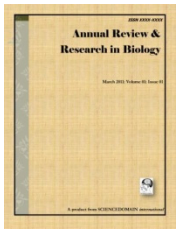

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Stem Cells and Regenerative Medicine – A Review

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Review Article

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ABSTRACT

Regenerative medicine is a multidisciplinary field concerned with the replacement, repair or restoration of injured tissues. This field emerged from the need for reconstruction in children and adults in whom tissue has been damaged by diseases, trauma and congenital anomalies. Stem cell research is a promising field with an alluring potential for therapeutic intervention, and thus begs a critical understanding of the long-term consequences of stem cell replacement. Stem cells have unrestricted potential to divide and this strength is used for the regeneration and repair of cells within the body during tissue damage. Research on stem cells is advancing knowledge about how an organism develops from a single cell and how healthy cells replace damaged cells in adult organisms. This promising area of science is also leading scientists to investigate the possibility of cell-based therapies to treat disease. In our present review we tried to provide the information about stem cells and their significant role in regenerative medicine for treatment of various diseases.

Keywords: Stem cells; embryonic stem cells; adult stem cells; stem cells treatment; regenerative medicine; stem cell therapy.

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CONTENTS

1. INTRODUCTION

Regenerative medicine is an emerging and rapidly evolving field of research and therapeutics to restore, maintain and improve body functions (Polak et al., 2008). Daar and Greenwood (2007) stated that regenerative medicine aims at 'repair, replacement or regeneration of cells, tissue or organs to restore impaired function'. It aids the body to form new functional tissue to replace lost or defective tissue. Ultimately, this will help to provide therapeutic treatment for conditions where current therapies are inadequate. Cell therapy and tissue engineering are part of the broader field of regenerative medicine, whose aim is the delivery of safe, effective and consistent therapies. The human body has an endogenous system of regeneration and repair through stem cells, where stem cells can be found almost in every type of tissue. This process is highly evolved through evolution, and so it is logical that restoration of function is best accomplished by these cells. Therefore, stem cells hold great promise for the future of translational medicine (NRC, 2002). Regenerative medicine is also a primer for pediatricians (Bajada et al., 2008; Julia and Polak, 2009; Vacanti, 2010; Longakar, 2010).

In the early 1900's European researchers realized that the various type of blood cells - white blood cells, red blood cells and platelets all came from a particular 'stem cell'. Stem cells were first studied by Becker et al. (1963), who injected bone marrow cells into irradiated mice and noticed that nodules developed in the spleens of the mice in proportion to the number of bone marrow cells injected. They concluded that each nodule arose from a single marrow cell. Later on, they found by evidence that these cells were capable of infinite self-renewal, a central characteristic of stem cells. Thus, stem cells by definition have two essential properties, i.e. the capacity of self renewal, and the capacity to differentiate into different cell lineages. Under the right conditions, or given the right signals, stem cells can give rise (differentiate) to the many different cell types that make up the organism (figure-1). Stem cell lineage determination is explained by several ideas, one among is focused on the stem cells microenvironment or 'niche'. A niche consists of signaling molecules, intercellular communication and the interaction between stem cells and their neighboring extracellular matrix. This three-dimensional microenvironment is thought to influence/control genes and properties that define 'stemness' of the stem cells, i.e. self-renewal or development to committed cells. An interesting theory put forward is that stem cells might be terminal differentiation cells with the potential to display diverse cell types, depending on the host niche. Adult stem cells that are implanted into a totally different niche (different germ layer) can potentially differentiate into cell types similar to those found in the new environment. The potential of stem cells and its plasticity are having invaluable properties for regenerative medicine (Singh and Williams, 2008). Beneficiaries of regenerative medicine include the increasingly ageing population, people with sports injuries and war casualties. The tremendous technological progress achieved during the last decade in gene transfer methods and imaging techniques, as well as recent increases in our knowledge of cell biology, have opened new horizons in the field of regenerative medicine. Genetically engineered cells are a tool for tissue engineering and regenerative medicine, albeit a tool whose development is fraught with difficulties (Sheyn et al., 2010; Voog and Jones, 2010). This review summarizes current knowledge of stem cells in regenerative medicine particularly in the treatment of various diseases.

1.1 Types of Stem Cells

There are two main types of stem cells, embryonic and non-embryonic. Embryonic stem cells (ESCs) are totipotent and, accordingly, they can differentiate into all three embryonic

germ layers. On the other hand, non-embryonic stem cells (non-ESCs), also known as adult stem cells, are just multipotent; their potential to differentiate into different cell types seems to be more limited (Lee and Hui, 2006). Embryonic stem cells are derived from the inner cell mass of a blastocyst (a very early embryo) and the adult stem cells are derived from mature tissue. A large variety of cell types have been used for regenerative medicine, including adult cells, resident tissue specific stem cells, bone marrow stem cells, embryonic stem cells (Guillott et a. 2007) and the recent breakthrough discovery of induced pluripotent stem cells from mature/adult cells (iPS) (Lensch. 2009).

1.1.1 Embryonic stem cells

Human embryonic stem cells (ES cells) are primitive (undifferentiated) cells that can self-renew or differentiate into all cell types found in adult human body (Edwards, 2004; Gardner, 2007; Bajada et al., 2008; Pelligrini and Luca, 2010). The derivation of mouse ES cells was first reported in 1981 (Evans and Kaufman, 1981; Martin, 1981) but it was not until 1998 that the derivations of human ES cell lines were first reported (Thomson et al., 1998). A new era in stem cell biology began in 1998 with the derivation of cells from human blastocysts and fetal tissue with the unique ability of differentiating into cells of all tissues in the body. Embryonic stem cells are derived from embryos at a developmental stage before the time that implantation would normally occur in the uterus. Each of the cells (blastomeres) of these cleavage-stage embryos is undifferentiated. The first differentiation event in humans occurs at approximately five days of development, when an outer layer of cells committed to becoming part of the placenta (trophectoderm) separates from the inner cell mass (ICM). The ICM cells have the potential to generate any cell type of the body, but after implantation, they are quickly depleted as they differentiate to other cell types with more limited developmental potential. The ICM derived cells can continue to proliferate and replicate them indefinitely and still maintain the developmental potential to form any cell type of the body (Figure 1).

Bongso et al. (1994) first described isolation and culture of cells of the inner cell mass of human blastocysts, and techniques for deriving and culturing stable hES cell lines were first reported in 1998 (Thomson et al., 1998). The trophectoderm was removed from 5^{th} day blastocysts consisting ICM of 30-34 cells, was placed into tissue culture. The possible sources of stem cells are embryos created via In vitro Fertilization (IVF) (Lanzendorf et al., 2001), embryos or fetuses obtained through elective abortion and embryos created via somatic cell nuclear transfer (SCNT) or cloning. They can be isolated by immunosurgery from the inner cell mass of the embryo during the blastocyst stage, and are usually grown on feeder layers consisting of mouse embryonic fibroblasts or human feeder cells (Richards et al., 2002). More recent reports have shown that these cells can be grown without the use of a feeder layer (Amit et al., 2003), and thus avoid the exposure of these human cells to mouse viruses and proteins. These cells have demonstrated longevity in culture by maintaining their undifferentiated state for at least 80 passages when grown using published protocols (Reubinoff et al., 2000; Bajada et al., 2008). The source of ESCs opens a Pandora's Box of ethical dilemmas, including the moral status of the embryo, the sanctity of life (Towns and Jones, 2004) and the possible use of saviour siblings as a source of ESCs. These add to the long-standing accusation to scientists of tampering with the natural process of life. The ethical debate relates to whether it is right to use human tissue in an abnormal manner. Life-saving situations where the strongest ethical arguments can be made to support the use of cells that are from an embryo that will not become an independent human life.

