A Mini Review on Stem Cells, Their Study Models, and Effect of Trace Elements

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Introduction

As defined by researchers stem cells are cells that have the ability of self-renewal through cell division and differentiate into a diverse array of cell lines (Ilic and Polak 2011).

In the general sense, stem cells need to fulfill the following four criteria to be classed as stem cells: (a) in order to maintain the stem cell population, stem cells should be capable of continuous self-renewal, (b) stem cells should have the ability to differentiate into a variety of mature cells, (c) stem cells should be able to integrate and differentiate into its source damaged site, and (d) lastly, stem cells should have the ability to differentiate into mature cells of a tissue even if the tissue doesn't suffer (Ma et.al. 2012).

With recent developments in the field and advancement of technologies like fluorescence-activated cell sorting (FACS) and magnetic activated cell sorting (MACS) along with enhanced isolation, culture, and molecular imaging techniques (Ma et.al. 2012), there has been much speculation of its use in therapy, regenerative medicine, and drug and toxicity screening (Ilic and Polak 2011). Essentially, cell-based therapy or regenerative medicine is a three-dimensional operation which includes involvement of researchers/clinicians and companies in a particular cell therapy, types of cells (autologous and allogenic) and the subsequent scale of manufacture, and finally integration of cellular therapy with clinical practice (Foley and Whitaker 2012).

Tackling degenerative disorders in the ever-aging human population is one of the biggest challenges faced by clinicians today with surgeries and drugs being the gold standard for treatment. Stem cells have been proven to have the ability to maintain and replenish tissues, and therefore, stem cells or stem cells coupled with gene therapy can be used as potential means for treating degenerative disorders and restoring tissue function.

Tissue restoration can be accomplished either through stem cell integration directly in the damaged/target tissues or by delivering complex signals to target tissues without any integration. For example, hematopoietic stem cells (HSCs) can restore tissue function by directly integrating into the target tissue, while mesenchymal stem cells (MSCs) tend to deliver the signals to target tissues like in ischemic cardiac injury. Infusion of MSCs has also shown therapeutic use in amelioration of symptoms in bleomycin-induced mouse lung injury. However, owing to lack of absolute evidence and experimental works still being carried out on the immunological and tissue trophic effects of MSCs, their therapeutic potential remains unclear. On the other hand, HSCs show engraftment into bone marrow during development as shown by the expression of CXC chemokine, stromal-derived factor-1(SDF-1), although SDF-1 and its receptor CXCR4 are not essential for bone marrow engraftment, thus desiring a lot more work to be carried out on localization and engraftment of stem cells before clinical application is accomplished.

E. Ray Banerjee, *Perspectives in Regenerative Medicine*,
DOI 10.1007/978-81-322-2053-4_2, © Springer India 2014

As a result of these barriers, recapitulating tissue structures is being used as an alternative for in this case vascular cells derived from human embryonic stem cells (ESCs) have the ability to amass into blood-carrying conduits (in vivo) and spontaneously perform anastomoses with the host vasculature, thereby indicating intrinsic morphogenetic assistance for cell-based therapy. In addition to this, bioengineered scaffolds will enhance and hasten the process of regenerative therapy for cardiomyocytes assemble into functional units on biocompatible thin films in vitro that can coordinate synchronous impulse propagation and can be shaped into 3D structures.

Preceding localization and engraftment of stem cells, we need to realize the implications of immune barriers on stem cell transplants. In terms of immunity, stem cells can be classified as autologous (taken from patient tissues) which doesn't spark an immune reaction and allogenic (taken from unrelated donors) which may spark immune reaction requiring immune suppression. In order to circumvent the problems of immune suppression in regenerative therapy, researchers have come up with genetically equivalent (isogenic) cells. These isogenic cells are produced by somatic cell nuclear transfer (SCNT; wherein adult somatic cell nucleus is injected into an enucleated oocyte) forming pluripotent ESCs from adult somatic cells. Alternatively, this is achieved by reprogramming adult somatic cells back to a pluripotent state using a set of transcription factors, also known as induced pluripotent stem cells (iPS cells).

N.B. ESCs produced by SCNT have only been done on animals and not humans yet (Daley and Scadden 2008).

