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New Advances in Surgical Applications of Stem Cells

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ABSTRACT

This is a structured review article on the recent applications of stem cells in surgery and its potential to regenerate previously thought to be non-repairable damage and cure what was deemed to be non-curable. This study will discuss what is a stem cell, classic and updated definition and functions, the classifications, the different sources for each type of stem cells and current applications of stem cells including different applications for different subtypes, whether it has been started in vivo or still in the in vitro stage and possible future uses.

Keywords: Stem cells, recent applications of stem cells, stem cell review, stem cell classification.

INTRODUCTION

Stem cells are considered the parent cells whose main function is to maintain and replace the cells in the tissues where they exist such as blood, bone marrow, skin, muscle, brain, liver, and others. Stem cells have been classified into embryonic stem cells (ESCs) and adult stem cells (ASCs). Evans and Kaufman (1981), first reported isolation of ESCs and since then Stem cells research became a very hot topic. (Heino *et al.,* 2008) However, before application of stem cell biology, the development of advanced techniques need to be understood to control functions of micro environment signals, tracking and guidance methods of the transplanted stem cells. (Metcalf 2008) Stem cells with a unique capability to self-renew and differentiate are the origin of all multicellular organ-ism. They are categorized by this differentiation capacity (Potency). (Re-generative medicine glossary 2009) Totipotent stem cells can differentiate to almost all lineages of the three embryonic germ layers (ectoderm, mesoderm, and endoderm) as well as germ cells, but not to extra embryonic lineages. (Pai-Jiun Ho *et al.,* 2012).

A third category of stem cells, multipotent stem cells can differentiate into at least two cell types. Most adult stem cells (ASCs) and somatic stem cells fall into this category and are sometimes considered as progenitor cells for certain cell types like hematopoietic lymphoid progenitors. These cells can only differentiate a few lineage- specific cell types and can be rapidly depleted. (Pai-Jiun Ho *et al.,* 2012).

MATERIAL AND METHODS

This paper is to review the recent uses of stem cells and its potency to over-turn the future of medicine, the aim of this study was to discuss the importance in the current research in relation to different specialties. Literature search was done using search engines including Pubmed, Medline, Cochrane Library and Embase. Following keywords were used; stem cells, regenerate potential, *in-vitro* regeneration. Two authors independently reviewed and selected relevant studies and extracted the data. 11982 articles were identified. The duplications were re-moved, excluded non-related texts, exclusion criteria: articles not related to human biology, comparison studies and articles related to animal biology only. After screening 281 papers were identified. of which, most recent 81 papers were chosen, Meticulous review of papers with reference highlighted for each.

RESULTS AND DISSCUSSION

Current definition of Tissue Stem Cells:
The amended definition of tissue stem cells proposed by Markus Loeffler (2002) is Stem cells are potentially heterogeneous population of functionally undifferen-tiated cells, capable of homing to an appropriate growth environment, proliferation, production of a large number of differentiated progenies, self-renewing, self-maintaining, regenerating the functional tissue upon injury, flexibility and reversibility in the use of these options

Classification and sources:
Stem Cells can be classified into Embryonic type and Adult type. **Embryonic stem cells** with the fertilization of oocyte to zygote and 8-cell morula to the early embryo, all are examples of the totipotent cells. **Embryonic germ cells** Human embryonic germ cells (hEGCs) are derived from the primordial germ cells of the gonadal ridge of 5-9 week old foetus.

Foetal stem cells: These are found in the foetal organs. Or isolated from the aborted foetuses like Neural crest stem cells, foetal hematopoietic stem cells, and pancreatic islet progenitors. The rich sources of hematopoietic stem cells are Foetal blood, placenta and umbilical cord while foetal brain contains Foetal neural stem cells

Umbilical cord stem cells Umbilical cord blood contains circulating stem cells which is characterised by exceeding the frequency of bone marrow and produce large colonies in vitro. Matrix cells from the umbilical cord are also known to contain useful stem cells termed Wharton's jelly.

Adult stem cells Hematopoietic stem cells: (bone marrow and peripheral blood) The hematopoietic stem cells involved in the production and maintenance of blood stem cells and their proliferation / differentiation into the cells of peripheral blood are derived early in embryogenesis from mesoderm. These cells then become deposited in specific hematopoietic sites within the embryo such as the yolk sac, liver and bone marrow. (Stem Cell and Developmental Biology Writing Group's Report (2004)).