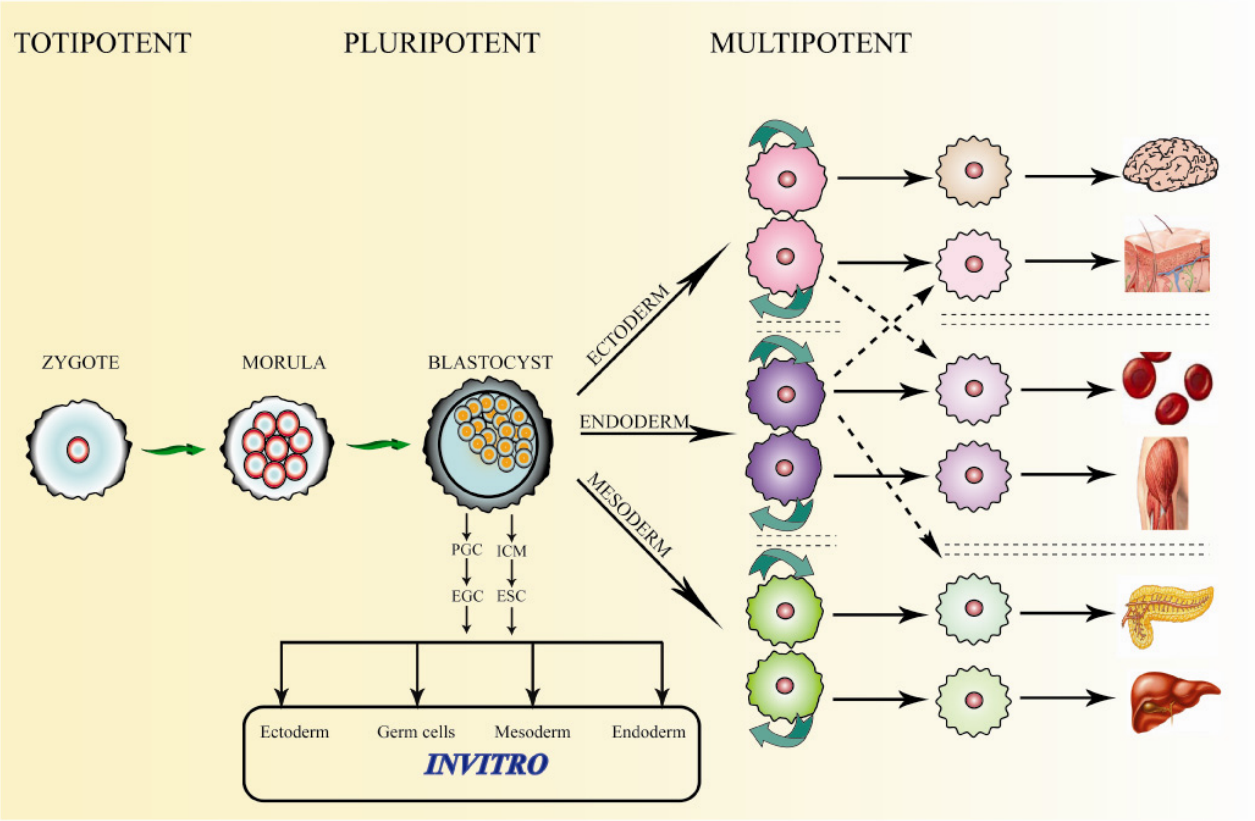

Fig. 1. General hierarchy for the stem cell niche

Zygote and early cell division stages (blastomeres) to the morula stage are defined as Totipotent. At the blastocyst stage, only the cells of the inner cell mass (ICM) retain the capacity (Pluripotent) to build up all three primary germ layers, the endoderm, mesoderm, and ectoderm as well as the primordial germ cells (PGC), the founder cells of male and female gametes. In adult tissues, multipotent stem and progenitor cells exist in tissues and organs to replace lost or injured cells. The dashed lines indicate the extent of possibilities of the adult stem cells may also be developing into cells of other lineage. Embryonic stem (ES) cells, derived from the ICM, have the developmental capacity to differentiate in vitro into cells of all somatic cell lineages as well as into male and female germ cells.

As non-ESCs use becomes more widespread, then acceptance of ESCs treatments may increase. When ethical obstacles are overcome, ESCs might be introduced for treating several conditions, including diabetes (Soria et al., 2000), spinal cord injuries (Hendricks et al., 2006) and liver (Duan et al., 2007) and heart transplantation (Kofidis et al., 2005). Recently Guenou et al. (2009) demonstrated that human embryonic stem cells (hESCs) can differentiate into mature keratinocytes able to generate a pluristratified epithelium on immunodeficient mice (Pelligrini and Luca, 2010). Jukes et al (2010) reviewed on chondrogenic and osteogenic differentiation of mouse and human embryonic stem cells (ESCs) and their potential in cartilage and bone tissue engineering.

Embryonic stem cells have been shown to differentiate into cells from all three embryonic germ layers *in vitro* (figure-1). Skin and neurons formed from ectodermal differentiation (Reubinoff et al., 2001; Schuldiner et al., 2001; Zhang et al., 2001; Adewumi et al., 2007), blood, cardiac cells, cartilage, endothelial cells, and muscle formed from mesodermal differentiation (Kaufman et al., 2001; Kehat et al., 2001; Levenberg et al., 2002) and pancreatic cells from endodermal differentiation (Assady et al., 2001). In addition, as further evidence of their pluripotency, embryonic stem cells can form embryoid bodies, the cell aggregations that contain all three embryonic germ layers, while in culture, and can form teratomas *in vivo* (Itskovitz-Eldor et al., 2000; Knoepler, 2009).

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1.1.1.1 Human embryonic germ cells

Embryonic germ cells are derived from primordial germ line cells in early fetal tissue. Unlike embryonic stem cells, animal experiments on embryonic germ cells have been limited. In 1998 the isolation, culture, and partial characterization of germ cells derived from the gonadal ridge of human tissue obtained from abort uses were reported (Shamblott et al., 1998). There are fewer data from animal embryonic germ cell experiments than from ES cell experiments, but it is generally assumed that the range of potential fates will be relatively limited compared to ES cells, because the embryonic germ cells are much further along in development (5-9 weeks). Fetal tissue may provide committed progenitors, but the feasibility of large scale sourcing and manufacturing of products utilizing such cells is questionable. Furthermore, the behavior of these cells *in vivo* is not well understood; significant research will be required to avoid unwanted outcomes, including ectopic tissue formation i.e., additional, unwanted tissue, tumor induction, or other abnormal development (Adewumi et al., 2007).

1.1.1.2 Amniotic epithelial cells

The latest addition to our repertoire of stem cells is amniotic fluid stem cells. The embryo is known to shed a variety of cells into the surrounding amniotic fluid during development. Amniotic epithelial cells (AECs) derived from the amniotic membrane in human placenta, also express the markers that are present on pluripotent ESCs and EGCs, such as Oct-4, Nanog, and alkaline phosphatase. They can also differentiate as ESCs and EGCs in the cell lineages from three germ layers, including pancreatic endocrine cells and hepatocytes (endoderm), cardiomyocytes (mesoderm), and neural cells (ectoderm) *in vitro* (Tamagawa et al., 2004; Miki et al., 2006; Nicol et al., 2007; De Coppi et al., 2007). Because of the observation that they proliferate at a high rate without apparent loss of pluripotency or teratogenic potential when transplanted in immunodeficient animals, amniotic fluid stem cells were credited with being a safer alternative to hESCs. Such claims, however, may be premature and these results must be independently verified, with further work required to

ascertain whether they really do have the same degree of pluripotency as hESCs (Abdelkrim et al., 2009).

1.1.2 Umbilical cord blood stem cells

In the late 1980s, umbilical cord blood (ucb) was recognized as an important clinical source of HSCS (Barker et al., 2003; Koh et al., 2004). Blood from the placenta and umbilical cord is a rich source of hematopoietic stem cells, and these cells are typically discarded with the afterbirth. Several approaches have been tested to overcome the cell dose issue, including, with some success, pooling of cord blood samples (Koh et al., 2004; Wagner et al., 2007; Harries et al., 2007; Abdelkrim et al., 2009). Cord blood stem cells have been in routine clinical practice for the past 20 years. The development of new therapeutic protocols in regenerative medicine requires the use of stem cells and umbilical cord blood is an important and readily available source of cells for these applications. The latest concepts in routine transplantation of cord blood are reviewed followed by the critical role of cord blood stem cells in regenerative medicine research and novel approaches using cord blood as a source of whole blood for transfusion (Seres and Hollands, 2010). cord blood stem cell technology has many advantages over embryonic and other adult stem cells for several reasons, including the following: (i) cord blood represents a potentially unlimited source of stem cells that can in theory be collected at every birth; (ii) cord blood is relatively simple to process and store using tried and tested technology and, once frozen in liquid nitrogen, is biologically stable; (iii) the collection of cord blood is a non-invasive procedure with no danger to either mother or baby. If cord blood is not collected, it is discarded as biological waste; and (iv) cord blood carries low risk of infection (Hollands, 2009).

