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Stem Cell Therapy for Breast Cancer: A Review

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Abstract:

In recent year there is growing interest about the role of stem cell therapy in disease. Stem cell therapy has been used in treating many disease conditions with a greater understanding of their biology , a major role of stem cells in the malignant process has been proposed. Breast cancer remains the most common malignancy among women worldwide, it is believed that cancer targeted therapies especially stem cell targeted therapy are superior to current treatments such as traditional chemotherapy or radiotherapy to overcome recurrence, metastasis and chemo-resistance. This review article details about the stem cells, normal human breast and stem cells application in treatment of breast cancer.

Keywords: stem cells, breast cancer, therapeutic effects

INTRODUCTION:

Breast cancer remains the most common malignancy among women worldwide, with an increase in incidence from 10.9 to 20 million new cases per year by the year 2020, and growing annual mortality from 6.6 to more than 10 million [1-3].

Stem cells are defined as cells that have the ability to perpetuate themselves through self renewal and to generate mature cells of a particular tissue through differentiation. Stem cells from a variety of organs might have the potential to be used for therapy in the future, but hematopoietic stem cells the vital element in bone marrow transplantation have already been used widely in therapeutics[4].

Studies in human and rat mammary gland suggests that stem cells are located in specific locations or stem cell niche [5].

A unique microenvironment is found in the stem cell niche which is required for the stem cell functions. Stem cells also play an important role in tissue repair and homeostasis. They potentially offer an unlimited source of specific cells for treatment of variety of diseases[6,7]. This review article aims in explaining the application of stem cell therapy in breast cancer.

WHAT IS A STEM CELL?

Stem cells are primal cells which are considered to be progenitor of more than 200 cell types present in human adult body. All stem cells are undifferentiated cells that are characteristically of the same family type. They retain the ability to divide throughout life and give rise to cells that can become highly specialized and take the place of cells that die or are lost.

The rigorous definition of a stem cell requires that it possess two properties: self renewal and unlimited potency. Self renewal means the ability to go through numerous cycles of cell division while maintaining the undifferentiated state. Unlimited potency means the capacity to differentiate into any mature cell type. In a strict sense, this makes stem cells either totipotent or pleuripotent. Multipotent and unipotent are also used to define stem cell potency. These properties can be illustrated in vitro using methods such as clonogenic arrays where the progency of cells is characterized[8].

Breast cancer stem cells(BCSCs):

Some indication that stem cells play a role in breast cancer comes from epidemiology data on breast cancer incidence following radiation exposure. Women exposed to radiation in their late adolescence following the Hiroshima and Nagasaki atomic blasts had the high susceptibility of breast cancer 20 to 30 years later compared to womens exposed at other age groups [9]. This suggests that adult mammary stem cells accumulate genetic changes leading to transformation over several years with eventual development of solid tumours. Recently, Al-Hajj and colleagues[10] showed that human BCSCs, identified on the basis of $CD44^{+}$, $CD24^{-/low}$, Lin^{-} expression could form tumours when as few as 100 cells were injected into non obese diabetic/ severe combined immunodeficiency disease mice. These cells have some of the key characteristics of stem cells. When 20,000 cells without this phenotype were used, they were unable to form a tumour.

Breast cancer stem cell as therapeutic targets:

In the past two decades, more than 30 new anticancer drugs have been introduced, but survival rates have improved only marginally for many forms of cancer[11]. In contrast to most cancer cells, cancer stem cells are slow-dividing and have less ability to undergo apoptosis and higher ability of DNA repair, making them more resistant to traditional methods of cancer treatment such as radiation and chemotherapy. In vitro experiments comparing differentiated breast cancer cells grown under monolayer conditions with $CD24^{-/low}$ $CD44^{+}$ cancer cells grown under mammosphere conditions showed that the stem cell-like population was more resistant to radiation [12]. For therapy to be more effective, debulking of differentiated tumours must occur followed by targeting of the remaining surviving, often quiescent, tumour stem cells. This could be accomplished by differentiating BCSCs through differentiating therapy or eliminating them via immunotherapy.

FUTURE PERSPECTIVE OF STEM CELL RESEARCH:

Low blood supply: Now the method to produce large number of red blood cells has been developed. In this method precursor red blood cells, called hematopoietic stem cells are grown together with stromal cells, an environment that mimic the conditions of bone marrow, the natural site of red blood cells growth. Erythropoietin, a growth factor, is added coaxing the stem cells to complete terminal differentiation to red blood cells [13].
Further research into this technique will have potential benefits to gene therapy and blood transfusion.

Baldness: Hair follicles also contain stem cells, and some researchers predict research on these follicle. Stem cell may lead to success in treating baldness through "hair multi-placation". This treatment is expected to work through taking stem cells from existing follicles, multiplying them in cultures, and implanting the new follicle cells which have shrunk during the aging process, which in turn respond to these signals by regenerating and once again making healthy air [13].

