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REVIEW ARTICLE

Applications of Stem Cells in Cancer Therapy: A Literature Based Studies

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ABSTRACT

Stem cells, are extraordinary kind of cells having unique ability of self-renewal, lineage differentiation and regeneration of damaged organ or parts of body. Stem cells experience asymmetric cell divisions, bringing forth two cells from each cell, one cell is alike to SCs in stemness whereas, other is differentiated into various lineage. These cells have been known for decades for their highest regenerative potential but their clinical applications remain delayed due to several unknown mechanisms of their actions. With the discovery of Cancer Stem Cells, it was described that understanding the stem cell biology is important for a proper way of cancer cure. Stem cells are successfully being transplanted in several clinical trials to treat the retinal disease, visual disorders including Retinitis pigmentosa, Stargardt's disease, wound healing, skin regeneration and age related macular degeneration. Their role in cancer progression is the hot debate of research by cell biologists as understanding their role will help to remove the hurdles in cancer therapy.
Keywords: Stem Cells, Applications of Stem Cells, Cancer Progression, Stem Cell therapy, Cancer Therapy

Stem cells concept was initiated at nearly the last of 19th century as a hypothesis was put forward to describe for the potentiality of self-renewal of various tissues such as blood, skin, etc. throughout the life, of an organism (1). Stem cells originated from adults have been clinically used since many years in treatment of several hematological tumors including leukemia. These cells were primitively isolated from the bone marrow (BM), however, they are at present successfully obtained from umbilical cord blood (2). Stem cells, are extraordinary kind of cells those have unique ability to self-renewal at self and conversion to differentiated cells (3). Stem cells experience asymmetric cell divisions, bringing forth two cells from each cell, one cell is alike to SCs in stemnessess whereas, other is differentiated into various lineage. The daughter cell maintains properties similar to stem cell throughout its cycle, at the same time its sister cell goes through cell divisions (4). Several clinical trials are being employed for stem cell transplantation such as for retinal disease. Fetal, UC, embryonic and BM derived SCs are used for the treatment of visual disorders including retinitis pigmentosa, Stargardt's disease and age related macular degeneration (5).

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SOURCES AND TYPES OF STEM CELLS

Stem cells can be successfully obtained from multiple anatomical locations, such as hair follicle, periosteum, adipose, bone marrow, liver, amniotic fluid and skeletal muscle and brain (6, 7) . Subsequently, successful isolation of MSCs from humans they are now being harvested from various other species including rat, horse, dog and mouse (6).

Stem cells are classified into two types:

1. Embryonic stem cells
2. Non- Embryonic stem cells: Adult stems cells and Fetal stem cells

Embryonic stem cells: Human pluripotent stem cells (hPSCs), such as ESCs are novel SCs, which has the potential to form germ layers and theoretically they are capable of differentiating adequate to 220 different cells of the body (8).
Teratoma formation is one of the desired properties of PSCs demonstrating their ability to differentiate. However, despite of all the benefits, harvesting and therapeutic use of ESCs is limited for use because it has thrown up debates regarding ethics and legalities as ESCs are obtained from inner cellular mass of blastocysts, which is an early stage of embryo (9).

Adult Stem Cells: Adult SCs are successfully obtained from the mesodermal tissues including bone marrow. They have potential to self-renew, can differentiate into mature cells of their resident environment, are multipotent, may have transdifferentiating abilities to further differentiate into mesenchymal tissues lineages such as marrow stroma, muscle, fat, cartilage, tendon, and bone (10, 11).
BM-SCs contain both HSCs and MSCs. HSCs can give rise to all blood types of cell of hematolymphatic system, such as, platelets, mast cells, neutrophils, eosinophil's, basophils, macrophages, erythrocytes, dendritic cells, B-T lymphocytes whereas, MSCs generate mesenchymal tissue lineages such as, cartilage, connective tissue, muscle, bone marrow, ligament and tendon (12, 13). HSCs can be identified by recognizing surface marker CD34 that separates SCs from various other hematopoietic cells (14).

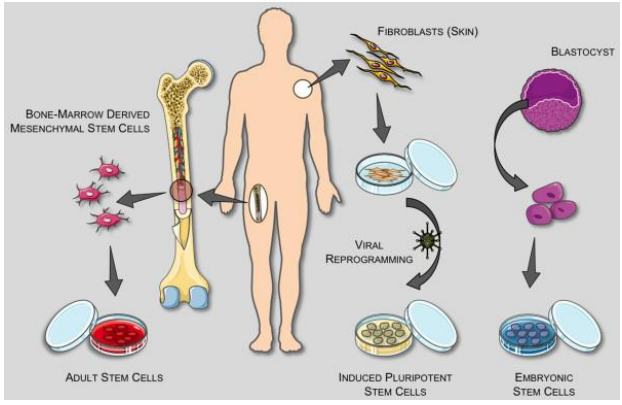

Fig. 1. Different types of Stem cells origin. Figure adapted from (15).