Stem Cell in Regenerative Therapy: Apart from HSCs having been used as therapy for leukemia and other types of cancer, there has been a drastic increase in the use of MSCs as potential treatment for bone and cartilage repair, spinal cord injury, lung fibrosis, cardiovascular repair, etc.

Examples: Orlic et al. (2001) through their works showed locally delivered bone marrow cells could regenerate myocardium, indicating stem cell therapy could be useful for treating coronary artery disease. Gussoni et al. (1999) showed that murine MSCs could be a potential tool for treating muscular dystrophy as the MSCs expressed dystrophin in conjunction with the sarcolemma when injected into the quadriceps muscle of *mdx* mice (Barry and Murphy 2004).

Stem Cells in Drug and Toxicity Screening: Pathological modeling and drug screening using stem cells more specifically human pluripotent stem cells holds exciting and promising opportunities to identify new therapeutic approaches. Pluripotent stem cells can be used in screening to identify and evaluate the effects of compounds on specific human cell types which are predisposed to potential toxicity. Firstly, this process involves differentiation of human pluripotent stem cells into cells of a desired tissue that we wish to inspect using the investigative drug, which can then facilitate the study of dose–response toxicity analysis. Till date most such studies have been carried out on human pluripotent stem cell-derived cardiomyocytes and hepatocytes. More recently, such drug screening studies have been carried out on human pluripotent stem cell-derived neurons to check for drug metabolism and to assess cellular toxicity. However, the one question that still needs to be addressed is whether such drug toxicity studies on human pluripotent stem cell systems corroborate with results observed in the complex in vivo environment (Maury et al. 2011).

Finally, it must be noted that in order to fully exploit the different forms of stem cells, we need a better understanding of organ morphogenesis. Further developments in developmental biology together with stem cell biology and tissue engineering hold the promise to ultimately transform regenerative medicine (Daley and Scadden 2008).

Classification of Stem Cells Based on Their Differentiation Potential

Based on differentiation potential stem cells can be classified into five groups, namely, totipotent/omnipotent, pluripotent, multipotent, oligopotent, and unipotent (Ilic and Polak 2011):

Totipotent/omnipotent—Cells with the ability to differentiate into embryonic and extraembryonic tissues and form a complete viable organism are called totipotent, e.g., zygote.

Pluripotent—Cells with self-renewal capacity and ability to differentiate into the ectoderm, mesoderm, and endoderm are classed as pluripotent. These cells are highly useful for regenerative medicine, e.g., ESCs and iPS cells.

Multipotent—Cells having the ability to differentiate to a limited number of cell fates or into closely related family of cells are termed multipotent. Unspecialized mesodermal MSCs having the ability to differentiate into connective tissues, bone, cartilage, and circulatory and lymphatic systems are an example of multipotent cells.

Oligopotent—Oligopotent progenitor cells have the ability to differentiate into only a few closely related cell types. Lymphoid or myeloid stem cells are examples of oligopotent cells. These cells can form various blood cells like B and T cells but not a different blood cell type like red blood corpuscles.

Unipotent—These cells can differentiate into only one cell type and have least potency among stem cells, e.g., muscle stem cells (Ilic and Polak 2011).

Classification of Stem Cells Based on Origin and Their Sources

Based on origin stem cells can be categorized into embryonic, fetal, perinatal, adult, and iPS (Ilic and Polak 2011).

Embryonic Stem Cells (ESCs)

ESCs are derived from the blastocyst (stage of embryo formed 5–6 days after fertilization). The blastocyst comprises of the inner cell mass (ICM) and the trophoblast which form the embryo and the placenta, respectively. The ESC lines are derived by separating the ICM from the trophoblast. The ICM is then transferred into cell plates where under specific conditions these cells can be maintained and propagated infinitely in an undifferentiated state. ESCs just like any other cell forms show genetic instability, and the addition or removal of a growth factor or precursor may initiate differentiation.

Fetal Stem Cells (FSCs)

Fetal stem cells are sourced from embryos of terminated pregnancies. Although not as potent as ESCs and unable to divide indefinitely in culture, FSCs have been used to produce neural stem cell lines, some of which are already facing clinical trials in the USA and UK.

