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Stem Cell a Novel Therapeutic Approach

Gaurav Kumar[1] *, Arvinder Singh Warraich[2]
[1]*Corresponding Author, Research Scholar, Potato Technology Centre, Karnal
[2] Research Scholar, ICAR-CSSRI Karnal

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ABSTRACT
Cells which have the potential to develop into many different types of cells in the body are known as stem cells. Stem cells act as a mother of all cells. Embryonic stem cells and adult stem cells are the two main sources of stem cells. Embryonic stem cells can come from the inner cell mass or embryo created through in vitro fertilization (IVF) and somatic cell nuclear transfer (SCNT). Stem cells are of different types like totipotent stem cells, pluripotent stem cells, multipotent stem cells, progenitor cells. In the body, Stem cells differ from other kinds of cells. Regardless of their source all stem cells have three general properties: they are unspecialized; they are capable of dividing and renewing themselves for long periods; and they can give rise to specialized cell types. This review also focuses on various factors responsible for regulatory mechanism of stem cell and different applications of stem cells like: hematopoietic stem cell therapy for autoimmune diseases, development of pancreas, gene therapy and stem cell approaches to the treatment of autoimmune diseases and future prospectation of stem cell. On- stem cell research continues to advance knowledge about how healthy cells replace damaged cells in adult organisms and how an organism develops from a single cell.

Key Words: Stem cells, IVF, SCNT, properties, applications

I. INTRODUCTION

On the behavior of the cells in the intact organism(in vivo), after transplantation in vivo or, under specific laboratory conditions (in vitro), many of the terms used to define stem cells often to a tissue that is different from the one from which the stem cells were derived. Because it has the potential to generate all the cells and tissues that make up an embryo and that support its development in utero, the example is fertilized egg said to be called as totipotent from the Latin totus, meaning entire. Until it produces a mature organism, the fertilized egg divides and differentiates. Humans known as adult mammals consist of more than 200 kinds of cells. These include nerve cells (neurons), muscle cells (myocytes), skin (epithelial) cells, blood cells (erythrocytes, monocytes, lymphocytes, etc.), bone cells (osteocytes), and cartilage cells (chondrocytes). For embryonic development, other cells which are essential but are not incorporated into the body of the embryo; include the placenta, umbilical cord, and extra embryonic tissues. From a single, totipotent cell—the zygote, or fertilized egg, all of these cells are generated. To describe stem cells most scientists use the term pluripotent that can give rise to cells derived from all three embryonic germ layers—mesoderm, endoderm, and ectoderm.

Properties of Stem Cell

In addition self-renewal, a number of properties and differentiation potential are frequently certified to stem cells, including the ability to undergo asymmetric cell divisions, exhibit extensive self-renewal capacity exist in a mitotically quiescent form, and clonally regenerate all of the different cell types that constitute the tissue in which they exist (Hall, PA, and Watt, FM 1989; Potten, CS, and Loeffler, M 1990).

Symmetric Versus Asymmetric Divisions

Stem cells are frequently thought to undergo repetitive, basically determined asymmetric cell divisions that produce one differentiated (progenitor) daughter and another daughter that is still a stem cell (Figure 1A). While there are clear examples of such lineages in Hirudo medicinalis, Drosophila melanogaster, and Caenorhabditis elegans, in mammalian systems, there is stronger evidence that stem cells divide symmetrically (Figures1B and 1C). The size of the stem cell pool to be regulated by factors that controls the probability of self-renewing versus differentiate divisions are allowed by symmetric division (Potten, CS, and Loeffler, M 1990).

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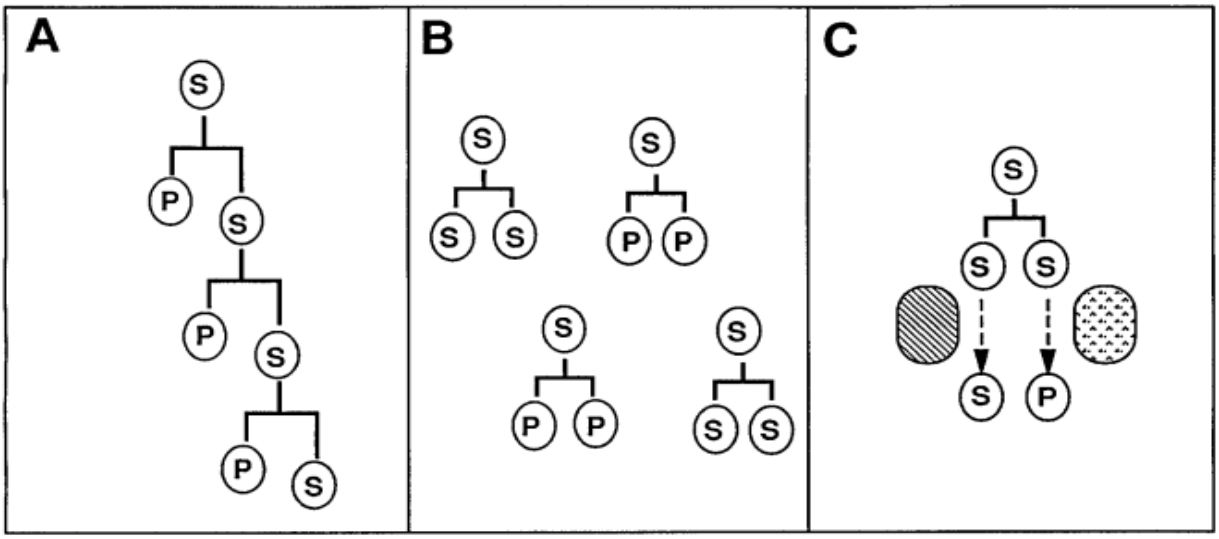
Figure1. In Stem Cell Lineages, possible Patterns of Cell Division "S" indicates stem cell; "P" indicates a committed or restricted (Sean J Morrison et al., 1997).