STEM CELLS IN CANCER PROGRESSION

The CSCs possibility has important approaches for development of therapeutics in cancer. Recently, studies shows BCSCs (16) and CSCs from various tumors, are resistant to both chemo and radiotherapy (17). Factors released by MSCs induce antitumor potentials which can reduce glioma proliferation, BC cells, hematoma, melanoma and lung cancer (18, 19). Hence, MSCs have capability of migrating towards the cancer cells (20-22) that can give rise to homing ability of MSCs, it further proposes that they can be helpful as therapeutic target agents to invade tumor cells (22).
To express MSCs, almost different 20 types of chemokine receptors have been described (23, 24). Chemokine have been shown to play a vital role in tumor growth and progression. Studies on BC suggested that levels of CXCL1, CXCL6 and CXCL8 increase after chemotherapy, aid in the survival of tumor cells and increases the CSC population. (25, 26). Expression of CXCL8 by malignant cells has been suggested to be one of the escape mechanisms used by cancer cells to evade cell death (25, 27). Cancer cells also release SDF-1, which suggest a vital part for SDF-1 in CXCR4 axis (28, 29). Yet, expression of CXCR4 is lower in

MSCs, intravenous injection of CX3CL1 strongly suppress lung metastasis and increase rate of survival of mice with lung metastasis cells (21). These studies indicate, chemokine provide survival benefits to breast cancer cells.

MSCs used as delivery agents can suppress growth of tumor and interferon (IFN)-β have proapoptotic and anti-proliferative outcomes (30, 31). BM-MSCs that express interferon (IFN)-α show low proliferation of cells, increasing apoptosis in a model of lungs metastasis (32).

Delivery of IFN-α by MSCs contributes enhanced apoptosis, was determined beneficial in various models of cancers such as prostate cancer (33), glioma (34) and melanoma (35). TNF-α an inflammatory cytokine has shown to support tumor growth and is highly expressed in breast carcinomas. As a matter of fact, detection of higher numbers of cells that express TNF-α in breast tumors have been found to be associated with raising tumor stage and involvement of node (36, 37). Moreover, breast tumors have been reported to express RANK and RANKL, a cytokine in TNF-α superfamily, their expression varies among different breast tumors (38, 39).With increasing histological grade, the expression of RANKL decreases, the tumors which holds that RANKL expression are estrogen receptor negative (ER^-) and are of high histological grade (40). It is documented that when there is a loss of RANKL in breast tumors as they become more aggressive, but the one that retain RANKL are of higher histological grade. RANK–RANKL signaling has been documented to play a major role in bone metastasis of breast cancer (41). Targeting chemokine, which are emerging as important factors involved in regulating breast CSCs, may provide promising therapeutic options to prevent therapy resistance and relapse in breast cancer patients.

The unique features of ASCs are in initiation of repair process in the organ following a severe injury and maintain the tissue homeostasis through cells regeneration of damaged areas as a result of apoptosis and injuries (42-44). Adult stem cell niches have been found in almost all organs of the human body, e.g. bone marrow, cornea, retina, brain, blood, kidney, liver etc.

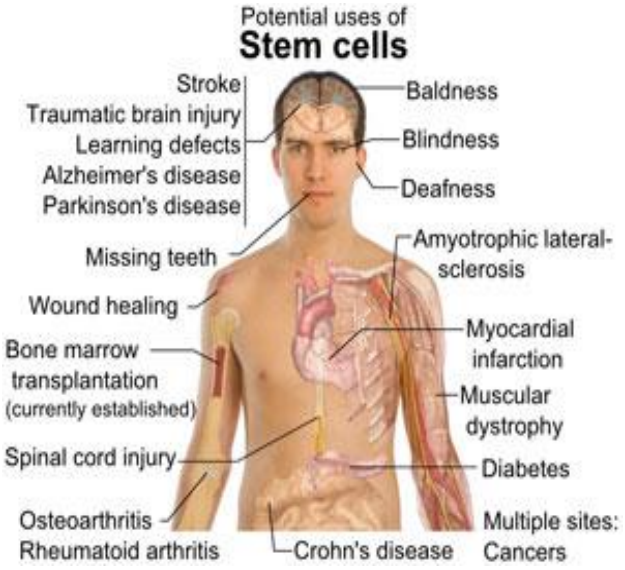

Fig. 2. Potential use of stem cells used in various diseases. Figure adapted from *http://www.stemcells.ph/autologous-fat-stem-cells-prevent-acute-rejection-of-kidney-grafts/.*

STEM CELLS AS THERAPEUTIC AGENTS

The application of stem cells to treat human diseases is by no means new, their major destination is to originate therapeutic therapies against serious injuries or chronic disorders in which body's reaction is not sufficient enough to repair normal function of tissues. WJMSCs hold a great therapeutic potential for tissue repair and regeneration in various *in vitro* studies of human diseases including cancer, heart problems, neurodegenerative disease, etc. (45, 46). MSCs are attractive nominees for cell based therapies as till now human trials of MSCs show no inauspicious reactions towards MSC transplants (47, 48). MSCs presents various approaches that makes them a perfect source of therapeutic agents in the field of regenerative medicine (10, 49, 50).

