, women.

RESULT AND DISCUSSION

Induced pluripotent stem cells (iPS)

iPS is defined as an attempt to reprogram multipotent stem cells from mature tissue into pluripotent stem cells so that cells that are genetically and epigenetically similar to embryonic stem cells express specific markers of embryonic stem cells. iPS cells reconstruct ESCs using their morphological and growth material, the expression of ESCs marker genes and the development of teratomas, such that overall gene expression happens through DNA methylation, comparable but still not identical to ESCs. Frequently used, this substance formed mostly of connective tissue (fibroblasts) which are extracted from dermis of the skin, capsule, stroma and mucous or serous membranes of numerous organs.[10] The method used in isolating fibroblast cells is done in 3 ways.

The first, most non-invasive method uses an explant so that cells can migrate from the tissue sample. The second method uses mechanical disaggregation using shear forces during a strong pipetting process or pressing the tissue into a mesh/sieve. The third method is tissue digestion with proteases (trypsin, collagenase or elastase) which separate the connections between cells or cells with their matrix.[11]

In simple terms, the iPS process is like reassembling mature somatic cells into ESCs using growth material so that they are found ESCs specific marker gene expression with teratoma formation. Thus overall gene expression occurs by DNA methylation making it similar but not identical to ESCs. The use of iPS cells as a generator of competent cells

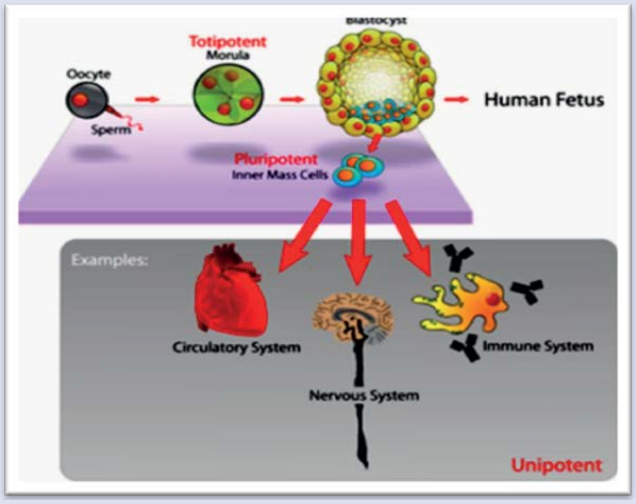

Figure 1: Stem cell differentiation potential.

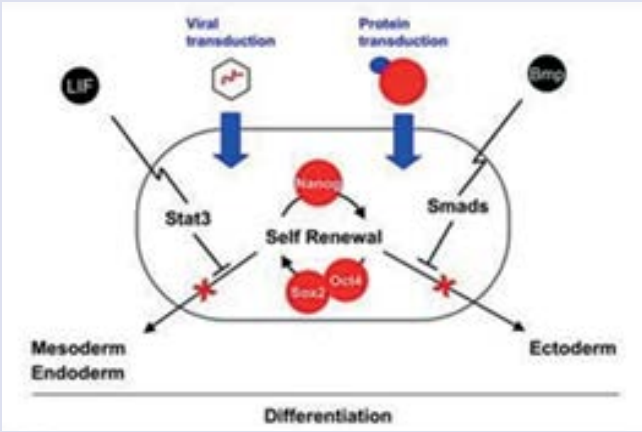

Figure 2: The process of retroviral transduction of intrinsic factor (Yamanaka factor) which can induce pluripotency and self-renewal in adult somatic cells.