1.1.3 Human adult stem cells

Stem cells that are found in developed tissue, regardless of the age of the organism at the time are referred to as adult stem cells. Adult stem cells encompass a variety of populations of undifferentiated cells and are found in most adult tissues, where they act as reservoirs during the normal turnover and regeneration of an organ or tissue. Both their potency and proliferative potential are typically narrower than those of their embryonic counterparts. Adult stem cells are hidden deep within organs, surrounded by millions of ordinary cells, and may help replenish some of the body's cells when needed. An adult stem cell is undifferentiated cells found among differentiated cells in many mammalian tissues contain stem cell populations that might self renew and generate somatic cells normally as well as mobilize, proliferate and differentiate. Until recently, it had been thought that a blood-forming cell in the bone marrow - which is called a hematopoietic stem cell, could not give rise to the cells of a very different tissue, such as nerve cells in the brain. Therefore, exploring the possibility of using adult stem cells for cell-based therapies has become a very active area of investigation by researchers. Rather, adult stem cells are defined by their functional properties: high proliferative potential, substantial self-renewal capacity and ability to differentiate into at least one type of mature functional progeny (Morrison et al., 1997; Weissman, 2002; Eckfeldt et al., 2005; Abdelkrim et al., 2009; Jones et al., 2010).

1.1.3.1 Hematopoietic stem cells

These cells discovery marked the beginning of modern day stem-cell research. Hematopoietic stem cells have characteristic morphologic appearances and cell-surface markers (Lagasse et al., 2000) that allow them to be labeled and tracked in the bloodstream and target tissues or to be isolated and cultured *in vitro* (Adewumi et al., 2007).

Haematopoietic stem cells represent less than 0.05% of the total bone marrow, but they have the potential to reconstitute all blood forming lineages. Because of the enormous clinical implications of such ability, the haematopoietic stem cell compartment has historically been the best characterized stem cell niche (Abdelkrim et al., 2009).

1.1.3.2 Mesenchymal stem cells

Mesenchymal stem cells (MSCs) are capable of self-renewal and differentiation into multiple cell lineages. MSCs are multipotent and are easily derived from a variety of tissues, including fat, skin and bone marrow. Presently, bone marrow is considered as a prime source of MSCs and also gingival (Tomar et al., 2010). These cells are fibroblastic in appearance and can be expanded for many passages. Most importantly, populations of mesenchymal stem cells (MSCs) are strongly adherent, therefore can be isolated by culturing marrow on an appropriate substrate and washing other cells off. Mesenchymal stem cells can give rise to many kinds of connective tissue cells including those responsible for remodeling of cartilage, bone, fat, and vascular tissue (Pittenger and Martin, 2004; Chen et al., 2008). MSCs are likely to participate in maintenance of the essential microenvironment necessary to support the hematopoietic stem cells in the bone marrow (Dennis and Caplan, 2004). MSCs can be isolated from circulating blood (Zvaifler et al., 2000), as well as from diverse nonhematopoietic tissues such as synovium (De Bari et al., 2001), adipose tissue (Zuk et al., 2001), trabecular bone (Noth et al., 2002), dermis (Young et al., 2001), dental pulp (Pierdomenico et al., 2005), and the lung (Sabatini et al., 2005). Although MSCs have been detected in the lung (Sabatini et al., 2005), their origin(s) remain unknown, and an evolving paradigm predicts that mesenchymal cells participating in lung repair derive from the bone marrow (Epperly et al., 2003; Fine, 2004; Hashimoto et al., 2004) and wound healing (Wu et al., 2007). Human adult mesenchymal stem cells (MSCs) are non-hematopoietic, adherent fibroblast-like cells with intrinsic ability of self-renewal and potential for multilineage differentiation. *In vitro* derived MSCs express a panel of characteristic surface markers such as Thy-1 (CD90), SH-2/endoglin (CD105), SH-3/4 (CD73), b-1-integrin (CD29), and CD44; and are negative for hematopoietic markers such as CD34, CD14, and CD45. MSCs differentiate *in vitro* primarily into the cells of mesenchyme lineage such as bone, cartilage, and adipose tissue (Chamberlain et al., 2007; Tomar et al., 2010).

1.1.3.3 Neural stem cells

Neural stem cells can be defined operationally as cells that can continuously self-renew and have the potential to generate intermediate and mature cells of both glial and neuronal lineages (Gage, 2000; Baizabal et al., 2003). Generally neuronal stem cells have been isolated from the brains of embryos and adults. Adult neural stem cells have the potential to differentiate into multiple cell types of the brain, mainly oligodendrocytes, astrocytes, and neurones, giving them a major therapeutic advantage over committed progenitor cells such as those used in transplants for Parkinson's disease. Moreover, these neural stem cells may be multipotent: when injected into blastocysts of mice they contributed to multiple types of tissues in the embryos (Clarke et al., 2000). One study reported the generation of blood from neuronal stem cells when transplanted into lethally irradiated recipients, but this has not yet been reproduced (Bjornson et al., 1999). These neuronal stem cells have also been observed to generate skeletal muscle when cultured with a cell line capable of differentiating into muscle or when injected into regenerating muscle (Galli et al., 2000). In brain-injury models neural stem cells (NSCs) proliferate in those neurogenic regions and are even able to migrate toward the site of damage. NSCs are multipotent and capable of self-renewing. *In*

vitro they cluster in ‘‘neurospheres,’’ which are able to differentiate into the 3 major neuroectodermal lineages (neurons, astrocytes, and oligodendrocytes) (Brignier and Gewirtz, 2010).

1.1.3.4 Pancreatic stem cells

The mammalian adult pancreas has three tissue types: the ductal tree, the exocrine acini, which produces digestive enzymes, and the endocrine islets of Langerhans, composed of insulin-producing β-cells, glucagon-producing α-cells, somatostatin-producing δ-cells, and pancreatic polypeptide-producing γ -cells. Moreover, the multipotent cell progenitors have also been identified within the ducts and islets in adult rodent and human pancreas (Seaberg et al., 2004, Bouwens et al., 2005). It has been reported that the multipotent PSCs isolated from the human fetal pancreas and expressing stem cell markers, such as nestin, ATP-binding cassette transporter (ABCG2), and KIT, as well as epidermal growth factor receptor (EGFR), hepatocyte growth factor receptor (c-Met), and glucagon-like peptide receptor were able to form the islet like cell clusters (ICCs) when cultured *ex vivo* (Suen et al., 2005). These ICCs can give rise to diverse pancreatic cell lineages, including insulin-secreting cells. Type 1 diabetes results from the autoimmune destruction of cells in pancreatic islets, and can be reversed by islet cell transplantation (Ma et al., 2008).

1.1.3.5 Skin stem cells

Numerous studies have revealed that the upper region of hair follicles, the bulge area, constitutes the principal niche of multipotent stem cells, which are responsible for the long-term growth of the hair follicles and epidermis regeneration after injury (Blanpain et al., 2004; Morris et al., 2004; Li and Xie, 2005; Rendl et al., 2005; Millar et al., 2005; Levy et al., 2005). More specifically, multipotent epithelial stem cells (bESCs) within the bulge area, which express CD34, K5, and α 6-integrin, are able to proliferate and give rise to the follicular epithelium, as well as to new cells constituting IFE and sebaceous glands after severe injury (Flores et al., 2005; Sarin et al., 2005). The bulge area in adult mammalian hair follicle also contains a pluripotent epidermal neural crest stem cell (eNCSC) population that shows several properties similar to embryonic neural crest stem cells (Sieber-Blum et al., 2004). The pluripotent eNCSCs in the bulge area are also able to self-renew and give rise to multiple cell lineages in vivo, including melanocytes, neurons, Schwann cells, smooth muscle cells, and chondrocytes (Sieber-Blum et al., 2004). It has been observed that each individual multipotent cell from melanoma spheres was able to differentiate, like eNCSCs under well-defined conditions, into multiple cell types, including melanocytes, adipocytes, osteocytes, and chondrocytes (Shihuan Kuang et al., 2007; Fang et al., 2005). The small clusters of multipotent stem cells, which express the specific markers, including K15, appear to reside near the basement membrane of the epidermis (Watt, 2002).