Mesenchymal stem cells (bone marrow stroma) Mesenchymal stem cells (MSCs) are present postnatally in the non-hematopoietic bone marrow stroma. They consist of reticular cells, adipocytes, osteogenic cells, smooth muscle cells, endothelial cells and macrophages. They can also be found in skin, fat and periosteum. MSCs are multipotent cells they can differentiate into cartilage, bone, muscle, ten-don, ligament and fat.

Gut stem cells The G.I.T epithelial lining shows continuous and rapid renewal throughout life that is maintained with populations of multipotent stem cells residing in distinct anatomic sites. **Liver stem cells** Mammals can potentially sur-vive surgical removal of at least 75% of the liver which can regenerate.

Bone and cartilage stem cells Mesenchymal Stem Cells in bone marrow can differentiate into bone and cartilage. However, in case of bone or cartilage injury,

bone has been found to contain both uncommitted stem cells as well as committed osteoprogenitor cells.

Epidermal stem cells (skin and hair) Keratinocyte is the most important cell type in the epidermis situated in the basal layer of the epi-dermis. Once these cells leave the bas-al layer, they undergo terminal differentiation into a highly specialized cell called a squame which either differentiates into hair shaft or the sebocyte that forms an outer skin layer between the environment and under-lying living skin cells. Epidermis also contains stem cells at the base of the hair follicle that allows for the re-growth of hair and skin cells.

Neuronal stem cells Nervous system is the organ with least regeneration potential. Continuous neurogenic turnover occurs in very limited areas of the central nervous system (CNS). The sub ventricular zone (SVZ) of the forebrain and the dental gyrus of the hippocampus both are considered reservoirs of new neural cells in adult mammals. In vivo, endogenous NSC can produce almost exclusively neurons, while a single NSC in vitro is competent to generate neurons, as well as astrocytes and oligodendrocytes.

Pancreatic stem cells Endocrine cells of the rat pancreatic islets of Langerhans, including insulin-producing beta-cells are re-ported to turnover every 40–50 days by apoptosis, proliferation and differentiation of new islet cells from pro-genitor epithelial cells located in the pancreatic ducts. rat and human pancreatic islets contained unrecognized cells that expressed the neural stem cell-specific marker nestin. These cells were distinct from ductal epithelium. However, it is not confirmed whether pancreas contains true stem cells. After isolation, these cells had extended proliferative capacity in vitro, could be cloned repeatedly and appeared to be multipotent

Eye stem cells In the adult mouse eye, Stem cells have been identified; Single pigmented ciliary margin cells were able to proliferate in vitro to form colonies of cells that can differentiate into retinal specific cell types (rod photoreceptors, bipolar neurons and Muller glia). The adult retinal stem cells were localised to the pigmentary ciliary margin.