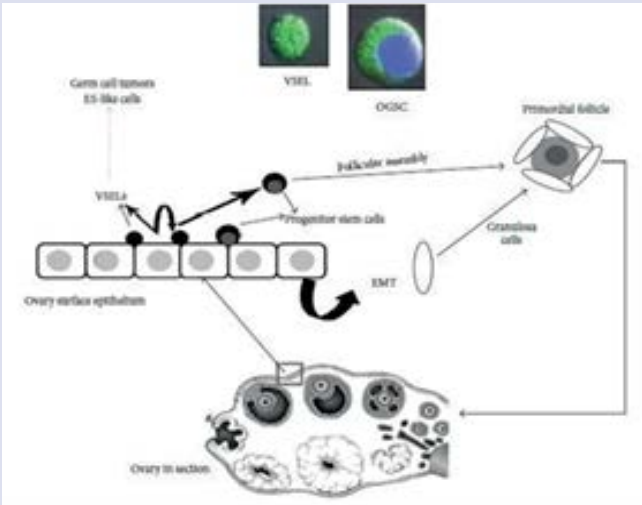

Figure 3: Planned model for postnatal oogenesis in mammalian ovaries.

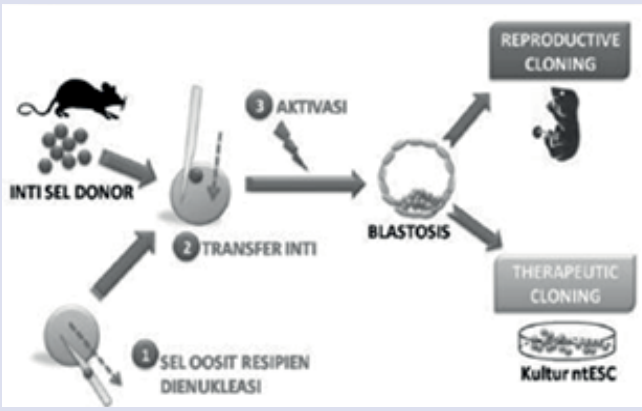

Figure 4: The transfer mechanism of somatic cell nuclear in mice.

in vitro provides an alternative to avoid social and ethical rejection but their ability to differentiate into viable cells as expected or gametes has not been proven.

Then, discovered many structures that spontaneously activate, resulting in the creation of parthenogenic embryos, but subsequently cease to function and degrade at an early developmental stage. EBs

are three-dimensional structures created by the agglomeration of undifferentiated ESCs. They consist of cells from endoderm, ectoderm and mesoderm (three germ layers) including gonadal cells.

Currently, the reprogramming process is carried out on the somatic cells of the adult individuals concerned (patient specific stem cells). The most widely used somatic cells are fibroblast cells and adipose cells. Two methods have been used to produce embryonal stem cells (ESc), namely by spontaneous dedifferentiation in culture by using pluripotency-promoting factors as lure and basic fibroblast growth factor (bFGF) or by eliminating leukemia inhibitory factor (LIF). The second method is by producing embryoid entities, three-dimensional structures (EBs). This process begins with gonadotropin stimulation and then the follicle secretes oocyte-like cells with a fragile zona pellucida. While the appearance of the meiotic protein SCP3 suggests that the cell is about to initiate the meiotic process, other meiotic proteins and chromosomal synapses are not found so that the meiotic process that occurs in these cells does not progress *in vitro*.

The cell procedure for reprogramming (iPS) requires an important factor called Yamanaka factor, first proposed by Yamanaka *et al* in 2006. It is a protein that is abundantly generated in embryonic stem cells and cells derived from adult somatic cells that differentiate into fully fledged stem cells. Pluripotent so that it can be used as an important marker that characterizes embryonic stem cells. The factor which is often abbreviated as 'SKOM' is an important transcription factor and is often used in reprogramming which consists of 4 kinds of transcription factors, namely:[12]

Sox2: A transcription factor from the Sox family (SRY related HMG-box) which is also expressed in embryos, embryonic cells, embryonal stem cells and neural stem cells. Disruption of Sox2 expression causes cell differentiation to be very fast, while embryos that do not express Sox2 will die because they cannot form primitive ectoderm (epiblast);

Klf4: First discovered as a tumor suppressor in gastrointestinal cancer. It is a known Kruppel-like transcription factor. Klf4 is associated with both tumor suppressor and oncogenic properties because it has recently been discovered that squamous and breast cancer cells overexpress this gene. Inhibitory effects of cell proliferation opposite to the action of c-Myc also occur due to ectopic overexpression of Klf4;