2. STEM CELLS VERSUS REGENERATIVE MEDICINE

Stem cells have the potential to create miracles. for the first time in history, it became possible for physicians to regenerate a damaged tissue with a new supply of healthy cells by drawing on the unique ability of stem cells to create many of the body’s specialized cell types. the prospect of exploiting stem cells more widely in regenerative medicine was encouraged by the development of human assisted conception and growing evidence that various adult cells retained greater versatility than had been suspected hitherto.

2.1 Embryonic Stem Cells in Regenerative Medicine

Although the term stem cells are often used in reference to repair cells within an adult organism, a more fundamental variety of stem cells is found in the early stage embryo. Similarly, there is now emerging evidence of benefit following transplantation of human embryonic stem cell derived neural progenitors and cardiomyocytes into animal models of parkinson's disease and myocardial injury respectively (Ben-hur et al., 2004: Kofidis et al., 2006; Singh and Williams, 2008; Liu et al., 2008). In the mouse, there is now proof of concept for the use of ES cell-derived tissues to treat models of diabetes (Serra et al., 2002), parkinson's disease (Frenck et al., 1998; Singh and Williams, 2008), myocardial infarction (Rufer et al., 1999), spinal injury (Reyes et al., 2001), and a severe genetic immune disorder (Abdelkrim et al., 2009). In as much as this type of experimentation with mouse ES cells has gotten under way in only the past 10 years, the progress is encouraging. For most cell types of interest, this is not yet really feasible, though in some areas (neural progenitors) pure populations of precursor cells may routinely be obtained from ES cultures, expanded in numbers, and differentiated into mature cells. For neurodegenerative diseases, it is better to transplant neural progenitor cells or fully mature neurons. conversely, recent evidence suggests that even in their undifferentiated state, human ESCS express discrete levels of HLA class I antigens that increase as the cells mature (Martin et al., 2005; Bajada et al., 2008). An interesting viewpoint has recently been proposed that irreversible arrest of cell division rather than the death of each and every cell correspond to the organism death of the embryo (Landry et al., 2004; Gardner, 2007). Embryonic stem (ES) cells are pluripotent cells that can give rise to derivatives of all three embryonic germ layers. Due to its characteristics, the patient-specific ES cells are of great potential for transplantation therapies. Considering future clinical use, the differentiation from ES to neurons, cardiomyocytes and many other types of cells provide basic cognition and experience to regenerative medicine (Ma et al., 2008).

2.2 Adult Stem Cells in Regenerative Medicine

Adult stem cell populations have been most thoroughly characterized in mouse and human bone marrow, where they continuously replenish the differentiated cells of the peripheral blood lost through attrition. From studies of the haematopoietic system it has been possible to define a stem cell as a cell with the capacity to self renew and to generate cells of multiple diverse lineage within the tissue in which the stem cell resides. The ability of the haematopoietic stem cells within bone marrow to give rise to all blood elements has been extensively exploited in the clinic for transplantation of bone marrow and stem cells. Recent reports suggest that some of these stem cells can differentiate outside of their tissue of origin. Both muscle and neural tissue appear to be a source of hematopoietic stem cells (Jackson et al., 1999; Galli et al., 2000; Ma et al., 2008), whereas bone marrow may house muscle precursor cells (Ferrari et al., 1998). Moreover, bone marrow stroma, which contains mesenchymal stem cells (Liechty et al., 2000; Abdelkrim et al., 2009), may also give rise to neurons and glia (Mezey et al., 2000; Woodbury et al., 2000; Ma et al., 2008). Indeed, the breadth of lineage capabilities for both the mesenchymal stem cells and hematopoietic stem cells of bone marrow are subjects of active study and lively debate (Liechty et al., 2000; Weissman, 2000; Gardner, 2007; Gorden, 2008; Bajada et al., 2008).

3. STEM CELL TREATMENT FOR MAJOR DISEASES

3.1 Stem Cells Therapy in Neurological Disorders

The mature central nervous system (CNS) has a limited capacity for self-repair; therefore many different cell-engineering strategies are used to regenerate damaged neurons. Stem cells will provide an inexhaustible source of neurons and glia for therapies aimed at cell replacement or neuroprotection in disorders affecting the brain and spinal cord. The most obvious and familiar application of stem cell research for nervous system disorders is through cell replacement therapy. The possibility of using stem cells as a source of neurons that can be implanted to replace cells and circuits lost in Parkinson's disease, amyotrophic lateral sclerosis (ALS), Huntington's disease, or Alzheimer's disease is an exciting prospect (Baizabal et al., 2003; Singh and Williams, 2008; Ma et al., 2008; Sheyn et al., 2010). Vawda et al. (2007) review potential sources of cellular replacements, including embryonic stem cells, fetal and neonatal neural stem cells and a variety of mesenchymal stem cells. They also reviewed published studies to illustrate where stem cell therapies have been evaluated for therapeutic gain and discuss the hurdles that will need to be overcome to achieve therapeutic benefit. Overall, they concluded that children with paediatric brain injuries or inherited genetic disorders that affect the brain are worthy candidates for stem cell therapeutics. Neurodegenerative diseases are characterized by progressive and gradual irreversible loss of physiologically active neurons over a period of several years, ultimately leading to significant morbidity and mortality (Steiner et al., 2006). The two most common age-related neurodegenerative disorders are Parkinson's and Alzheimer's diseases.

3.1.1 Parkinson's disease (PD)

Parkinson's disease (PD) is a very common neurodegenerative disorder that affects more than 2% of the population over 65 years of age. PD is pathologically hallmarked by the presence of intraneuronal Levy bodies and a progressive neurodegeneration of dopaminergic neurons in the substantia nigra, resulting in depletion of striatal dopamine. This is clinically manifested in motor dysfunctions and rigidity, sometimes combined with rest tremor and postural changes (Fahn et al., 2003). Factors that support this notion include the knowledge of the specific cell type (DA neurons) needed to relieve the symptoms of the disease. It is thought that PD may be the first disease to be amenable to treatment using stem cell transplantation. The hope is that research on human ES cells may reveal methods for producing an infinite supply of dopamine neurons for transplant into patients and the isolation of human embryonic stem (hES) cells (Thomson, et al., 1998) has stimulated research aimed at the selective generation of specific cell types for regenerative medicine.

At NIH, Lee et al., (2006) have used a progressive expansion, selection, and differentiation strategy to convert mouse ES cells to a mixed population of mature neurons in tissue culture with up to 30% having the characteristics of dopamine cells. Using different approach, Kawasaki et al., (2000) have generated dopamine neurons from mouse ES cells without embroid body formation. Clinical trials of the transplantation of human fetal dopaminergic neurons have shown that cell replacement can produce major, long-lasting improvement in some patients (Lindvall et al., 2004). So it is promising that cells with properties of dopaminergic neurons have been generated *in vitro* from stem cells of various sources, such as ES cells and stem cells isolated from bone marrow and fetal brain (Takagi et al., 2005). To make stem-cell therapy for PD, dopaminergic neurons with the characteristics of substantia nigra neurons must be produced in large numbers. Some patients will need implants in several areas of the brain (Piccini et al., 2005); optimum recovery will require a

tailor-made grafting procedure based on preoperative imaging. It will also be necessary to develop strategies that hinder disease progression. One possible approach to prevent the death of existing neurons could be to transplant human stem cells engineered to express neuroprotective molecules such as glial-cell-line-derived neurotrophic factor (GDNF) (Behrstock et al., 2006).