Perinatal Stem Cells

Perinatal stem cells can be classed into three groups based on their origin: amniotic fluid stem cells, placental stem cells, and umbilical cord stem cells.

Amniotic Fluid: Amniotic fluid stem cells are obtained from the amniotic fluid by amniocentesis (which results in ~1 % chance of miscarriage) from 4th week onwards as the embryo is surrounded by the amniotic fluid at this point. The amniotic fluid is rich fetal epithelial cells which have shown characteristics similar to MSCs. Having gained popularity as a potential tool for regenerative therapy, these cells are being widely cryopreserved.

Placenta: Stem cells care collected from the placenta at the end of pregnancy (terminal placenta). Stem cells isolated from the amnion and placental villi show characteristics of both MSC and HSC progenitors. Placental blood is also a rich reservoir of stem cells. Placental stem cells do not divide indefinitely in vitro. Currently, clinical trials are being conducted to determine its use for therapy in limb ischemia.

Umbilical Cord: Umbilical cord blood collected from the umbilical cord after childbirth is rich in stem cells and has use in treating hematopoietic system disorders. However, due to the limited yield of cord blood stem cells and their limited expansibility, it is quite difficult to treat anyone above the age range of 5–7 years. As a result,

private cord blood stem cell banks are also preserving placental blood along with cord blood to increase the quantity of stem cells. Recent research has shown Wharton's jelly (present within the umbilical cord and composed of mucopolysaccharides) to house fibroblasts and macrophages. These fibroblasts have been implicated to have stem cell potential.

Adult Stem Cells (ASCs)

Adult stem cells are tissue-restricted undifferentiated cells that multiply by cell division to replenish dying cells and regenerate damaged tissues. For example, human epidermis gets renewed every 3–4 weeks. Adult stem cells can be multipotent or oligopotent or unipotent depending on its specificity. Although in vitro proliferation of these cells is very limited, researchers across the world are trying to figure out ways to stimulate these cells for differentiation into different cell types to be used for repairing tissue damage (regenerative therapy). ASCs can be easily isolated from bone marrow, adipose tissues, and peripheral blood. Clinical trials across the world are being conducted on ASCs with variable success.

Bone Marrow: The success story of bone marrow stem cells has been in the successful transplant of bone marrow in the treatment of hematopoietic disorders as it is the safest form of cell therapy. More recently, autologous bone marrow stem cells are being used to treat neurological disorders (e.g., multiple sclerosis, amyotrophic lateral sclerosis, Alzheimer's), arthritis, heart and eye disorders, muscular degeneration, diabetes mellitus types 1 and 2, etc.

Adipose Tissue: In comparison to other tissues, adipose tissues house more stem cells. Stem cell markers are expressed in ~ 50 % of nucleated nonfat cells extracted through liposuction. Although clinical trials are in progress, the major problem with adipose-derived stem cells is to extract sufficient quantity of cells for therapy; also, only ~2 % of infused cells get engrafted in organs (Ilic and Polak 2011).

Peripheral Blood: Peripheral blood stem cells (PBSCs) can be collected from peripheral circulation (requires mobilization with hematopoietic growth factors). PBSCs cells are now being increasingly used as a source of allogenic transplants in emergency cases. However, we still need a better understanding of immunological reactions (graft-versus-host disease or GVHD) in PBSC transplants (Cutler and Antin 2001).

List of Adult Stem Cells: Hematopoietic stem cell, bone marrow stromal cells (MSCs), neural stem cells, and epithelial stem cells (http://stemcells.nih.gov/staticresources/info/basics/StemCellBasics.pdf, page 11).

iPS Cells

In 2006, Shinya Yamanaka's team at Kyoto University, Japan, created the first iPS cell lines from mouse fibroblasts by introducing the following four factors: Oct 3/4, Sox2, c-myc, and Klf4. This was then followed up by human iPS cells in 2007. These cells have the ability to differentiate indefinitely in vitro with the capability of forming any mature human cell type and, therefore, can be used to dispel immunosuppressants completely in the case of patients receiving iPS cell treatment. Unfortunately, there are still a few doubts in the use of iPS cell with some of them being a safe delivery method for iPS cell precursors without severely affecting the genome, xeno-free culture condition, etc. (Ilic and Polak 2011).