(A) In this figure all divisions are obligatorily non symmetric and controlled by a cell-intrinsic mechanism. Note that in this type of lineage no amplification of the size of the stem cell population is possible. (B) In this figure, a population of four stem cells is shown, during which all divisions are same, but half the time undergoes for self-renewing. The steady state behavior of this population is non distinguishable from that of a population of stem cells like that shown in (A). However, the probabilities could in principle be different than 0.5 for self-renewing versus differentiate divisions (Potten, CS, and Loeffler, M 1990). (C) A lineage in which individual stem cell divisions are asymmetric with respect to daughter cell fate, but not basically so, as in (A). Owing to different local environments (shaded ovals), the daughters behave differently. Samples of all of the patterns in (A)–(C) are found in nature, including combinations of (B) and (C).

Self-Renewal Capacity

Murine HSCs have limited self-renewal potential, while in case of mouse have a potential to self-renew for the lifetime (Morrison, SJ, and Weissman, IL 1994). In larger, longer-lived animals, such as humans, however it is not at all clear that HSCs self-renew for an entire lifespan; rather, successive subsets of stem cell clones may become activated with increasing age (Abkowitz, JL et al., 1990). Even in small, short-lived organisms, there is clear evidence that stem cells have life-time less than that of the entire animal. For example, after about 26 days one of the two somatic stem cells in the Drosphila ovary dies or differentiates (Margolis, J, and Spradling, A 1995). Therefore, not all stem cells have unlimited self-renewal potential. In tissues where serial transplantation of isolated cells is technically impossible, it is often difficult to judge the self-renewal capacity of putative stem cells in vivo. The simple existence of progenitor cells in an adult tissue is not in reality evidence that these cells have undergone extensive self-renewal, as is sometimes assumed, because they may simply have persisted in quiescent form. In case of fetal and embryonic HSCs, there are, moreover, clear cases of stem cells that exist only transiently during development. In males and females early in gestation, Oocyte production ceases by birth while that of sperm continues into adulthood, yet both cells derive from primordial germ cells (PGCs) whose stem cell properties are indistinguishable (Donovan, PJ 1994). Thus, not all stem cells self-renew into maturity, and not all adult stem cells reflect self-renewal of fetal cells. Adult stem cells in some cases, finally may derive neither by Self renewal nor by the persistence of fetal cells, but rather may represent a distinct stem cell class that develops from a transient fetal stem cell population (Morrison, SJ, and Weissman, IL 1994). This makes the entire concept of self-renewal capacity "for the lifetime of the organism" unsafe as a criterion for stem cells.

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Mitotic Quiescence

Not all but Another property shared by some, , stem cells is that they divide slowly or rarely. In the skin (Lavker et al., 1993) and bone marrow (Morrison, SJ, and Weissman, IL 1994) this is thought to be true for stem cells. More rapidly other kinds of stem cells divide, however. Somatic stem cells and mammalian intestinal crypt stem cells have been projected to divide every 12 hours (Potten, CS, and Loeffler, M 1990; Margolis, J, and Spradling, A 1995) in the Drosophila ovary. It could be normally true that in adult tissues, stem cells are more likely to cycle slowly, but this quiescence is not an essential property of stem cells.

Regenerative Capacity

The ability to redevelop clonally the entire adult tissue from which they were derive, meaning all cell types that comprise that tissue is the another characteristic attributed of stem cells (Potten, CS, and Loeffler, M 1990). This is an extremely difficult criterion to satisfy, in practice generally. For example, certain classes of blood cells, such as some kinds of T cells, even in the hematopoietic system are only produced during fetal life and are maintained in the adult by propagation of committed cells (Ikuta et al., 1990). Adult HSCs therefore can replace most, but not all, blood cells found in the adult tissue (Morrison, SJ, and Weissman, IL 1994). Neurons and sustentacular (glial) cells derive from the mature olfactory epithelium, but retroviral lineage analysis has shown that only the neurons are regenerated from stem cells in the basal layer (Caggiano et al., 1994). These examples demonstrate cases where stem cells redevelop only a subset of the differentiated cell types in a given tissue. All self-renewing pluripotent progenitors to be stem cells, reserving this category only for the subset with the “most ancient” characteristics are not considered by some authors. This results in a trend to hamper incrementally the stem cell explanation to smaller and smaller subsets of cells. The concept of a most ancient progenitor is inherently unclear because it often is based on largely untested expectations about the properties that correlate with primitiveness. If we are to be aware of the biology of self-renewal and pluripotency, then all self renewing pluripotent progenitors in a given tissue should be examined.