Regarding human stem cell therapy, scientists are developing a number of strategies for producing dopamine neurons from human stem cells in the laboratory for transplantation into humans with Parkinson's disease (Anderson and Lenz, 2006, Singh and Williams, 2008). To overcome the shortcomings of fetal/embryonic tissues as sources for neural grafts and invasive surgical procedures, embryonic stem cells (Ho and Li, 2006), neural stem cells derived from fetal or adult brain (Sanberg, 2007) and other tissue stem cells derived either from bone marrow or umbilical cord blood have been experimentally applied to generate dopaminergic neurons (Singh and Williams, 2008). Such cells will help to provide a clinically competent and effective therapeutic regime without the need for further interventions. Stem cells graft strategies are: *in vitro* pre-differentiation to dopaminergic neurons prior to transplantation; or *in vivo* differentiation of stem cells after implantation into the striatum or substantia nigra. The most important clinical issue is the ability to generate functional dopamine neurons and establish the role of other cell types, such as glial cells, present in the mesencephalic fetal grafts in the differentiation and function of these neurons. Site-specific integration in to the brain parenchyma is essential to replace dopamine in a physiologically natural fashion. This requires transplanting a cell population with a high percentage of live cells secreting a consistent and standard amount of dopamine that is capable of interlinking with the host cells to replace damaged neuronal circuitry without immune rejection. Importantly, the loss of a single phenotype of cells, together with the uniform pathology that characterizes Parkinson's disease, suggests treatment regimes based on the substitution of this single neuronal cell type. The successful generation of an unlimited supply of dopamine neurons could make neurotransplantation widely available for Parkinson's patients at some point in the future.

3.1.2 Alzheimer's disease (AD)

Alzheimer's disease (AD) is characterized by neuronal and synaptic loss throughout the brain, involving the basal forebrain cholinergic system, amygdala, hippocampus and several cortical areas. Patient's memory and cognitive performance is progressively impaired; they develop dementia; and are likely to die prematurely. Current therapies, such as treatment with acetyl cholinesterase inhibitors to enhance cholinergic function, give only partial and temporary alleviation of symptoms. The pathological changes seen in AD offer an extremely problematic situation for cell replacement. Given the widespread and progressive damage in the brains of patients with AD, it is unlikely that the mechanisms for instructing transplanted NS cells to differentiate into new neurons will be intact. In theory, transplanting cholinergic neurons generated from NS cells *in vitro* could prevent cognitive decline caused by the degeneration of basal forebrain cholinergic neurons. But to provide long-lasting symptomatic benefit, this approach would require the existence of intact target cells within the patient's brain, and these are highly likely to be damaged. However, because stem cells can be genetically modified and have migratory capacity after transplantation, they could be used for the delivery of factors that can modify the course of the disease. In support of this approach, basal forebrain grafts of fibroblasts that produce nerve growth factor (NGF)- which counteracts cholinergic neuronal death, stimulates cell function and improves memory in animal models have been of some benefit in patients with AD (Tuszynski et al., 2005). Cell-based treatment should therefore have the potency to differentiate into the three requisite

cell types, be capable of engraftment and survival as transplants, and cause axonal regeneration and directional synaptogenesis, thereby inducing simultaneous morphological and functional modulation of cells and the disease environment. The engrafted cells contribute to functional restoration by providing neurons for processing and transmitting signals, oligodendrocytes for remyelination and neurotrophic factors to defend the existing host cells (Singh and Williams, 2008).

3.2 Stem Cells in the Regeneration of Skeletal Muscle Cells

Muscle injuries and trauma are common phenomena and may result in diminished muscle function and structural deformation. Although muscle tissue has a regenerative ability, it is limited and decreases with the age of the patient; once muscle loses its ability to regenerate, the defect fills up with scar and adipose tissue. Muscle dystrophies are severe diseases and often lethal, as in the case of Duchenne muscular dystrophy (DMD). DMD is caused by the absence of a key protein, dystrophin, which causes chronic degeneration of the myofibers. Although extensive studies of this disease have been made, there is still no therapy that will prevent or halt the muscle deterioration. Muscle regeneration thus seems an attractive treatment (Jarvinen et al., 2007; Jukes et al., 2010; Sheyn et al., 2010). The capacity for this regenerative response is primarily due to a mononuclear cell population termed satellite cells. In 1961, Alexander Mauro utilized ultra structural techniques and identified the satellite cells as a rare cell population that is resident in adult skeletal muscle of the frog. The satellite cells either fuse to form multinucleated myotubes or re-establish a residual pool of quiescent satellite cells that have the capability of supporting additional rounds of regeneration (Shihuan Kuang et al., 2007; Fabien et al., 2007). Pulse-chase experiments have suggested that the satellite cell pool was heterogenous and promoted the notion that a pool of satellite cells maintained a residual pool consistent with a self-renewal mechanism (Schultz et al., 1996). More recent studies using cultured myofibers demonstrate that activated satellite cells principally differentiate and express MyoD family members. In contrast, activated satellite cells may exit the cell cycle, re-establish a quiescent state, and stimulated to reenter the cell cycle, suggesting that satellite cells are capable of self-renewal or replenishment of a residual pool of cells (Olguin and Olwin 2004; Zammit et al., 2004; Shihuan Kuang et al., 2007).

Collins et al. (2005) observed that the transplantation of one myofiber containing as few as seven satellite cells gave rise to >100 new myofibers containing >25,000 differentiated donor myonuclei. Importantly, these transplanted satellite cells gave rise to anatomically distinct satellite cells that participated in the repopulation of myofibers following a newly induced injury with a myotoxin. Further studies will unravel the mechanisms that direct the self-renewal process, define the proliferative capacity of the satellite cell population *in vivo*, and a hierarchical satellite cell cascade (Weismann et al., 2000). The satellite cell hierarchy will serve as a platform for cell-based therapies (Stephane et al., 2007). The development of tissue-specific scaffolds that can successfully imitate and support proper muscle tissue organization and allow muscle vascularization and innervation will clearly promote regeneration field (Rawlands et al, 2007; Fujita et al., 2009; Jukes et al., 2010). Finally, muscle dystrophies, such as DMD, affect the various muscles of the body in a multifocal manner, making it harder to treat damaged muscles with a local implantation method (Benchaouir et al., 2007). To address this challenge, intra-arterial and systemic cell-delivery techniques must be improved and understanding of the homing mechanism of stem cells must be increased.

3.3 Stem Cells in Cardiac Repair

Cardiovascular disease is a leading cause of death throughout the world. Globally each year, approximately 16.7 million people die of cardiovascular disease, accounting for 29% of all deaths in that time period (WHO, 2006; Sheyn et al., 2010). Restoration of cardiovascular function is the ultimate goal of stem-cell-based therapy. In principle, cardiovascular stem cells can improve cardiac function via *de novo* cardiomyogenesis, enhanced myocardial neovascularization and prevention of postinfarct remodeling. Stem cell transplantation to improve cardiac function has received mixed results in human clinical trials (Liu et al., 2008). Strategies to regenerate damaged cardiac tissue by cardiomyocyte transplantation may limit post infarction cardiac failure (Kofidis et al., 2005; Liu et al., 2008). Recent research is providing early evidence that adult and embryonic stem cells may be able to replace damaged heart muscle cells and establishes new blood vessels. Cardiomyocyte, the heart muscle cell that contract to eject the blood out of the heart's main pumping chamber (the ventricle). Two other cell types are important to a properly functioning heart are the vascular endothelial cell, which forms the inner lining of new blood vessels, and the smooth muscle cell, which forms the wall of blood vessels. The potential capability of both embryonic and adult stem cells to develop into these cell types in the damaged heart is now being explored as part of a strategy to restore heart function to people who have had heart attacks or have congestive heart failure (Figure 2). Various types of stem cells are using in cardiac therapy, which has been described below.

3.3.1 Embryonic stem cell

Human ES cell derived cardiomyocytes display structural and functional properties of early-stage cardiomyocytes that couple electrically with host cardiomyocytes when transplanted into normal myocardium (Kehat et al., 2004). In theory, infinite numbers of cardiomyocytes could be obtained from human ES cell clones. Human ES cells differentiate into spontaneously beating cells with a cardiomyocyte phenotype. When transplanted into infarcted myocardium, ES cell derived cardiomyocytes engraft and improve cardiac function in several rodent models (Yang et al., 2002; Min et al., 2002) (figure-2). In view of the risks associated with the broad differentiation potential of ESCs *in vivo*, only sporadic reports employed these cells in their uncommitted state to repair the damaged heart (Hodgson et al., 2004; Kofidis et al., 2004; Kofidis et al., 2005). The differentiation of ESCs into cardiomyocytes has been attributed to the paracrine effects of host signals, including members of the TGF-β superfamily of proteins (Behfar et al., 2002; Kofidis et al., 2005a).