Pathway of Stem Cell Activity

Stem Cell Niche

Stem cell niche are specific anatomical region within a particular tissue which houses the stem cell population. This site regulates tissue regeneration, repair, and maintenance and protects stem cell from depletion and the host tissue from overproliferation, thereby maintaining tissue physiology in organisms. It may be mentioned here that an abnormal niche activity can result in healthcare disorders, e.g., cancer. Understanding the "niche," therefore, is important to improve regenerative medicine.

Essentially there are three factors governing niche function and maintenance, namely, the extracellular matrix, paracrine factors, and metabolism. An example of the effect of extracellular matrix includes the expression of osteopontin (OPN), a matrix protein. OPN deficiency in animals shows an increased HSC number which is dependent on the stem cell microenvironment. Paracrine factors have been implicated in niche activity too, for example, unpaired (UPD) is produced by niche cells that regulate stem cell renewal through JAK–STAT signaling in drosophila testis. And lastly, an example of the effect of metabolism on stem cell niche is the site-active bone remodeling where there is a very high concentration of calcium levels which modulate osteoclast and osteoblast activity.

Finally, it may be said that a better understanding of the stem cell niche and its manipulation can aid regenerative therapy and can be used as a target site to treat cancer or at least limit the malignancy of cancer stem cells (Scadden 2006).

Stem Cell Mobilization and Homing

Migration of HSCs from the bone marrow into the blood is termed stem cell mobilization. Mobilization of HSCs is clinically carried out using granulocyte colony-stimulating factor (G-CSF) along with cyclophosphamide as stimulants. However, following mobilization HSCs home back to the bone marrow indicating stem cell release and the subsequent homing is a sequential process playing a vital part in animal/human physiology.

HSCs present within the bone marrow constantly produce high levels of lymphoid and myeloid blood cells (with limited life span) which are released into the circulating blood, while stem cells maintain their undifferentiated state. But a closer look suggests that a very small amount of quiescent progenitor cells are also released into the peripheral bloodstream. Out of the multiple theories suggested for HSC mobilization, one suggests that mobilization enables the constant repopulation of progenitor cells within the constantly changing bone ultrastructure (i.e., bone degradation and formation). Clinical or experimental mobilization of stem cells can be induced by cytokines such as G-CSF, GM-CSF, interleukin (IL)-7, IL-3, IL-12, and stem cell factor (SCF) and chemokines such as IL-8, Mip-1α, and Groβ and chemotherapeutic agents like cyclophosphamide and AMD1300 (Plerixafor). Stem cell mobilization followed by CD34+ isolation has become a major source of stem cell transplantation (Lapidot and Petit 2002).

HSC mobilization and homing are both regulated by the internetworking of cytokines, chemokines, and proteases. Mobilization of HSCs is mainly brought about by the loss of cell to cell contact (due to the downregulation of cell adhesion molecules) and desensitization of chemokines signaling, mainly the SDF-1/ CXCR4 axis. On the contrary, upregulation of cell adhesion molecules and activation of the chemokines signaling pathway (SDF-1/CXCR4 axis) are responsible for HSC/stem cell homing. Lastly, it may be said that a better understanding of all the involved signaling cascades is required for a better understanding of stem cell mobilization and homing (Suarez–Alvarez et al. 2012).

Stem Cell Differentiation and Plasticity

Classification of stem cells based on their differentiation potential has been mentioned earlier in this review (Ilic and Polak 2011). With regard to stem cell plasticity, it may be mentioned that initially it was believed that stem cells housed in a particular tissue could only differentiate into specific cell lines of that particular tissue type. For example, neural stem cells would only generate neural cells. Recent studies and experimental evidences have proven that embryonic and adult stem cells are more plastic than previously considered. For example, irradiated mice when injected with neural stem cells have shown reconstitution of hematopoiesis. Such examples have also been seen in drosophila when cells were transplanted between the imaginal disks (undifferentiated cells that form legs and wings in drosophila) and some transplanted cells acquired the