Different types of stem cells

Not all stem cells are the same. There are ranges in a stem cell’s capability to discriminate into a mixture of specialized cells. Into a greater variety of cells, some stem cells can discriminate than others. They are categorized by their range of flexibility, and there are four types of stem cells. They are categories as totipotent stem cells, pluripotent stem cells, multipotent stem cells, and progenitor stem cells into the widest variety of cells**,** Totipotent stem cells can differentiate. Because they contain all the genetic information required to create all the cells in the human body in addition to the placenta, which nourishes the human embryo in the womb, they are known as "master" cells of the body. During the first few divisions of a fertilized egg, human cells are only totipotent. The cells start to specialize, after three to four divisions of the totipotent cells. At this point, the cells become pluripotent. In the human body, Pluripotent stem cells can give rise to all the different cell types but they do not contain the genetic information to create a placenta. During its earliest stages, these stem cells are primarily found in the human embryo. Within a specific type of tissue or organ, Multipotent stem cells that can divide and grow into several differentiated cell types. For example, a sweat gland cell; however, it would not be able to grow into a nerve cell or any other kind of cell a multipotent skin stem cell could divide and grow into a hair follicle cell or heart cell. In the skin tissue, A multipotent skin stem cell could only divide and grow into the different types of cells found. Apart from the skin and bone marrow, these multipotent stem cells can be found in many places in the adult human body.

Different sources of stem cells

From different places diverse types of stem cells are derived or isolated. Researchers first identify or derived or extract the Pluripotent stem cells from the human embryo. Multipotent stem cells, which were isolated from adults are isolated and identify cell surface markers and functional markers that allows differentiation between stem cells and the other cells in the tissue, or by placing a cluster of cells in a medium that particularly supports stem cells. These processes are then followed by placing the pluripotent or multipotent stem cells into various cultures that will either cause the stem cells to differentiate or stimulate growth of the stem cell lines. The different types of stem cells are as follows: From the inner cell mass of a blastocyst-stage embryo, Embryonic stem (ES) cells which is pluripotent stem cells are derived. In an artificial environment, A blastocyst-stage embryo is a human embryo that has not been implanted into a uterus about five days after being fertilized. A blastocyst has two parts. Trophoblast, or outer cell ring is the first part. The outer cell ring

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is looks like a hollow ball and is prepared up of the specialized cells that would ultimately form a placenta if the embryo were implanted. Inside the outer cell ring is a weight of about 30 cells known as the inner cell mass. Researchers in 1998 at the University of Wisconsin first isolated and extracted the inner cell mass. Whilst many researchers notice the potential and flexibility of ES cells makes them especially important for research purposes, it is important to note that extracting the ES cells destroys the embryo. ES cells can come from embryos created with the somatic cell nuclear transfer (SCNT) procedure, but they could also come from embryos created via in vitro fertilization (IVF) procedures, otherwise called therapeutic cloning. In the SCNT procedure first removing the nucleus which has a genetic information, or DNA, of an adult, from a somatic cell (any cell found in the human body that is not an egg or sperm cell). Then into an enucleated oocyte, the somatic cell's nucleus is inserted. In the female body enucleated oocytes are the cells that develop into eggs from which the nucleus has been removed. The same procedure is used in reproductive cloning embryos from in vitro fertilization procedures. This has not yet been completed with human cells and no human embryo has as so far been produced using this procedure. In the SCNT procedure, the derived stem cells would be genetically similar to the cells of the adult who gave the somatic cell. This fact would make these stem cells, particularly valuable for medical therapies, because the organs and tissues can be cultivated from stem cells that are genetically identical to a person who requires an organ or tissue transplant. The problems of transplant rejection could be greatly reduced, or even eliminated, thus increasing chances for recovery. From an aborted human embryo/fetus, embryonic germ (EG) cells come. Into the reproductive cells (egg and sperm) of the human body these cells would have developed. From a five to nine week old aborted embryo or fetus, the EG cells is typically extracted and placed in a medium to produce EG stem cell lines just as is done in ES cell procedures. In 1998 at Johns Hopkins University the first derivation of stem cells isolated from aborted human embryos/fetuses occurred. These cells have more potential to differentiate into a wide variety of cells than they originally believed are found by researchers. In the human body of a particular tissue or organ, adult stem cells are pluripotent, multipotent, and progenitor stem cells found along with the differentiated cells. Adult stem cells found in the body are used to substitute and repair the tissue or organ in which they are found. For example, in the bone marrow the stem cells of the hematopoietic (blood and lymph) system are multipotent stem cells make red blood cells, blood clotting cells, and white blood cells.