Missing teeth: The work on tooth generation has reached to a stage that it will be available to the general population in that decade. In theory, stem cells taken from patient could be coaxed in the lab into turning into a tooth bud which, when implanted in the gums, will give rise to a new tooth, which would be expected to take two months to grow. It will fuse with jaw bones and release chemicals that encourage nerve and blood vessels to connect with it [13]

Deafness [14]: Those have been success in regrowing cochlear hair cells with the use of stem cells
.
Blindness and vision improvement [14]: Since 2003 research has been successfully transplanted retinal stem cells into damaged eye to restore vision. Using embryonic stem cells, scientist become able to grow sheet of top potent stem cells in the laboratory. When these sheets are transplanted over the damaged retina, the stem cells stimulate neural repair, eventually restoring vision.
Bone regeneration: Mesenchymal stem cells can be pumped and cutters expanded from animals and human and have been shown to regenerate functional tissue when delivered to the site of musculoskeletal defects in experimental animals. [15]

Present scenario in stem cell therapy [15]:
Following types of stem cell therapy is possible in present scenario
Allogenic stem cell therapy : matched or unmatched
Syngeneic stem cell transplant: Identical twin
Autologous stem cell transplant
Cord blood stem cell transplantation
Nonmyeloablative stem cell transplant
However stem cell therapy has some inherent complications such as infection, regimen, toxicity, carcinogenicity, immune deficiency and mortality due to co-occurrence of complications.

Clinical application and potential use of embryonic and adult stem cells [16]:
There are many ways in which human stem cells can be used in basic research and in clinical research. These are:
Embryonic stem cells have been used to study specific signals and differentiation steps required for development of many tissues.

Genetic therapy: Embryonic stem cells benefit the gene therapy by the following ways:
First human embryonic stem cells could be genetically manipulated to introduce the therapeutic gene. This gene may either be active or awaiting later activation, once the modified embryonic stem cells has differentiated into the desired cell type. Recently published reports establish the feasibility of such an approach [17]
Embryonic stem cells may additionally be indirectly beneficial for cellular gene therapy. Since these cells can be differentiated to many cell types, including presumably tissue specific stem cells, they may provide a constant in vitro source of cellular material. Such "adult" stem cells derived from embryonic may thus be utilized to optimize protocols for propagation and genetic manipulation technique [18].

Brain damage [19-21]
In case of brain injury although reparative process appears to initiate, substantial recovery is rarely observed in adults suggesting a lack of robustness. Recently from research conducted in rats subjected to stroke suggested that administration of drugs to increase the stem cell division rate and direct the survival and differentiation of newly formed cells could be successful.

Cancer:
Research at Harvard Medical school caused intracranial tumor in rodents. Then they injected human neural stem cells. Within days the cell had migrated into the cancerous and produced cytosine deaminase, an enzyme that converts a non-toxic pro-drug into a chemotherapeutic agent. As a result, the injected substance was able to reduce tumor mass by 80 percent [22,23].

Heart damage:
Several clinical trials targeting heart diseases have shown that adult stem cell therapy is safe. However none of these trials have proven efficacy. Recently the use of patients own bone marrow derived stem cells and peripheral blood derived stem cells is becoming popular [24,25].

Controversies in stem cell research :
Stem cell research is a minefield of ethical problems because stem cells that offer the most potential for study must be harvested from human embryo that are few days old. In 1996, the birth of Dolly the sheep- the world first successfully cloned mammal- ignited a firestorm of protest and concern. The most famous controversy in stem cell research has been Hwang's claim of cloning a dog. Hwang's work was able to offer an alternative to use of actual human embryo by cloning several human embryos,

helping to eliminate the need for new embryos. Hwang claimed he had successfully cloned 30 human embryos, claims that have shown to be lies. Unfortunately, the use and study of embryonic stem cells are currently clouded by ethical controversy. Adult stem cells offers a unique alternative in that they may be isolated, studied, or manipulated without harming the donor. Currently, several obstacles for use of adult stem cells as therapy exist. First, the ability to identify most adult stem cells is impeded by lack of stem cell markers. Second, in vitro systems for manipulating adult stem cells populations are often not well defined. Finally, our understanding of how adult stem cells are regulated within their niche is in its infancy.

Ethical Concerns In Stem Cell Research:

In the case of embryonic stem cell research, the end that scientists hope to achieve is the relief of human suffering. That this is a humanitarian and worthy end is not in dispute. The controversy is about the means, namely, the consumption of the donated embryos. More particularly, embryonic stem cell research and therapy would use donated embryos that, by virtue of donor instructions, will never uttered. Recent research suggests that tumour formation may result from the development of cancer stem cells by the deregulation of normal self-renewal pathways of tissue stem cells[25].

CONCLUSION:

Stem cell poses a great future for therapeutics world by promising treatment options for the diseases which are considered as non curable nowadays. However, research and trials are required to refine and optimize conditioning regimens and modalities of supportive care.

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