positional identity of the new location (Maves and Schubinger 1999) and also in humans where XY liver cells were seen in women receiving male hematopoietic stem cell transplants, suggesting hepatocyte generation from HSCs (Alison et al. 2000; Theise et al. 2000). Reasons implicated for such plasticity is transdifferentiation, where a differentiated cell takes on another differentiated phenotype or, alternatively, stem cells first differentiate into a common progenitor cell before redifferentiating into another distinct cell types. In conclusion it may be said that stem cells establish and maintain their differentiated state via epigenetic signals. Changes in their lineage are brought about not only by nuclear transfer or cell fusion but their immediate milieu and extracellular signals (Frisen 2002).

Neural Stem Cells as a Model for Stem Cell Development

It has been seen in mouse development that the spinal neural tube at day 8 (E8) of embryonic development consists of over 50 % stem cells and at day 10 (E10) of embryonic development the telencephalon contains 5–20 % stem cells. However, with further embryonic development, these stem cells start yielding progenitor and differentiated cells, and as a result, the stem cell pool is diluted. For example, there is a 40 % drop in stem cell concentration in the spinal neural tube at E12, and at postnatal day 1, the stem cell concentration drops to 1 %.

During development the body axis patterning occurs due to signaling systems that impart positional information. Thus, it may be said that signaling molecules can control the regional specificity of progenitor cell populations if progenitor cells respond differently to different concentrations of signals. In the case of the nervous system, the prominent patterning in anterior–posterior and dorsal–ventral axes occurs early accompanied with neural induction. In vertebrates the study of neurospheres isolated from different regions of the CNS shows region-specific markers, thereby indicating regional specificity of stem cells in early development. Similarly, basal forebrain stem cells when cultured show formation of neurons expressing high-concentration GABA (γ-amino butyric acid). Hence, vertebrate stem cells seem to be positionally specified.

Apart from positional information, stem cells are also guided by temporal information which is seen in progenitor cells during stage developmental changes, e.g., mid- or hindbrain progenitors are unable to differentiate in telencephalic progenitors after E13.5 in mouse. As developmental stages proceed, the neural crest stem cells produce fewer neurons as compared to early stage neural plate; additionally, the range of neurons generated by the late neural crest is also restricted.

With regard to signaling, it has been seen in mammals that during the different stages of development, stem cells react differently to signaling molecules. Signaling molecules like FGF, BMP, and Noggin have been implicated to influence neural stem cells from neural induction through adulthood, but stem cell response to these factors varies with stages. A similar example is seen in drosophila where transcription factors such as hunchback, Krüppel, castor, and grainyhead regulate production of different neurons at different times. Such mode of action could possibly be controlled by a cell-intrinsic timing mechanism.

Perhaps, just like in the nervous system, stem cell development in general is influenced by the accompaniment of environmental cues along with intrinsic timing mechanism (Temple 2001).

Stem Cell Engraftment

As discussed earlier in introduction section.

Model of Stem Cell Research

Drosophila Melanogaster

Earlier in this review it has been mentioned that the formation and maintenance of stem cells depends on its surrounding support cells along with extracellular secretions. However, studies

in drosophila have shown new niches that lack a stable population of support cells (Pearson et al. 2009).

Drosophila Germ Line Stem Cells (Model of Niche Regulation)

Germ line stem cells (GSCs) are retained by both drosophila sexes during most of their adult life. Although drosophila ovary and testis have different organizations, the arrangements of their respective GSC niches share architectural similarities. In the case of the ovarian niche, 2–3 female GSCs (fGSCs) are in constant contact with stromal hub cells, and in the case of testis, approximately 8 male GSCs (mGSCs) are in contact with stromal hub cells. Both cap and hub cells are implicated in forming the respective stem cell niches. Pearson et al. have stated that in drosophila, stromal stem cells form a stem cell-independent microenvironment mainly because of their organization, cell adhesion properties, and extracellular signal expressions. Thus, cells that are capable of responding to the niche environment because of their intrinsic mechanism are able to populate and self-renew. This phenomenon has been seen in both male and female drosophila GSC niches which includes the actual GSCs and the differentiating germ cells. This model has enabled researchers to outline the niche functionality in several species where stem cells are maintained in niches with similar properties (Pearson et al. 2009).