Regulatory Mechanism of Stem Cell

For obtaining pluripotent stem cells without destroying human embryos Altered nuclear transfer (ANT) is one of several methods that have been suggested. ANT suggests to modify the nucleus of a somatic cell and/or the cytoplasm of an enucleated oocyte such that when these two are merged, they do not produce a zygote, beside they form a cell capable of producing pluripotent stem cells without disturbing an embryo.

How Does A Mouse Embryonic Stem Cell Stay Undifferentiated

As declared earlier, a true stem cell is capable of maintaining itself in a self-renewing, undifferentiated state for an indefinite period. Characterization of the undifferentiated condition of the embryonic stem cell by specific cell markers helped the scientists for better understand how embryonic stem cells—under the right culture conditions— replicate for hundreds of population doublings and do not differentiate. To date, two major areas of investigation have provided some hints. One hint includes attempts to be aware of the effects of secreted factors such as the cytokine leukemia inhibitory factor on mouse ES cells in vitro. The second hint includes study of involves transcription factors such as Oct-4. Oct-4 is a protein expressed by human ES cells and mouse in vitro, and also by mouse inner cell mass cells in vivo. The cell cycle of the ES also seems to play a role in differentiation preventing. From studies of these various signaling pathways, it is understandable that many factors must be balanced in an exacting way for ES cells to remain in a self-renewing state. If the balance changes, ES cells begin to differentiate.

Induction of Pluripotent Stem Cell from Adult Human Fibroblasts by Defined Factors

From the inner cell mass of mammalian blastocysts, embryonic stem (ES) cells are derived which have the ability to grow indefinitely while maintaining pluripotency (Evans, MJ, and Kaufman, MH 1981; Martin, GR 1981). These properties have led to expectations that human ES cells might be useful to screen effective and safe drugs, to treat patients of various diseases and injuries, such as juvenile diabetes and spinal cord injury and understand disease mechanisms (Thomson et al., 1998). Use of human embryos,

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however, faces ethical issues that prevent the applications of human ES cells. For their effective application like in case of patient- or disease-specific ES cells, it is difficult to generate. Induce pluripotent status in somatic cells by direct reprogramming is one of the ways to circumvent these issues (Yamanaka, S 2007). Through retrovirus- mediated transfection with four transcription factors, namely Oct3/4, Sox2, c-Myc, and Klf4, induced pluripotent stem (iPS) cells can be generated from mouse embryonic fibroblasts (MEF) and adult mouse tail-tip fibroblasts (Takahashi, K., and Yamanaka, S 2006). Mouse iPS cells are impossible to differentiate from ES cells in morphology, proliferation, gene expression, and teratoma formation. Furthermore, mouse iPS cells can give rise to adult chimeras, which are competent for germline transmission when it transplanted into blastocysts (Maherali et al., 2007; Okita et al., 2007; Wernig et al., 2007). The combination of a small number of factors is proof of principle that pluripotent stem cells can be generated from somatic cells.

Wnt signaling and stem cell control

To control over various types of stem cells, Wnt signaling has been implicated and may act as a niche factor to maintain stem cells in a self-renewing state. As current knowledge, Wnt proteins bind to receptors of the Frizzled and LRP families on the cell surface. The signal is transduced to ß-catenin, which then enters the nucleus and makes a complex with TCF to activate transcription of Wnt target genes during the numerous cytoplasmic trust components. Through tyrosine kinase receptors, Wnts can also signal, in particular the ROR and RYK receptors, leading to other modes of Wnt signaling. Wnt signals controlled themselves these ligands and receptors, which are energetically expressed, frequently transcriptionally by, to ensure the right balance between growth and differentiation during the growth of tissues. On a variety of stem cells, including neural, mammary and embryonic stem cells, isolated Wnt proteins play a active role on it. Wnt proteins act to maintain the undifferentiated state of stem cells, whilst other growth factors instruct the cells to grow in general. These other factors include FGF and EGF, signaling through tyrosine kinase pathways**.** Ideally however, the state of differentiation of stem cells is accomplished by supplying outside signals, extra-cellular factors, rather than genetic manipulation. In vivo, these signals and the micro-environment constitute a niche in which stem cells are present and compete for limiting concentrations of growth factors, thereby maintaining a balance between self-renewal and differentiation of the cells. The best candidate factors are the ones that regulate cell fate decisions in normal embryos and those include members of the BMP, Hedgehog, FGF and Wnt molecules, plus small molecules such as retinoic acid. In that group, the class of Wnt proteins stands out because of numerous functions during development. Indeed, Wnt signaling and Wnt proteins are important for the maintenance of stem cells of various lineages. In the digestive tract, the classic example is the crypt of the colon the loss of transcription factor TCF4 leads to depletion of stem cells (Korinek et al., 1998). In the hematopoietic system the Wnt pathway has also been implicated as a self-renewal signal Reya et al., 2003; Willert K et al., 2003). Gain of β-catenin activity or Loss of the tumor suppressor APC leads to excess of stem cells and cancer alternatively (Bienz M, Clevers H. 2000; Jamieson CH et al., 2004).