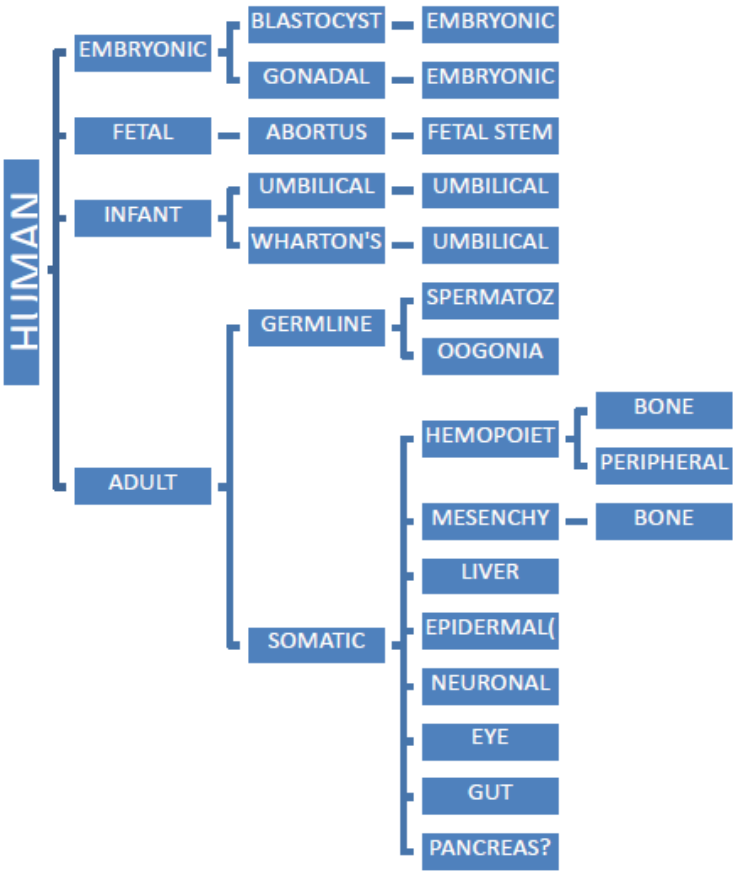

Fig. 1

Recent applications of stem cells in surgery

Although stem cells are known from a long time, the clinical application of stem cell transplantation began with the exposure of civilian populations to lethal doses of radiation in 1945. we will discuss both the applications of both human embryonic stem cells (hESCs) and adult stem cells (ASCs).

APPLICATION OF hESCs:

Neural Regeneration

Nervous system can be affected by accidental injury, inherited chronic disorders, or degeneration. Studies on Stem cells in treating neural disorder are based on the concept of cell re-placement of damaged cells to restore normal function. hESC differentiation to neural progenitors of the ectodermal lineage has been reported by many researchers. (Shin *et al.,* 2006) Nerve cells generated from these neural progenitor cells have been used in animals for the effective repair of stroke (Daadi *et al.,* 2008) and spinal cord injury. (Sharp *et al.,* 2010) hESCs have been reported to differentiate to neuroepithelial cells at a high efficiency. However, hESCs differentiation to mature neural cell types usually produce a mixed cell population, which can be controlled by the culture condition and addition-al treatment of growth factors (Shimada *et al.,* 2009) or small molecule compounds. (Li *et al.,* 2008)

In vivo models of spinal cord injury reported to be repaired by hESC differentiated oligodendrocytes, which can repro-duce myelin sheaths. (Hu *et al.,* 2009) hESC experimental therapies on neurodegenerative diseases such as Parkinson's Disease and Alzheimer's disease are also under investigation. Parkinson's disease is a degenerative disorder caused by the depletion of dopamine containing cells in the midbrain. hESC differentiated dopaminergic neurons which can secrete dopamine were derived for the possible treatment of Parkinson's disease in animal models. (Ben-Hur *et al.,* 2004, Friling *et al.,* 2009) It has also been considered for Alzheimer's disease, which is caused by loss of basal forebrain cholinergic neurons. Production of motor neurons from hESCs has been successful and used in ex vivo study of Alzheimer's disease (Bissonnette *et al.,* 2011).

The first clinical trial using hESCs ap-proved by the Food and Drug Administration (FDA) is for treatment of spinal cord injury patients. Oligodendrocyte progenitor cells from differentiated hESCs promote nerve growth and help repair the myelin sheaths of the injured nerves. (Strauss *et al.,* 2010).

Cardiovascular Repair

Prevalence of cardiovascular diseases is constantly increasing around the world, heart failure being the commonest cause of death in many countries. Other conditions include: coronary heart disease (CHD), congestive heart failure (CHF) and hypertension. The major cause of heart fail-ure is infarction of cardiomyocytes. Current treatments are for symptomatic relief and might decrease risk factors but are not curative; Stem cell therapy therefore is exceedingly at-tractive as it offers the curative possibility. After a successful trial of skeletal myoblast implantation in a patient with infarction for a heart fail-ure stem cells have been considered a treatment option for ischemic heart failure. hESCs are known to differentiate to myocytes which morphologically resemble cardiomyocytes display normal cardiomyocyte function and electrophysiological properties. (Pekkanen-Mattila *et al.,* 010, Xu *et al.,* 2008)

Hepatic Regeneration

Differentiation of hESCs to hepatocytes-like cell has been reported recently. Cells derived from hESCs have shown metabolic functions like normal hepatocytes. hESCs first differentiate to endodermal progenitor cells and then to hepatocytes. The procedure hence requires multiple culture medium in different stages and long periods of cultivation but is an evolving option. (Duan *et al.,* 2010, Lavon *et al.,* 2010, Touboul *et al.,* 2010).

