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EDITORIAL

Stem Cell Biology: A New Hope in Regenerations and Replenishments Therapy

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Stem cells are unspecialized cells that have immense potential to self-renew indefinitely and can also be differentiated into mature cells with specific functions. Commonly, stem cells come from two main sources: Embryos formed during the blastocyst phase of embryological development (embryonic stem cells) and Adult tissue (adult stem cells). The stem cells potency could be totipotent or pluripotent i.e. can be shaped into any or all type of mature cells, or multipotent (can be programmed into many type) or unipotent (programmed into one type) from progenitor cells. Multipotent stem cells can be isolated from several mesenchymal sources, usually bone marrow, and characterized in almost every tissue in which they have been analyzed. The Ontario Cancer Institute for the first time introduced stem cell research by relating self-renewing cells within the bone marrow of mice in 1963. In 2002, investigators at the University of California, Los Angeles defined a novel adult stem cell population isolated from adipose tissue (ADSC). They were pluripotent and capable of forming multiple cell types within all 3 germ layers. At current, ADSC remain one of the most commonly utilized populations in the stem cell field [1].

In mammals including humans, stem cells are characterized in the inner cell mass of blastocysts (early embryo) termed as embryonic stem cells (ESCs). The scientists first discovered ways to isolate and culture ESCs from early mouse embryos in 1981, nearly 37 years ago (Evans and Kaufman, 1981). These cells were pluripotent as these stem cells can be differentiated into a *very wide range* of tissue types or all cell types of an individual. So in future the differentiation of ESCs could be targeted to treat certain incurable disease and in cell transplantation therapies, but it has ethical concerns as destruction of human embryos is not acceptable. Thus, Somatic cell nuclear transfer (SCNT) discovered, it is a laboratory tactic for generating a viable embryo from a body cell and an egg cell. The technique consists of taking an enucleated oocyte (egg cell) and implanting a donor nucleus from a somatic (body) cell. This technique has been used in cloning animals (such as Dolly the sheep), but is not full proof, so again it creates a threat as the same theme could be used to clone humans. To circumvent this limitation, scientist Shinya Yamanaka, Nobel Prize laureate (2006), created a breakthrough by identifying induced pluripotent stem cell (iPSC), in this approach some specialized adult cells can be "reprogrammed" genetically to assume a stem cell-like state. They initially reprogrammed mouse skin cells into iPSCs by inserting just four functioning genes (Klf4, Oct3/4, c-Myc, and Sox2) into the cells (Takahashi and Yamanaka, 2006). The development of iPSCs from individual skin cells has opened up a new world of research. This embryo-free technique is a powerful way to generate cell lines from a patient's own tissues. Cell reprogramming technology provides a novel approach to derive iPSCs directly from a patient's somatic cells without embryo involvement and thus overcomes ethical concerns. Although cell reprogramming is very attractive because of its potential for future cell replacement therapy, several potential challenges need to be overcome before any possible applications can be made [2].

Recently, Stimulus-triggered acquisition of pluripotency (STAP) technique is established where several cell types, comprising the brain, skin, lung, and liver were exposed to stress, including low pH, approximately 20% of the cells

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that survived from stress reprogrammed to multipotent stem cells without introduction of any exogenous genes. This has enabled generating cells with pluripotency from patients without damage of an embryo or introduction of exogenous genes. This technology may open a new vista in stem cell biology and research in carcinogenesis. Further, it has also been found that Adult stem cells in various tissues or organs have roles in maintaining and repairing the tissue, where they were found. Usually, the number of "adult" stem cells in each tissue is very low, and once extracted from the body, their capability to divide is restricted, making generation of huge quantities of stem cells challenging.

Further, role of stem cells in cancer came in 1994 with a study of human acute myeloid Leukemia, in which an AML-initiating cell population was identified from AML patients by transplantation into severe combined immune-deficient (SCID) mice. These stem cells of cancer are now termed as Cancer Stem cells, these populations are identified by surface makers of CD44, CD24, CD29, CD90, CD133, epithelial-specific antigen (ESA), and aldehyde dehydrogenase1 (ALDH1) as observed from different tumors [3, 4]. The subsequent reports shows presence of CSCs in a variety of tumors, including Leukemia, breast, colon, pancreas, lung, prostate, melanoma, and glioblastoma [3–6].