Some degree of cardiomyogenic commitment was claimed to enhance engraftment of the cells into the myocardium, attenuate the probability of ESCs to acquire undesired cell lineages, and thereby reduce the risk of teratoma formation (Tzukerman et al., 2003). Although immature myocytes have been obtained from ESCs and their morphological, phenotypical, and functional properties characterized (Hess et al., 2003; Kehat et al., 2004), the residual growth potential of the committed cells was not established. There are no rigorous methodologies for ESC differentiation into cardiomyocytes *in vitro*. It is emblematic that eight distinct growth factors have forced ESCs to acquire only in part a specific cell phenotype while other undesired cells were consistently present in the preparations (Benvenisty, 2000).

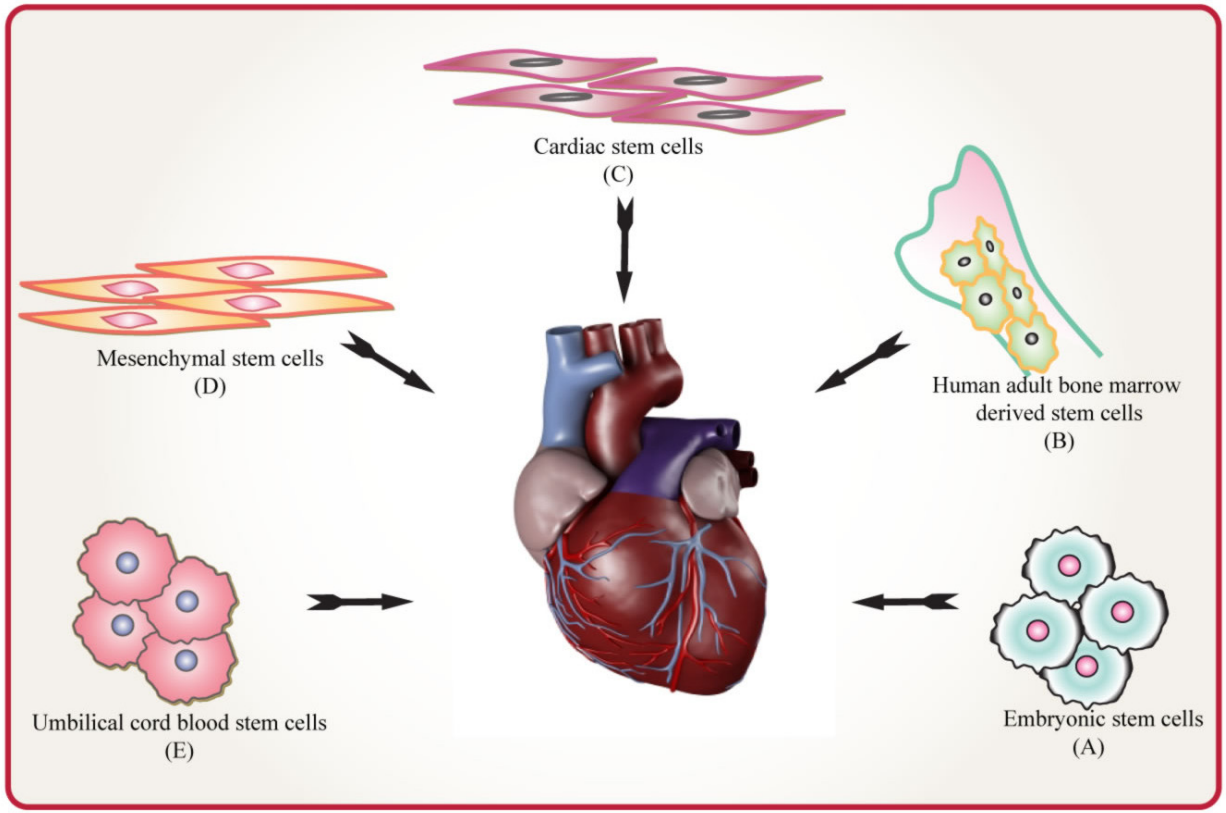

Fig. 2. Cardiac repair by different stem cells

(A): Embryonic stem cell generates the cardiomyocytes and improves cardiac function in infarcted heart. (B): Human adult bone marrow stem cells generate the myocytes, endothelial stem cells and smooth muscle cells in ischemic myocardium. (C): Cardiac stem cell forms the cardiocyetes and coronary vessels in the infarcted heart. (D): Mesenchymal stem cells (MSC) differentiate into cardiomyocytes and endothelial cells in vivo when transplanted to the injured heart and cured the infracted heart. (E): The umbilical cord blood stem cell homed to the infarcted hearts; it reduced infarct size, and enhanced neovascularization with capillary endothelial cells of human.

3.3.2 Human adult bone marrow–derived stem cells

Bone marrow elements contribute to cardiac repair in the infarcted heart served as the rationale for adult bone marrow cell therapy after myocardial infarction (MI). The main attraction of bone marrow-derived stem cell transplantation for scientists remains their innate plasticity. Proof of principal has been shown by trans-differentiating marrow stromal cells into cardiomyocytes *in vitro*. This has mainly been accomplished by treating cells with chemicals promoting DNA demethylation, such as 5-aza-deoxycytidine (Kuethe et al., 2004). Orlic and coworkers (2001) have shown that lineage-negative, c-kit–positive bone marrow–derived cells differentiate into new cardiomyocytes after MI. Murry and colleagues (2004) reported that lineage-negative, c-kit^{++} cells did not differentiate into cardiomyocytes. Despite the conflicting evidence regarding the ability of bone marrow derived cells to transdifferentiate, their efficacy in preventing remodeling has been demonstrated in many laboratories; therefore, clinical efficacy trials have progressed in parallel with ongoing mechanistic laboratory trials to determine the precise molecular mechanism by which these cells exert their beneficial effects.

In the past 5 years, bone marrow mononuclear cells (BMMNC) transplantation has become the most widely studied cell-based therapy for human applications. These experiments demonstrated the capacity of adult BMSCs to give rise to new myocytes, endothelial cells, and smooth muscle cells in ischemic myocardium. Moreover, in murine models of bone marrow stem cell (BMSC) therapy it is extremely difficult to assess the specific effects of myocyte versus nonmyocyte (e.g., endothelial cell) differentiation on the functional improvement in myocardial performance after injury. Therefore, we must be cautious in attributing benefit to a specific cell when the bone marrow contains cells of multiple lineage and phenotype, not to mention the host of potential regulatory factors released by these cells. Indeed, the whole concept of bone marrow hematopoietic stem cell (HSC) plasticity, at least recently, has been questioned by experiments that demonstrate that single labeled HSCs injected into lethally irradiated mice reconstitute peripheral blood leukocytes, but do not contribute appreciably to nonhematopoietic tissues (Wagers et al., 2002). Further information is also necessary on the homing and organ-specific differentiation signals required for various stem cells, and this includes characterization of integrin and other adhesion molecule structure/function relationships on these cells. This creates a conceptual hurdle and technical challenge when trying to assess the therapeutic potential of bone marrow stem cell therapy for human myocardial regeneration. For instance, without knowing the contribution, if any, of human bone marrow to cardiomyocyte formation in vivo, clinical trials of these cells seem premature. Currently, we do not have sufficiently specific bone marrow stem cell markers to allow study of stem cell activity in human hearts of nontransplanted subjects, an area that requires further investigation. However, it is likely that future intense efforts to characterize unique stem cell surface markers will make such analysis possible.

3.3.3 Cardiac stem cells

Several laboratories have recognized undifferentiated cells that are clonogenic, express stem and endothelial progenitor cell (EPC) antigens/markers, and appear to have the properties of adult cardiac stem cells in the adult heart of small and large mammals, including humans. These cells most likely mediate endogenous mechanisms for minor repair and for replacement of ongoing cell turnover within the adult heart. Cardiac progenitor cells are multipotent *in vitro* and give rise to cardiomyocytes and coronary vessels *in vivo* (figure-2), thus possessing the fundamental properties of stem cells (Beltrami et al., 2003; Oh et al.,

2003; Messina et al., 2004; Linke et al., 2005; Pfister et al., 2005; Tomita et al., 2005; Dawn et al., 2005). This discovery has provided the missing link between the documentation of small dividing myocytes (Anversa et al., 2006; Levy et al., 2005) and the uncertainty concerning the origin of these repopulating cells, and it has laid the groundwork for the possibility of introducing the use of these cells in the treatment of the failing human heart (Levy et al., 2005; Dawn et al., 2005). Messina and coworkers (2004) reported on the identification of cardiospheres, clusters of self-adherent cells that grew from cultured adult cardiac tissue derived from both human and murine hearts. These cells were shown to be clonogenic and capable of transdifferentiation *in vitro*, and they induced both myocardial and vascular regeneration after MI.