Drosophila Somatic Stem Cell Niche (Intestine and Ovaries)

Intestinal stem cells (ISCs) in drosophila midgut have been determined using genetic lineage markers. The ISCs associated with the basement membrane along with their daughter cells via armadillo-rich junctions. However, ISCs don't seem to be connected to any stromal cell types suggesting existence of self-renewing stem cells which are not characterized by stromal cells. It may also be noted that the differentiation of daughter cells depends on Notch signaling as is seen in neural stem cells suggesting intrinsic factors at play in ISC stem cell renewal.

In the case of the ovary, existence of stem cells in the ovary has been known for long. The ovary has been stated to have two types of somatic stem cells, namely, follicle stem cells (FSCs) and escort stem cells (ESCs). FSCs are present in the germarium (2 FSCs/germarium) that encapsulates the 16-cell germ cyst and plays a major role in determining the polarity of the developing oocyte. It was recently found (Buszczak et al. 2007) that FSCs like ISCs lack stable stromal cell contact, and FSC daughter cells displace other FSCs within the same germarium indicating that the microenvironment of each FSC might be a niche and the intrinsic factors expressed by the FSCs regulate their asymmetric division and extracellular environment. In further studies (Song et al. 2007), it has been stated that a number of signaling pathways may be involved in controlling FSC self-renewal and maintenance; however, these signaling molecules are produced by distant cells which are also associated with regulating the fGSC niche, suggesting that specialized support cells don't necessarily have to be in contact with their target stem cells to regulate the niche and its activity (Pearson et al. 2009).

Drosophila Neuroblasts

Drosophila neural stem cells, also called neuroblasts (NBs), have been implicated as stem cells without a niche. The NBs right from embryogenic stages through to larval stages give rise to an array of sensory tissues. Approximately 60 NBs divide to form two daughter cells, one of which is the larger, apical daughter which remains as NBs while the basal cell transforms into the ganglion mother cell (GMC) which then undergoes further division prior to differentiation.

NBs also have a strong association with the epithelial cells in order to maintain their proper polarity and/or cell division with regard to their neighboring cells, suggesting extrinsic cues have a hand in NB division. However, studies by Wei et al. 2011 have shown that in comparison to GSCs, NB self-renewal and GMC production are regulated by intrinsic factors involving polarity, the mitotic apparatus, and distribution of fate determinants, thus, suggesting NB self-renewal

and regulation are independent of the niche (Pearson et al. 2009).

Drosophila Hematopoietic Stem Cell Niche

Recent studies and publications have identified hematopoietic precursor (HP) cells in the embryonic and early larval stages which form hemolymph cells. The evolution of molecular markers has enabled scientists to identify and locate regions of the drosophila lymph gland where hematopoiesis occurs and is controlled by a group of cells known as the posterior signaling center (PSC). Similar to the ovarian GSC niche, the contact between PSCs and HP cells seems to be the most important factor in the maintenance of stem cells, thereby suggesting the probability of PSCs forming the stromal component of the niche (Pearson et al. 2009).

Multipotent Stem Cells in *Drosophila* Kidney

The drosophila renal organs also known as Malpighian tubules (MT) seem to contain proliferating stem cells in the proximal segment. Scientists using lineage tracking technique have managed to identify a small subpopulation of "small nuclear" cells in the proximal segment which are multipotent and are termed renal and nephric stem cells (RNSCs). These cells have been implicated in differentiating into renal cysts in the proximal segment and types 1 and 2 cells in the upper tubule segment. Also, strong JAK–STAT signaling plays a major role in specifying MT cell lineage, while the weaker JAK–STAT signal plays a role in the formation of RNSC daughter cells (renal blasts).

RNSCs therefore don't seem to have an organized niche system or associate with any cell type; rather, RNSC self-renewal seems to be regulated by JAK–STAT signaling. Nevertheless, scientists are studying this model further to determine if there are any intrinsic or other unidentified extrinsic cues which influence RNSC differentiation and self-renewal (Pearson et al. 2009).