Oct 3/4 or POUS5F1: A catalytic subunit belonging to the POU family that has a role in expressing specifically on embryos, embryonal cells and embryonal stem cells. The pluripotent nature will be maintained by embryonal stem cells if there is 1 copy of the Oct3/4 gene, but if there is a 2-fold overexpression of the Oct3/4 gene, it causes differentiation into endoderm and primitive mesoderm;

c-Myc: Helix-loop-helix/leucine zipper as factor of transcription which is regulated by STAT3 and contributes to the pluripotency of mouse embryonic stem cells. Another role of these transcription factors is in cell growth, differentiation and proliferation and is a proto-oncogene that plays a role in cancer pathogenesis because it causes cell cycle acceleration from G to S1 phase.

Thus in theory, the new gametes that are inherited are actually genetically similar to the recipient of the implanted gametes through the reprogramming process. Cells produced by this technique are referred to as induced pluripotent SC (iPS) which do not involve the embryo so that it is ethical, societal and legal considerations that will make it possible to substitute ESCs in therapeutic treatment. iPS cells are pluripotent fibroblast cells derived from mouse or human tissue that have been reprogrammed by adding factors known to promote pluripotency to their genome by means of retroviral transfection.

Ovarian cell cryopreservation transplant

Various methods have been tested using stem cells to treat infertility problems, from repairing ovarian tissue so that it can function optimally to creating cells with the same characteristics as oocytes in adult individuals (postnatal oocytes). Donnez reported a healthy pregnancy and live delivery after orthotopic transplantation of cryopreserved ovarian tissue in patients with ovarian damage caused by chemotherapy in 2004.

Use of endometrial progenitor cells

According another research said, endometrial cells are the most active cells in the human body because they are renewed every month every cycle and consist of glandular and stromal epithelial cells. Multipotent stem cells are identified in the basal layer which is a reservoir of differentiated cells that will build the endometrial layer. Stem cells migrate and expand in response to systemic hormonal changes, such as changes in serum estradiol levels into progenitor cells that will develop into certain cells such as epithelial, stromal and vascular cells depending on the microenvironment. This regeneration process supports implantation in pregnancy.

Ovarian surface cell utilization (OSE)

Pinskey reported that he ovarian surface epithelium contains proliferating germ stem cells and has been shown to enhance postnatal folliculogenesis (PINSKEY). They also provided a new breakthrough stating that proliferative germ stem cells (GSCs) can develop into oocytes and that folliculogenesis can occur in the postnatal mammalian ovary.

This discovery provides a new breakthrough in the treatment of infertility in women by utilizing ovarian tissue from the patient himself, but it is necessary to further prove the characteristics and genetic material contained therein by analysis of gene expression or through RNA isolation.

Somatic cell nuclear transfer (SCNT)

Is a method used to transfer the nucleus of somatic cells (in this case stem cells) with new genetic material into the cell body of the recipient oocyte whose nucleus has been removed first. This somatic cell nuclear transfer (SCNT) technique includes 3 main steps, namely: removal of the oocyte cell nucleus that will be used as a recipient (enucleation) then insertion of the somatic cell nucleus into the recipient oocyte (nuclear transfer) and finally activation or reconstruct oocyte induction.[13]

This technique is better known as 'cloning' and has only been used on animals in the form of mice, sheep and cattle with the aim of producing animals that are genetically and phenotypically better than the parent oocyte donor itself. However, it is possible that this technique is applied to couples who have problems in having offspring so that genetically healthy individuals are produced. That is, the resulting individual is protected from unwanted congenital abnormalities, especially in older couples. In humans, this technique can be combined with the IVF (*In Vitro* Fertilization) technique to produce a zygote which can later be transferred to the patient's uterus or through a surrogate mother.[14]

CONCLUSION

From the results of this study, it can be seen the potential of stem cells (stem cells) in treating infertility in women. Further studies are needed, especially pre-clinical and clinical trials so that they can be widely applied.

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This manuscript has not been published and is not under consideration for publication to any other journal or any other type of publication (including web hosting) either by me or any of my co-authors. This paper is free from plagiarism and has been checked by Turnitin. The authors have been read and agree to the Ethical Guidelines.