Cardiac stem cells can be harvested from patients and expanded *ex vivo* to generate large numbers of cells. A recent report by Urbanek et al. (2005) demonstrated that cardiac stem cells increase in number immediately after MI, but in the chronic phase, the numbers fall, and the remaining cardiac stem cells have less regenerative potential. To date, there are no clinical trials of human cardiac stem cells. However, Smith et al. (2005) demonstrated that cardiospheres could be grown from human endomyocardial biopsy specimens. These cardiospheres represent an easily accessible option for autologous stem cell therapy, making the possibility of clinical testing of this approach feasible. The Specialized Centers for Cell-Based Therapy initiative of the NHLBI has funded clinical trials of cardiac stem cells that should begin in the near future. Skeletal myoblasts or satellite cells are the reservoir of regenerative cells for skeletal muscle tissue; they have the ability for self-renewal and differentiation if muscle injury occurs (Kuethe et al., 2005). They have many desirable features as donor cells, including the ability to be amplified in an undifferentiated state *in vitro* and high resistance to tissue ischemia. A growing body of experimental data and initial clinical studies has shown not only engraftment of donor cells but also improvement in global cardiac pump function.

3.3.4 Mesenchymal stem cells

MSCs differentiate into cardiomyocytes and endothelial cells *in vivo* when transplanted to the heart in both noninsured and MI models (Mangi et al., 2003; Davani et al., 2003; Chen et al., 2008) (Figure-2). These results suggest that MSCs act by regenerating functionally effective, integrated cardiomyocytes and possibly new blood vessels. MSCs also have been injected into infarcted myocardium via catheter-based approach in pigs, resulting in regeneration of myocardium, reduced infarct size, and improved regional and global cardiac contractile function (Amado et al., 2005). Importantly, the latter study used allogeneic MSCs, which did not produce evidence of rejection, whereas autologous cell-based therapy poses no risk of rejection, an “off the shelf” allogeneic cell product would be much more cost effective and much easier to administer and could potentially allow delivery of greater numbers of cells than autologous cell therapy. As such, MSCs may allow allogeneic cell therapy while avoiding rejection (Sheyn et al., 2010).

3.3.5 Umbilical cord blood stem cells

Several populations of cells derived from UCB are the possible sources of stem cells for cardiac repair. Kogler and colleagues (2004) have described a population of cells from human UCB called unrestricted somatic stem cells. Human unrestricted somatic stem cells (Kim et al., 2005) when delivered by direct injection at thoracotomy in immunosuppressed pigs after MI, improved perfusion and wall motion, reduced infarct scar size, and enhanced global cardiac function. Ma et al. (2005) injected human mononuclear UCB cells, a small

fraction (1%) of which were $CD34^+$, intravenously 1 day after MI in NOD/scid mice. The cells homed to the infarcted hearts, reduced infarct size, and enhanced neovascularization with capillary endothelial cells of both human and mouse origin (Figure 2). Intramyocardial injections of MSCs are used to treat a variety of cardiovascular diseases as well as non-cardiovascular conditions (Seres and Hollands, 2010). The clinical success of cell therapy can be advanced if two seemingly unrelated tasks are undertaken: unification of clinical protocols and tweaking of gene modification to meet the specific disease at hand.

3.4 Stem Cells in Orthopedic Research

Despite the natural and physiological regenerative capacity of bone, large bone defects, such as those observed after bone tumor resection and severe fracture, lack a template for orchestrated regeneration and require bone grafting. Approximately 5–10% of all fractures are associated with impaired healing, resulting in significant patient morbidity, psychological stress, and economic cost to society. After bone injuries, several molecular mechanisms establish bone repair from stem/progenitor cells. Inflammation factors attract regenerative cells which expand and differentiate in order to build up a bone highly similar to that before injury. Bone marrow (BM) mesenchymal stem cells (MSCs) as skeletal stem cells and endothelial progenitors (EPCs) are at the origin of such reparation mechanisms (Deschaseaux et al., 2010). Novel developments in total joint arthroplasty and recent progress in understanding the plasticity of stem cells and in applying knowledge to the design of constructs to repair tissue are also described. The multidisciplinary approach to understanding the mechanisms of tissue degradation and the development of therapeutics for eliciting a reparative response is leading to the development of novel therapeutic strategies. Furthermore, exciting advances in the manufacture and characterization of scaffolds, combined with the emerging availability of multipotential stem cells, likely will lead to important advances in efforts to engineer replacement musculoskeletal tissues (Sheyn et al., 2010).

Several studies demonstrated the existence of cells (specifically, cells in tendon and ligament) with multilineage differentiation potential. Traditionally, it has been assumed that differentiated cells in tendon and ligament have a stable phenotype. Lee et al. (2006a) reported that cells derived from synovial fluid in knees with anterior cruciate ligament injury can differentiate into osteoblasts, adipocytes, and chondrocytes. Steiner et al. (2006) reported that cells derived from culture specimens of the anterior cruciate ligament obtained at the time of anterior cruciate ligament reconstructive surgery also have multilineage differentiation potential. In that study, the investigators were careful to remove the synovial covering over the torn anterior cruciate ligament in order to obtain anterior cruciate ligament cells; nonetheless, the possibility remains that synovial-derived cells had infiltrated the torn anterior cruciate ligament after injury. De Mos et al. (2006) reported that cells derived from human tendon also have multilineage differentiation potential, which may explain the findings of increased glycosaminoglycan deposition, calcifications, and lipid accumulation in degenerative tendon. Additional support for the potential of stem cells to improve meniscal healing was provided by a study involving the injection of synoviumderived stem cells labeled with green fluorescent protein into the knees of wild-type rats that had a full-thickness defect in the meniscus (Mizuno et al., 2006). The transplanted cells remained in the meniscal defect and promoted healing in comparison with untreated meniscal defects.

Bone regeneration is a complex biological process involving a well-coordinated interplay between different local or systemic soluble factors, extracellular matrix, MSCs and EPCs. While there is compelling evidence that *ex vivo* expanded MSCs can effectively repair critical

bone defects, this has not be proven as yet for native MSCs in either animal or human models, due to the lack of a consensus regarding their phenotypic properties, and also because convincing data about their perivascular anatomic location have only recently started to emerge. Likewise, although several studies have reported the important role of EPCs in bone healing, there is an ongoing controversy regarding the different populations isolated in mice and human beings in terms of their characteristics and their potential functional and/or phenotypic overlap (Deschaseaux et al., 2010). Therefore, although recent advances on the field favour the potential of MSCs and EPCs in bone regeneration considerable research needs still to be done to unravel the biology of these cells in bone turnover.

3.5 Stem Cell in Cancer Therapies

Several *in vitro* and *in vivo* studies carried out with variety of cancer cell line types and on different animal models to discover new therapeutic targets to block the growth and/or survival of the cancer cells. Stem cell transplantation may also constitute an option as adjuvant therapy for cancer, particularly in the patients receiving high doses of chemotherapeutic agents and/or radiation that, along with killing cancer cells cause the severe damage to normal tissues and/or destroy the hematopoietic cells. Thus, the stem cell transplants might replace the endogenous stem cells destroyed by high-dose cancer treatment, thereby producing healthy hematopoietic cell lineages and improving the immune system defense (Phatak et al., 2007; Knoepfler, 2009).

The autologous or allogeneic transplantation of UCB, and BM stem cells and their progenitors might be effectuated in combination with HDCT for numerous aggressive cancer forms to replace BM and blood-forming cells that have been destroyed by chemotherapy. AML and high-grade lymphoma are among the principal types of cancer that are usually treated with hematopoietic cell support as adjuvant therapy (Wang et al., 2005; Aoudjhane et al., 2005). The different subtypes of AML appear to result from distinct mutations at the level of HSCs, the appearance of which may give rise to primitive leukemic stem cells (LSCs) possessing a specific phenotype, such as CD90-, CD117-, and $CD123^+$ (Cui et al., 2003). These malignant LSCs are able to self-renew, might generate a heterogeneous AML cell population, thereby maintaining leukemic blasts (Wang et al., 2005; Hope et al., 2004). Interestingly, it is also proposed that the maintenance of LSCs in quiescent status might contribute to their survival after chemotherapeutic treatment and leukemia relapse (Senugupta et al 2007). Moreover, the *ex vivo* expansion of HSCs or the mobilization of HSCs from BM into the peripheral blood by using mobilizing agents such as G-CSF and AMD3100 might also lead to a great number of stem cells and their progenitors in bloodstream, thereby decreasing the recovery time after HDCT (De Clercq et al., 2005).