Wnt signaling and embryonic stem cells

Since the isolation of human ES cells, the use of ES cells as a regenerative tool has become closer to reality. But a problem to date is that most embryonic stem cells (mouse and human) are cultured in the presence of mouse embryonic fibroblasts (MEFs), serum and other animal products, which can introduce unwelcome pathogens into the ES cell culture. To be able to culture ES cells animal product-free, it is of critical importance to define all factors that maintain ES cells in an undifferentiated state. Although progress has been made toward culturing mouse and human ES cells, serum and feeder-free, leukemia inhibitor factor (LIF) and BMP4 for mouse and basic fibroblast growth factor only a few of the presumably many factors have been well defined, (Ludwig TE et al., 2006). Given its prominent role in adult stem cell systems, it is plausible that Wnt signaling plays a role in ES cell culture. There are many lines of evidence, mostly coming from mouse ES cell research there are many lines of evidence, mostly coming that Wnt signaling components are involved in ES cell control. For example, Pereira et al. showed that one of the genes required for ES cell self-renewal is TCF3, a Wnt controlled transcription factor, repressed nanog, (Pereira L, Yi F, Merrill BJ 2006). Furthermore, Jeanisch and co-workers have shown that over expression of another self renewing gene Oct-4 causes dysplastic lesions of progenitor cells and increased β-catenin transcriptional activity (Hochedlinger K et al., 2005). Other evidence includes that by activation of Wnt signaling which genetically eliminating the function of the negative

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regulator APC, promotes the undifferentiated phenotype of mouse ES cells (Kielman et al., 2002).

Niche-mediated control of human embryonic stem cell self-renewal and differentiation

In the spatial organization of human embryonic stem cell (hESC) cultures complexity creates diverse microenvironments (niches) that influence hESC fate. This study demonstrates that the rate and trajectory of hESC differentiation can be controlled by engineering hESC niche properties. The balance between differentiation inducing and inhibiting factors regulate by niche size and composition. Mechanistically, a niche size-dependent spatial gradient of Smad1 signaling is generated as a result of antagonistic interactions between hESCs and hESC has derived extra-embryonic endoderm (ExE). These interactions are mediated by the localized secretion of bone morphogenetic protein-2 (BMP2) by ExE and its antagonist, growth differentiation factor-3 (GDF3) by hESCs. Micropatterning of hESCs treated with small interfering (si) RNA against GDF3, BMP2 and Smad1, as well treatments with a Rho-associated kinase (ROCK) inhibitor demonstrate that independent control of Smad1 activation can rescue the colony size-dependent differentiation of hESCs. Our results illustrate, for the first time, a role for Smad1 in the integration of spatial information and in the niche-size-dependent control of hESC self-renewal and differentiation. Important regulators of hESC self-renewal have been emerged with one of the members of the transforming growth factor-beta (TGF-b) super-family, and the fibroblast growth factors (FGFs) (Rao BM, Zandstra PW 2005).The effect of TGF-b signaling is mediated by binding to cell surface type I and type II receptors with threonine/serine kinase activity. The type II receptor phosphorylates the type I receptor when ligand binding which in turn phosphorylates intracellular receptor-Smads (R-Smads) (Shi Y, Massague J 2003). Upon phosphorylation, the R-Smads associate with Smad4 and localize to the nucleus and activate transcription. Activin, nodal and TGF-b signal through type I receptors activin receptor-like kinases (ALKs) ALK4, ALK5 and ALK7 and the R-Smads, Smad2 and 3. The bone morphogenetic protein (BMP)/growth and differentiation factor (GDF) family signals through ALK1, ALK2, ALK3 and ALK6 and Smads 1, 5 and 8. Inhibitory-Smads (I-Smads), Smad6 and Smad7, negatively regulate TGF-b and BMP signaling by preventing R-Smads from binding to Smad4 or by forming stable interactions with the activated type I receptors.With active Smad2/3 signaling, maintenance of hESCs is mediated and the suppression of BMP signaling proceeding through Smads 1/5/8 (Besser D 2004; James D et al., 2005; Xu RH et al., 2005). For the differentiation of hESC to trophectodermal and primitive endodermal lineages high levels of phosphorylated Smad1 (pSmad1) have been associated (Xu RH et al., 2002; Pera MF et al., 2004).Various isoforms of the FGF family, consisting of at least 22 ligands, mediates its effects through four distinct cell-surface FGF receptors (FGFRs1–4) (Dailey et al., 2005; Eswarakumar VP et al., 2005; Mohammadi M et al., 2005). FGF binding to FGFR is stabilized by cell-surface heparan-sulfate proteoglycans (HSPGs) that act as low-affinity receptors for FGFs. Ligand binding induces dimerization of FGFR and initiates receptor tyrosine kinase activity and signaling through the Ras-mitogen-associated protein kinase (MAPK), phosphatidylinositol-3 (PI-3) kinase and phospholipase C-g PLC-g) pathways. For the culture of undifferentiated hESCs suggesting an important role for FGFs in the regulation of hESC fate exogenous FGF-2 is routinely used (Rao BM, Zandstra PW 2005). Despite the addition of exogenous factors that manipulate the activation of the FGF and TGF-b pathways, the local cellular microenvironment and hence the signaling inputs varies significantly in hESC maintenance cultures. In fact, it is likely that hESCs are exposed to a wide range of signaling environments by virtue of the properties of hESC colonies (size, distribution and culture condition-specific associated differentiated cells), and individual hESC position in a particular colony. For mouse ESC has been demonstrated by Davey RE, Zandstra PW (2006), hESC and their progeny interact to form supportive and nonsupportive microenvironments (‘niches’) that influence cell fate. For the maintenance of undifferentiated hESCs, the hESC-derived fibroblasts have been used as feeder layers indeed (Stojkovic P et al., 2005), demonstrating an interplay between hESCs and differentiated cells in culture Bendall SC et al., 2007).