CONFLICTS OF INTEREST

There are no conflicts of interest related to the writing process nor research process of this paper.

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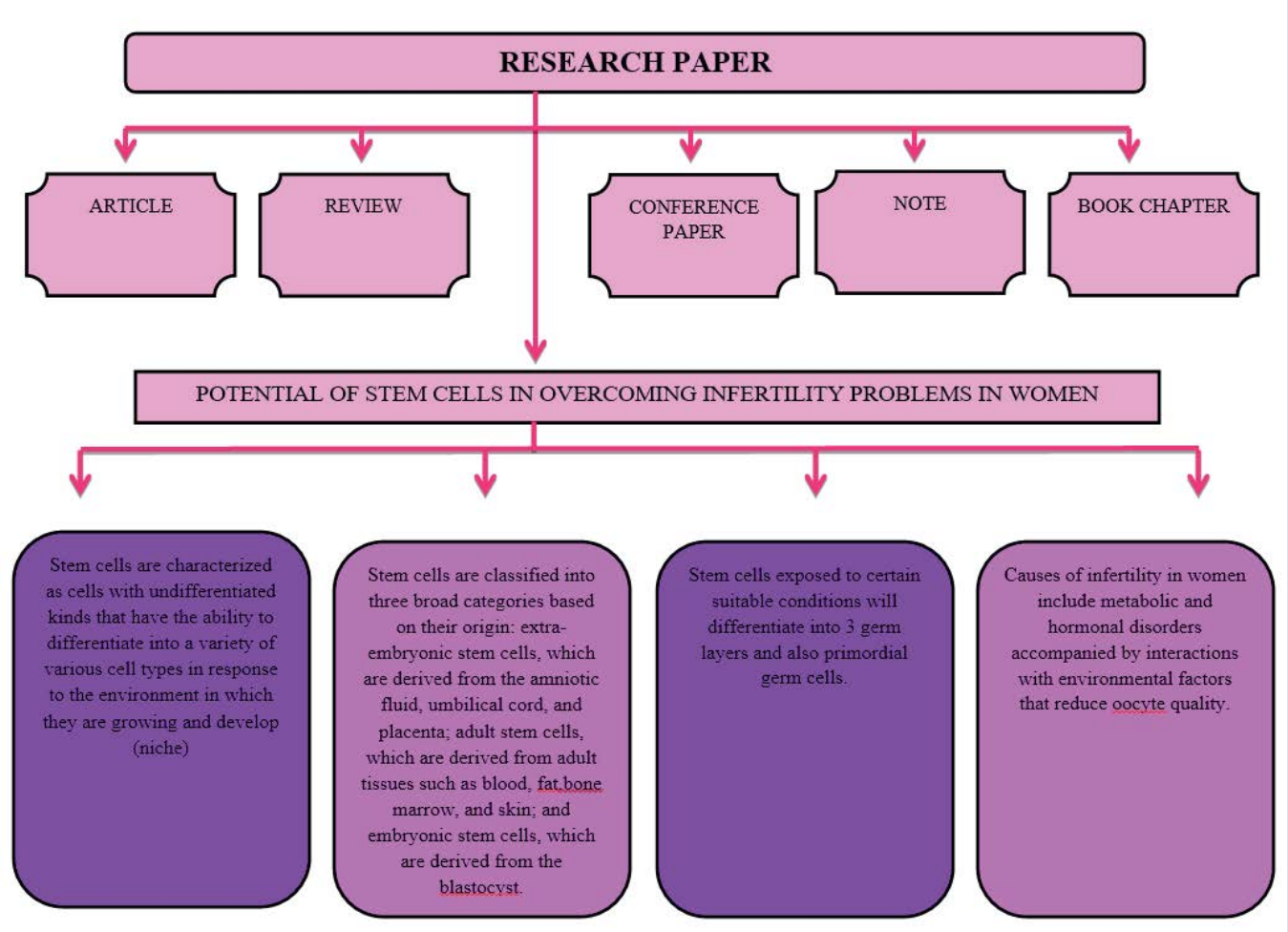
GRAPHICAL ABSTRACT



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