The differentiated HSC-derived progenitors, such as dendritic cells, which are among the most efficient cells of the immune system in presenting an antigen to helper/cytotoxic T lymphocytes, might also be used as adjuvant treatment in cancer immunotherapy to eliminate the neoplastic cells that express immunogenic antigens at their surface (Perillo et al., 2004; den Brok et al., 2005). Furthermore, UCB also contains a substantial amount of $CD16^-/CD56^+$ natural killer cells that might be expanded in the presence of IL-12 or IL-15 and that show a high rate of proliferation and cytotoxic effects against some cancers, particularly leukemia (Cohen et al., 2004). In addition, the chemoprotection against myelotoxicity induced by HDCT may also be counteracted by genetic manipulations in HSCs conferring to their progenitor's resistance to certain cytotoxic effects of drugs, such as the expression of MDR1.

3.6 Stem Cells in the Treatment of Diabetes

Type I diabetes represents a major disease entity that has tremendous appeal as a target for cell replacement therapy. Embryonic stem cells (ESCs) have been studied based on their multipotential capacity. It has been reported that insulin-producing cells could differentiate from murine (Soria et al., 2000; Lumelsky et al., 2001) and human ESCs *in vitro* (Assady et al., 2001; Segev et al., 2004). The regenerative property of ESCs has been further evidenced by the results that transplantation of ESC-derived cells normalized or ameliorated elevated blood glucose levels in diabetic mice (Soria et al., 2000; Hori et al., 2002; Blyszczuk et al., 2003). The generation of ES-derived insulin-producing pancreatic endocrine cells may be critical to the treatment of diabetes (Mfopou et al., 2007). This enabled lineage selection and maturation of insulin-expressing cells, upon transplantation, resulted in the normalization of glycemia in streptozotocin-induced diabetic mice (Soria et al., 2000). In contrast, the spontaneous differentiation of mES cells *in vitro* generated only a small fraction of cells (0.1%) with characteristics of insulin-producing β-like cells (Shiroi et al., 2002). The insulin-positive clusters, however, failed to normalize high blood glucose levels in transplantation experiments (Lumelsky et al., 2001). Rather than producing insulin themselves, most of the cells took up this hormone from the culture medium (Rajagopal et al., 2003; Singh and Williams, 2008).

By modifying the differentiation protocols and using genetically modified mES cells, two groups successfully generated insulin-producing cells (Blyszczuk et al., 2003; Leon-Quinto et al., 2004). Blyszczuk et al., (2003) showed that constitutive expression of the pancreatic developmental control gene Pax4 and histotypic differentiation were essential for the formation of insulin expressing cells, which were found to contain secretory granules typical of both embryonal and adult β-cells. Importantly, these cells coexpressed C-peptide and normalized blood glucose levels after transplantation into diabetic mice (Mfopou et al., 2007; Blyszczuk et al., 2004). Similarly, lineage selection using mES cells transfected with a plasmid containing the Nkx6.1 promoter upstream of a neomycin-resistance gene could be used to generate insulin-producing cells that normalized glycemia after transplantation into diabetic animals (Leon-Quinto et al., 2004). Also treatment of mES cells with a phosphoinositide 3-kinase (PI 3-K) inhibitor during terminal stages of differentiation generated ES cell progeny expressing various β-cell specific markers. Following engraftment into diabetic mice, these cells also improved the glycemic status and enhanced animal survival (Hori et al., 2002). Initial experiments with hES cells indicate that *in vitro* differentiation generates 1% insulin-secreting cells that show at least some characteristics of pancreatic endocrine cells (Assady et al., 2001). A modification of the differentiation protocol (Lumelsky et al., 2001, Rajagopal et al., 2003) allowed the generation of insulin producing clusters from hES cells (Segev et al., 2004), but further improvements are necessary for generating functional islet like cells. These reports are provocative, but much additional work remains to characterize the functional nature of the cells as glucose regulators, and to document adequate, regulated production of insulin, which in one case was some 50 - fold less than native β cells (Lumelsky et al., 2001). Indeed, some of these reports have been called into question by subsequent studies showing that apoptotic cells can take up insulin from the culture medium and give the illusion of producing insulin without actually doing so (Rajagopal et al., 2003).

Some difficulties in generating beta cells from ES cells may stem from attempts to apply factors characteristic of late pancreatic development to essentially very early-stage cells. Real clinical impact awaits the clear directed differentiation of appropriate cell populations. Since the end of the 20th century, bone marrow–derived cells have been reported to give

rise to endodermal-origin cells (Petersen et al., 1999; Krause et al., 2001). In the pancreatic tissue, several reports described the regeneration of bone marrow–derived pancreatic beta cells based on mouse syngeneic or allogeneic transplantation assay. Ianus et al., (2003) first suggested the contribution of bone marrow–derived cells to generate insulin-producing cells. Hess et al. (2003) further demonstrated the improvement of blood glucose levels following bone marrow transplantation using chemically induced diabetic mice. Although donor bone marrow–derived insulin-producing cells were present in the recipient mice, the authors suggested that the improved glucose levels in diabetic recipient mice were due to the regeneration of host-derived beta cells rather than that of donor bone marrow–derived insulin-producing cells as evidenced by increased numbers of BrdU-labeled green fluorescent protein (GFP) - insulin+ cells, not GFP+ insulin+ cells at 4–7 days after transplantation. Lanus et al. (2003) reported the donor (Ins2-Cre mice) bone marrow–derived insulin-producing cells in recipient (Rosa-lox-GFP mice) pancreatic tissue, which could likely be generated through a fusion-independent mechanism. On the other hand, bone marrow–derived stem cells contributed to the regeneration of other endodermal tissue–derived cells, such as hepatocytes, through cell fusion (Terada et al., 2002; Alvarez-Dolado et al., 2003). Regeneration of pancreatic tissue is a complex mission due to the complicated structure and function of the tissue. An enhanced understanding of the genes involved in pancreatic differentiation, better control of insulin levels, and successful transplantation of islet cells will dramatically improve the care of patients with diabetes.

4. FUTURE PROSPECTIVES

Studies of human ES cells have demonstrated an enormous potential for generating tissues of therapeutic value. Adult stem cells (ASC) can be coaxed into differentiated cells not normally associated with their “committed” state. The stimulation of endogenous stem cells is based on the possibility that self-repair could be induced or augmented by stimulating the patient’s own stem cells by administrating growth factors. Bone marrow cells, for example, can be mobilized by stem cell factor and granulocyte- colony stimulating factor. In the case of myocardial infarction, these mobilized cells seem to be home to an infarcted region to promote myocardial repair. It is currently unclear whether the activation process or the release of factors from activated stem cells is more important to this therapeutic approach. A recent study showed that transplantation of adult bone marrow-derived cells reduces hyperglycemia in diabetic mice by initiating endogenous pancreatic tissue regeneration. Engraftment of bone marrow-derived cells to ductal and an islet structure was accompanied by rapid proliferation of recipient pancreatic cells and neogenesis of insulin-producing cells of recipient origin. This strategy may represent a previously unrecognized means by which bone marrow derived cells can contribute to tissue restoration. Many potential endogenous stem cell sources (liver, brain, skin, heart, bone marrow, and intestine) are now recognized to be present in humans. Stimulation of endogenous sources of stem cells is currently only achievable from bone marrow. With the rapid advance of stem cell research, it is likely, however, that further advances will be made so that endogenous supplies can be mobilized to more readily repair and replace damaged tissues following injury. We still have many challenges ahead of us but researchers, clinicians, regulators and healthcare practitioners all recognise the immense potential of this nascent field and wish to provide solutions rather than hurdles. I hope one can look forward to many years of exciting research with immense clinical potentials and to be able to provide, in years to come, many solutions to unmet clinical needs.

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