Cell Shape, Cytoskeletal Tension, and RhoA Regulate Stem Cell Lineage Commitment

By many cues Commitment of stem cells to different lineages is regulated in the local tissue microenvironment. Here we demonstrate that cell shape regulates the promise of human mesenchymal stem cells (hMSCs) to adipocyte or osteoblast outcome. Human mesenchymal stem cells allowed to adhere, flatten, and spread underwent osteogenesis, while outspread, round

cells develop into adipocytes. By modulating endogenous RhoA activity, Cell shape regulated the switch in lineage commitment. Expressing dominant-negative RhoA committed hMSCs to become adipocytes, while continuously active RhoA caused osteogenesis. However, the adipogenesis or osteogenesis mediated by RhoA which was conditional on a round or spread shape, respectively, whilst continuous activation of the RhoA effector, ROCK, induced os-teogenesis independent of the cell shape. This RhoA-ROCK promise signal requisite actin-myosin generated tension. These studies exhibit that mechanical cues experienced in developmental and adult contexts, personified by cell shape, cytoskeletal tension, and RhoA signaling, are integral to the commitment of stem cell application.

Application of Stem Cell

Hematopoietic Stem Cell Therapy for Autoimmune Diseases

The current treatments for many autoimmune diseases include the systemic use of anti-inflammatory drugs and potent immunosuppressive and immune modulatory agents (i.e., steroids and inhibitor proteins that block the action of inflammatory cytokines). However, despite their profound effect on immune responses, these therapies are unable to induce clinically significant remissions in certain patients. In recent years, researchers have contemplated the use of stem cells to treat autoimmune disorders. Discussed here is some of the rationale for this approach, with a focus on experimental stem cell therapies for lupus, rheumatoid arthritis, and type 1 diabetes. The immune-mediated injury in autoimmune diseases can be organ-specific, such as type 1 diabetes, which is the consequence of the destruction of the pancreatic beta islet cells or multiple sclerosis which results from the breakdown of the myelin covering of nerves. These autoimmune diseases are amenable to treatments involving the repair or replacement of damaged or destroyed cells or tissue. In contrast, non-organ-specific autoimmune diseases, such as lupus, are characterized by widespread injury due to immune reactions against many different organs and tissues. One approach is being evaluated in early clinical trials of patients with poorly responsive, life threatening lupus. This is a severe disease affecting multiple organs in the body, including muscles, skin, joints, and kidneys as well as the brain and nerves. Over 239,000 Americans, of which more than 90 percent are women, suffer from lupus. In addition, lupus disproportionately afflicts African-American and Hispanic women. A major obstacle in the treatment of non-organ-specific autoimmune diseases such as lupus is the lack of a single specific target for the application of therapy. The objective of hematopoietic stem cell therapy for lupus is to destroy the mature, long-lived, and auto reactive immune cells and to generate a new, properly functioning immune system. In most of these trials, the patient's own stem cells have been used in a procedure known as autologous (from "one's self") hematopoietic stem cell transplantation. First, patients receive injections of a growth factor, which coaxes large numbers of hematopoietic stem cells to be released from the bone marrow into the blood stream. These cells are harvested from the blood, purified away from mature immune cells, and stored. After sufficient quantities of these cells are obtained, the patient undergoes a treatment of cytotoxic (cell-killing) drug and/or radiation therapy, which eliminates the mature immune cells. Then, the hematopoietic stem cells are returned to the patient via a blood transfusion into the circulation where they migrate to the bone marrow and begin to differentiate to become mature immune cells. The body's immune system is then restored. Nevertheless, the recovery phase, until the immune system is reconstituted represents a period of severely increased susceptibility to bacterial, fungal, and viral infection, making this a high-risk therapy. Recent reports advise that this replacement therapy may fundamentally change the patient's immune system. Richard Burt and his colleagues conducted a long-term follow-up (one to three years) of seven lupus patients who underwent this procedure and found that they remained free from active lupus and improved continuously after transplantation, without the need for immunosuppressive medications. One of the hallmarks of lupus is that during the natural progression of disease, the normally diverse repertoire of T cells become limited in the number of different antigens they recognize, suggesting that an increasing proportion of the patient's T cells are auto reactive. Burt and colleagues found that following hematopoietic stem cell transplantation, levels of T cell diversity were restored to those of healthy individuals. This finding provides evidence that stem cell replacement may be beneficial in reestablishing tolerance in T cells, thereby decreasing the likelihood of disease recurrence.