Apart from niche-related studies, other studies in drosophila have shown stem cells to actively participate in maintaining the niche environment. This has been shown by the requirement of constant Notch signaling to form FCS to maintain stromal stem cells. In the absence of this signaling cascade, the stromal stem cells seem to disappear. Also, cell adhesion and the extracellular matrix (ECM) also play a major role in niche morphogenesis monitoring stem cell migration, rearrangement, and formation of structures, e.g., the epithelial sheet. DE-cadherin, β-catenin, and Gtpase to some extent play an important role in this regard (Pearson et al. 2009).

In conclusion it may be said that drosophila and drosophila stem cells act as a simple model which can be extrapolated to understand more complex animal or human models, and therefore, drosophila has immense significant value in the study of stem cells, their niche, and their mode of function.

Conclusion

Individuals suffering for lifelong threatening conditions are hoping for some cure or amelioration of symptoms through the use of stem cells as therapy. It is, therefore, the need of the hour for both scientists and physicians to understand stem cells in a way that will enable them to optimize the use of stem cells in treating complex ailments (Ilic and Polak 2011).

Effect of Lithium: A Trace Element on Stem Cells

Trace elements are important limiting factors in cell signaling and therefore of prime consideration as candidates for modulation of differentiation activity in the ultimate determination of cell fate. The following review summarizes for the reader salient features of important work done in the field using lithium which is also an important antidepressant.

I. In vivo administration of lithium carbonate (doses: 0.5–5.0 meq/L) demonstrates significant increase in:
   (a) Bone marrow CFUs
   (b) Bone marrow organ cellularity

(c) Peripheral blood WBC with maximum effect at day 4 post lithium injection at 1.0 meq/l concentration

Further increase in lithium concentration decreases the CFU level below normal (specially at 5 meq/l).

Gallicchio and his team concluded that lithium may modulate granulopoiesis by increasing the CFU stem cell compartment, thereby directly channeling differentiation into the granulopoietic pathway.

Under the influence of lithium, granulopoiesis is favored over erythropoiesis (Gallicchio and Chen 1980).

II. Referring to the above work, it has been suggested that lithium may enhance granulopoiesis in two different ways, either a direct action on stem cells or an inhibition of the suppressor cell that inhibits hematopoiesis (Barr and Galbraith 1983).

III. Apart from increased granulopoiesis, lithium has been used as a tool for osteogenic differentiation in animal models. High-throughput microarray profiling of lithium-stimulated human mesenchymal stem cells (MSCs) has shown high collagen 1 synthesis along with enhanced expression of Runx2, alkaline phosphatase, and bone sialoprotein.

Effects of lithium seen on MSCs are reduction in the rate of proliferation, increase in alkaline phosphates activity, and suppression of adipogenesis, osteoclastogenesis, and immune response genes.

It may therefore be concluded that MSCs when treated with lithium promote osteogenesis or osteogenic differentiation (Satija et al. 2013).

IV. More recently lithium has been implicated in effectively promoting induced pluripotent stem cell (iPSC) generation from both mouse embryonic fibroblasts and human umbilical vein endothelial cells (HUVEC).

By adding lithium chloride for a short period of time (day 3–8) during iPS cell formation, researchers have managed to obtain high-quality iPSCs with efficiency greater than 10 % in both four-factor and three-factor induced reprogramming of mouse embryonic fibroblasts and also increased two-factor OS- or one-factor OCT4-mediated reprogramming of HUVECs.

Furthermore, it has been reported that Li protects neurons from a variety of pro-apoptotic stimuli and facilitates neurite outgrowths and axonal remodeling which might help to restore neural functions in damaged sites (Wang et al. 2011).

Lithium may be used to check for altered stem cell proliferation and yield with special focus on MSCs (derived from various sources) when treated with Li chloride/carbonate. Additionally MEFs may be charged with lithium in combination with other factors to form feeder and iPSCs which can also be checked for differentiation into AE cell types.

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http://www.springer.com/978-81-322-2052-7

Perspectives in Regenerative Medicine

Ray Banerjee, E.

2014, XIX, 152 p. 79 illus., 44 illus. in color., Hardcover
ISBN: 978-81-322-2052-7