Treatment of Diabetes

The concept of treating dia-betes with β-cell transplantation al-though seems a clinical possibility is very limited by the shortage of donors. The generation of insulin-secreting cells from hESCs has recently gained much interest in curing for diabetes (Bonner-Weir *et al.,* 2005, Sahu *et al.,* 2009). This process however, is quite complex as is often the case for differentiation of endodermal cell types. Recent evidence suggests differentiation of hESCs into insulin secreting cells by stepwise differentiation which might have a significant positive impact in future (Champeris Tsaniras *et al.,* 2010, Noguchi et al 2010, Van Hoof *et al.,*2009) Differentiation of hESCs towards mesenchymal Lineages Mesenchymal stem cells

(MSCs) are multipotent cells and they can differentiate into osteoblasts, adipocytes, chondrocytes and myocytes. First isolated from the bone marrow, MSCs can be used in a few orthopedic applications such as bone, tendon, articular cartilage, ligaments, and part of the bone marrow (Friedl *et al.,* 2009, Giannoni *et al.,* 2009). Adipocytes can also be differentiated from hESCs. Adipocytes are in the light for the research of lipid metabolism and obesity. (Hannan *et al.,* 2009) Hematopoietic Development (HSC) However, HSCs are rare and cell numbers decrease with age Thus, generation of hematopoietic progenitors from hESCs is still vital. (Bhatia *et al.,* 2007, Wang *et al.,* 2005) Erythrocytes are also derived from hESCs and can carry oxygen. (Ma *et al.,* 2008), hESCs can also generate macrophages (Odegaard *et al.,* 2007), megakaryocytes (Klimchenko *et al.,* 2009) and functional platelets. (Gaur *et al.,* 2006) Cancer Therapy Cancer is one of the major causes of morbidity and mortality in the world. Uncontrolled growth of cancer cells results in invasion and destruction of adjacent tissues. Current management of cancer include surgery, radiation and chemotherapy. It has been reported recently that cell-based therapies can be used to treat cancer cells. hESC-derived HSCs can differentiate to NK cells (Knorr *et al.,* 2010, Woll *et al.,* 2009), which can produce cytokines and perform antibodymediated or direct cell-mediated cytotoxicity on target cells. (Knorr *et al.,* 2010)

Additionally, dendritic cells, the professional antigen-presenting cell, have also been developed from hESCs and used to target cancer cells. (Sen-ju *et al.,* 2010, Su *et al.,* 2008)

Other Applications of hESCs: Drug Discovery and Toxicity Testing

Adult stem cells:

Adipogenesis Regeneration of fat cells

Osteogenesis Regenration of bone

Chondrogenesis Regeneration of cartilage

Cardiac repair and neovascularization Regeneration of cardiac muscles

Myogenesis Regenration of skeletal muscles

Hepatogenesis Regeneration of liver cells

Non-mesenchymal applications:

Neurogenesis Regeneration of nerves ad brain cells

Emerging applications

Immune modulation Potential cure for immune system dis-orders and auto immune diseases.

Gene therapy Emerging potential to modify genetic disorders

SUMMARY AND CONCLUSION

Stem cells are unspecialized (undifferentiated) cells that are characteristically of the same family type (lineage). They retain the ability to replicate and divide throughout life and give rise to highly specialized cells and take the place of cells that die or are lost. Cell-based tissue engineering for tissues repair and regeneration has emerged as promising feature for the future. SCs are still the major development stream for treatment; the studies showed that fetal derived embryonic stem cell applications have just started. In the future research studies, it will be important to find how to identify cell unique markers
and mapping lineage development. Based on the development of stem cell biology, MSCs will play an important role in clinical applications and tissue engineering. In the near future, the research direction would be expected to the application of adult stem cells for the human studies in phase I and phase II.

Basic and clinical research accomplished during the last few years on embryonic, fetal, amniotic, umbilical cord blood, and adult stem cells has revolutionized the regenerative medicine and cancer therapy by providing the possibility of generating multiple therapeutically useful cell types. These new cells could be used for treating numerous genetic and degenerative disorders namely age related functional defects, hematopoietic and immune system disorders, heart failures, chronic liver injuries, diabetes, Parkinson's and Alzheimer's diseases, arthritis, and muscular, skin, lung, eye, and digestive disorders as well as aggressive and recurrent cancers. There is an evidence to suggest that these could be successfully treated by stem cell-based therapies.

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