Development of the Pancreas

In the pancreatic ducts, during fetal development, novel endocrine cells appear to begin from progenitor cells. During fetal development, many researchers maintain that some variety of

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islet stem cell can be found intermingled with ductal cells and that these stem cells give rise to novel endocrine cells as the fetus develops. Ductal cells can be differentiated from endocrine cells by their structure and by the genes they express. For example, ductal cells normally express a gene known as cytokeratin-9(CK-9), which encodes a structural protein. On the other hand, beta islet cells, express a gene called PDX-1, which encodes a protein that initiates transcription of the insulin gene. These genes, known as cell markers, are useful in identifying particular cell types. Following birth and into maturity, the source of new islet cells is unclear, and some controversy exists over whether adult stem cells exist in the pancreas. Islet stem cell-like cells can be found in the pancreatic ducts and even in the islets themselves are considered by some researchers. Others maintain that the ductal cells can differentiate into islet precursor cells, while others hold that new islet cells originate from stem cells in the blood. Several methods for isolating and cultivating stem cells or islet precursor cells from fetal and adult pancreatic tissue are used by researchers. In addition, from embryonic stem cell lines, several new hopeful studies indicate that insulin-producing cells can be cultivated.

Gene Therapy and Stem Cell Approaches for the Treatment of Autoimmune Diseases

In most research protocols, DNA containing the therapeutic gene is transferred into cultured cells, and these cells are then administered to the animal or patient. At the site of the injection or in the circulation, DNA can also be injected directly. Under perfect conditions, the DNA is taken up by the cells and produce the therapeutic protein encoded by the gene. Currently, there is a wide amount of gene therapy research been conducted in animal models of autoimmune disease. The goal is to modify the aberrant, inflammatory immune response that is characteristic of autoimmune diseases (Prud'homme, GJ 2000; Tsokos, GC and Nepom, GT 2000).Researchers most often use one of two general strategies to change the immune system. Block the actions of an inflammatory cytokine (secreted by certain activated immune cells and inflamed tissues) by transferring a gene into cells that codes for a "decoy" receptor for that cytokine is the first strategy. A gene is transferred that encodes an anti-inflammatory cytokine, redirecting the auto inflammatory immune response to a more "tolerant" state is the second approach. By using these approaches in many animal studies, promising results were achieved and these studies give an advanced understanding about the disease processes and the particular inflammatory cytokines involved in disease progression (Prud'homme, GJ 2000; Tsokos, GC and Nepom, GT 2000). Serious problems with the development of effective gene therapies for humans remain, however. Foremost among these are the difficulty of consistently transfer genetic material into adult and slowly dividing cells (including hematopoietic stem cells) and of producing long-term expression of the intended protein at levels that can be tightly controlled in response to disease activity. Importantly, embryonic stem cells are significantly more permissive to gene transfer compared with adult cells, and embryonic cells continue protein expression during extensive self-renewal. Whether hematopoietic stem cells, other than adult-derived stem cells, are similarly amenable to gene transfer has not yet been determined. Ultimately, stem cell gene therapy should allow the development of new methods of immune modulation in autoimmune diseases. One example is the genetic modification of differentiated tissue cells or hematopoietic stem cells with a "decoy" receptor for the inflammatory cytokine interferon gamma to treat lupus. For example, gene transfer of the decoy receptor, through DNA injection, arrested disease growth in a lupus mouse model Lawson et al., 2000). Other investigators have used a related but different approach in a mouse model of type 1 diabetes. Interleukin-12 (IL-12), an inflammatory cytokine, plays a important role in the development of diabetes in these mice. The investigators transferred the gene which has the target of autoimmune injury in type 1 diabetes in the modified form of IL-12, which blocks the activity of the natural IL-12, into pancreatic beta islet cells. The onset of diabetes in these mice was prevented by the islet cell gene therapy (Yasuda et al., 1998).