Current Progress in Regeneration and Replenishment Therapy

Presently, blood stem cells are the only type of adult stem cells that are now commonly used as bone marrow transplant. Now the emerging researches on "Adult neural stem cells" are important as relative lack of recovery is noticed from central nervous system (CNS) injury and in neurodegenerative diseases. Further, the iPSCs and Mesenchymal Stem Cells are also being utilized to make cardiomyocytes or to attenuate myocardial injury, several kinds of neurons, liver cells, and hematopoietic stem cells etc., for possible cell replacement therapy. The Food and Drug Administration (FDA) regulates the use of adult stem cells. In 2006, the FDA adopted 21 CFR 1271, which has applicability over human cells and tissues to include any "transfer into a human recipient." Formerly, the code was specified for transfer "into another human," excluding autologous cells. Since then, cells that are more than "minimally manipulated," even if they are intended for autologous use, are subject to similar regulations as manufactured drugs.

Stem Cell Therapy and Osteoarthritis

Stem cell therapy is also popularized in Osteoarthritis, which is evident from scientific database as Sixty-one of 3172 articles were reported on osteoarthritis, in which 2390 patients were treated by adipose-derived stem cells (ADSCs) or bone marrow-derived stem cells (BMSCs). But these studies have limitations of no high quality evidence and long-term follow-up [7]. The Drug Controller General of India (DCGI) recently approved its stem cell-based therapy to treat cartilage defects. Cartilage repair procedure has been developed where the body's own cartilage cells are cultured, multiplied and implanted into the patient's damaged joint leading to new cartilage regeneration and avoiding the need for early joint replacement.

Stem Cell Therapy and Cancer

Stem cell transplants, including peripheral blood, bone marrow, and cord blood are used for cancers affecting the blood or immune system, such as leukemia, lymphoma, or multiple myeloma. Generally, Blood cancers utilizes hematopoietic stem cells (which includes Bone marrow transplant (BMT), Peripheral blood stem cell transplant, and Cord blood transplant). These stem cells are blood-forming stem cells. Thus they maintains sufficient frequency of blood cells. Now, MSCs (mesenchymal stem cells) cell membranes are also programmed with doxorubicin-containing porous silica nanorattles that could be used for tumor-tropic therapy. This method would increase and extend intra-tumoral drug spreading and also able to promote cell apoptosis more than free drug or drug delivery systems using silica nanorattles alone. Thus, stem cell-mediated Nanoparticles-based drug delivery shows promise in cancer treatments. Further, the stem cell-like memory T cell populations (combination of memory cell and naive T cell) causes steady-state activation profiles collective with the self-renewing "stemness" of undifferentiated cells able to undergo antigen-driven differentiation into central memory, effector memory and effector T cells, and this permits them to confer robust adaptive immunity thus, it may help in activating immune therapy [8]. Further, normal stem cells attract CSCs (Cancer Stem Cells), so it can possibly be used to target CSCs in cancer therapy. Interactions between normal stem cells and CSCs suppress tumor proliferation, angiogenesis, and metastasis, and reduce inflammation and apoptosis. Researchers assessed the potential of NSCs and HSCs in anti-glioblastoma therapy.

Stem Cells Therapy and Diabetes

Notable advancement has also been made with regard to the generation of functional beta cells from human stem cell populations over the past 35 years. The underlying approach is to closely recapitulate the path that pluripotent stem cells take during embryogenesis, from the creation of definitive endoderm, to pancreatic endoderm, to endocrine progenitors, and ultimately to pancreatic islet cells. Presently, efforts have been on generating single hormone-positive beta cells capable of glucose-stimulated insulin secretion (GSIS). Further, a human clinical trial examining the safety and efficacy of a "functional cure" for type 1 diabetes is underway. Trials of the novel islet cell replacement therapy developed by ViaCyte involve a device containing stem cells being implanted into a patient with type 1 diabetes. It's expected these cells will then mature into human islet tissue with insulin-producing beta cells that produce insulin on demand.

Stem Cells Therapy and Miscellaneous Diseases

The first use of hESC-derived cellular product took place in a spinal cord injury trial in 2010, and since then a small number of hESC-derived RPE transplant trials have been performed. There are several diseases and disorders where stem cell based trials are in progress, as Autism Spectrum Disorder (ASD), Parkinson Disease, Alzheimer's disease, Stroke and traumatic brain injury repair, spinal cord injury, Renal diseases, Liver Diseases, Myocardial infarction, restore and repair vision, hearing etc. [9]. Thus scientists are relentlessly exploring the state of art in transforming stem cells into various required type of cells (like cardiomyocytes, hepatocytes, nephrons etc.). So in coming years of medicine, the stem cell therapy may open new vistas to treat these organ specific chronic and untreated disease.

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