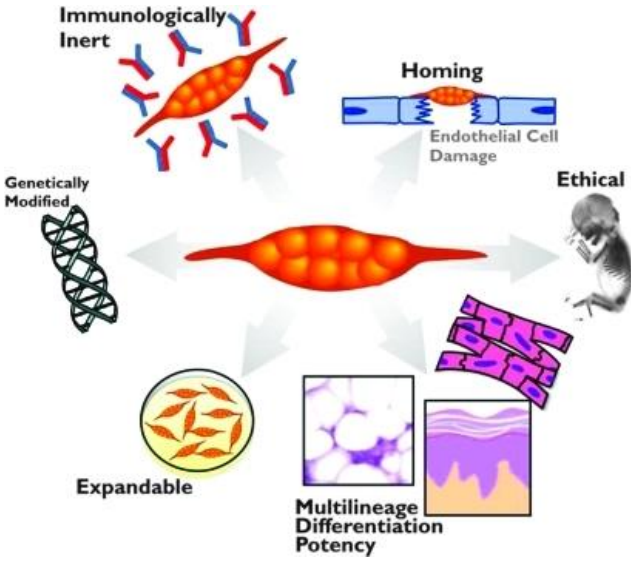

Fig. 3. Advantages of mesenchymal stem cell therapy. Figure adapted from ref. 46.

Once MSCs are transplanted, they home to inflammatory site. Hence, immunosuppression may not be required into an allogeneic host transplantation (51, 52). MSCs derived from BM adult actively take part in the rehabilitation of damaged tissue by any injury or disease (53). Bone marrow was first transplanted in the 1950s (54). The first important discovery came in 1968 with two reports of successful allogeneic transplantation in two patients, one was X-linked immune deficiency and the other was Wiskott-Aldrich syndrome (55). More recently, in 1988, using umbilical cord blood the first successful transplant was performed on a child with Fanconi's anemia (55).

Hematopoietic SCs from either UCB, BM or peripheral blood are the most common source of cells as cell based therapies for both hematological and non-hematological disease (56, 57). WJMSCs, like neural SCs and MSCs migrate towards the site of tumor growth (35, 58, 59). WJMSCs to express interferon beta were injected intravenously into mice suffering human breast carcinoma (MDA 231) tumors. This treatment cut down the tumor bulk and WJMSCs were found near the tumors (60). Other studies documented that WJMSCs were found admirable to repair photoreceptor damage (61) for tissue engineering (62).

Embryonic stem cells having ability to produce a theoretically unlimited supply of normal and differentiated cells, have gained attention on the potential importance of these cells in toxicology, drug discovery (63, 64), tissue engineering (65, 66) as well as gene and cellular therapy (67, 68) for a wide range of human diseases including Parkinson's and other neurodegenerative diseases (69, 70) diabetes (71), cardiac and vascular therapy (72-74).

CONCLUSION

Over the last decade, stem cells have emerged as a potential therapeutic agent for chronically injured tissue, with MSCs being widely studied for such therapies. Stem cell research has seen an exponential growth in recent years and it has been the topic of discussion among almost all scientific, political, religious and ethical communities because of their therapeutic potential and associated ethical issues. In this mini-review, current clinical applications of stem cells, associated problems of their translation for clinical practice has been discussed. Millions of articles have been published describing their properties based on the key genetic and epigenetic factors but still there is much left to be discovered especially about their interactions.

Stem cells are being used in clinical practice especially for drug screening purpose based on the patient-specific pluripotent cells and cancer stem cells. What makes stem cell research so exciting is its tremendous potential to benefit human health and the opportunities for interdisciplinary research that it presents. Almost every day there are reports in the media of new stem cell therapies.

Stem cells without any doubt have the potential to cure almost all uncured diseases such as ageing, cancer, diabetes, blindness and neurodegeneration etc. This is also worth mentioning that it is essential to be realistic about the time and steps required to take new therapies into the clinic. For example, it is exciting to be able to induce ES cells to differentiate into cardiomyocytes in a culture dish, but that is only one very small step towards effecting cardiac

repair. The overriding concerns for any new treatment are the same: efficacy, safety and affordability.

CONFLICT OF INTEREST

The authors declare no-conflict of interest with any person or organization.

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