Future Prospectation of Stem Cell

Turning on the Brain's Own Stem Cells as a Repair Mechanism

To spark the repair mechanisms already in a patient's brain to fix damage that these mechanisms could not otherwise manage by Parkinson's researchers. Because it holds promise, this strategy is less developed than cell implantation (Bjorklund, A and Lindvall, O 2000). From embryonic or adult sources, researchers may use stem cells, not to replace lost cells directly, but rather to turn on the body's own repair mechanisms in the future. On the other hand, researchers may find successful more effectively drug treatments which help a patient's own stem cells and repair mechanisms. Stem cells occur in two locations, the

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sub ventricular zone one of an area under fluid-filled spaces called ventricles in the adult primate brain. The other one is dentate gyrus of the hippocampus very few new neurons in primates normally appear in either place, which is why the process escaped notice until recently. When the brain is injured, stem cells in these two areas proliferate and migrate toward the site of the damage showed in the mid- 1990s by researchers. The researchers are now trying to discover how far this type of response can go toward ameliorating certain kinds of damage. For Parkinson's disease, recent research shows the direction that this may be heading. James Fallon et al., 2000) studied the effects of transforming growth factor alpha (TGF) on rat brain of a protein which is a natural peptide found in the body from the very earliest stages of embryonic development forward that is important in activating normal repair processes in more than a few organs, including liver and skin. The brain's normal repair process may never be adequately triggered in a slowly developing degenerative disease like Parkinson's and that providing more TGF can turn it on to suggest by Fallon's studies. Specifically, TGF injected into healthy rat brain causes stem cells in the sub ventricular zone to proliferate for several days, after which they disappear found by Fallon. A two things happen if the researchers make similar injections into rats in which they first damage the Nigro-striatal neurons with a toxin called 6-hydroxydopamine a regularly used animal model for Parkinson's Disease. Fallon observes what he calls a "wave of migration" of the stem cells to the damaged areas, where they differentiate into dopamine neurons after several days of cell growth. Mainly, the treated rats do not show the behavioral abnormalities related to the loss of the neurons. Till date the beneficial effect on symptoms is the result of the newly formed cells or some other tropic effect is however not clear (Fallon et al., 2000).

Stem Cell's Future Role in Spinal Cord Injury Repair

The aims of researchers are trying to respond against Parkinson's disease by regenerating damaged tissue. Due to a regenerative therapy Parkinson's is a relatively easy target need only replace one particular cell type in one part of the brain. Larger hurdles are faced against therapies for other disorders. After serious spinal cord injury, complete restoration, for example, is probably distant in the future, if it can ever be done at all. Including neurons many cell types are destroyed in these injuries that carry messages between the brain and the rest of the body. Getting to grow these neurons past an injury site and connect appropriately with their targets is extraordinarily difficult. Because spinal cord injury patients would advantage greatly from an even limited restoration of lost functions gaining partial use of a limb instead of none, or restoring bladder control, or being freed from pain. Such incomplete restoration of part of a patient's lost function is, for some less serious types of injury, possibly a more achievable goal. In many spinal injuries, the spinal cord is not actually cut and at least some of the signal-carrying neuronal axons are undamaged. Because the cells called oligodendrocytes, the surviving axons no longer carry messages, which make the axons' insulating myelin sheath, are lost. Learning to replace these lost myelin-producing cells have the first step recently made by the researchers (Raisman, G 2001). For example, stem cells can aid remyelination in rodents have shown by the researchers (Liu et al., 2000; Mcdonald et al., 1999). Specifically, they create that injection of mouse embryonic stem cells, oligo dendrocytes derived could remyelinate axons in chemically demyelinated rat spinal cord and the treated rats regained limited use of their hind limbs compared with the controls. They are not confident, however, whether the limited increase in function they observed in rats is actually due to the remyelination or an unidentified tropic effect of the treatment. Spinal injury researchers highlight that much more basic and preclinical research must be done before attempting human trials using stem cell therapies to repair the damaged nervous system. In spite of the fact that there is much basic work left to do and many fundamental questions still to be answered, researchers are hopeful that an effective repair for once unpromising nervous system damage may eventually be achieved. Whether through activating the body's own stem cells in vivo or developing replacement cells, investigate on the use of stem cells for nervous system disorders is a quickly advancing field. This research tries to gives to answer key questions about how to fix nervous system damage and how to restore key body functions damaged by disease or disability.

II. CONCLUSION

Stem cells are a subject of intense and increasing interest due to their biological properties and potential medical importance. In this review authors tried to give information about the regulatory mechanism of stem cell. A few salient points emerge. First, the pluripotent stem cell can derive through an altered nuclear transfer without destroying embryo. Second, two factors like cytokine leukemia inhibitory factor and Oct-4 are

responsible to stem cell remain undifferentiated. Third, it is now clear that by transduction of four defined transcription factors named as Oct3/4, Sox2, Klf4, and c-Myc which is a generation of induced pluripotent stem (iPS) cells, capable of germline transmission, from mouse somatic cells. Human embryonic stem (ES) cells were similar to human iPS cells in morphology, gene expression, epigenetic status of pluripotent cell-specific genes. Furthermore, these cells could differentiate into cell types of the three germ layers in vitro and in teratomas. These findings demonstrate that iPS cells can be generated from adult human fibroblasts. Through involvement of various factors Wnt signaling act as a niche factor maintain self renewing state of stem cell. Niche act as a indicator for stem cell differentiation.

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