REVIEW ARTICLE

Stem Cells: Spatio-temporal Diversity and Therapeutic Applications

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ABSTRACT

Stem cells are cells of special kind with immense self-renewal and differentiation/trans-differentiation potential. Therefore, they are capable of providing various functional, structural and homeostatic supports to almost all kind of tissues and organs throughout the life. They are pervasive, and found to reside in almost all the organs, especially within the organ-specific anatomical niche so as to provide optimal access for better performance and tissue homeostasis as well as can be used as cellular backup, help repair damage and maintenance of concerned organs. These organ's in-built niches and microenvironments help maintain substantial repertoire of stem cells throughout life of multicellular organisms. These cellular repertoires of stem cells, however, decline with the age and deteriorating health status of an individual. Furthermore, meticulous research works of several decades have broadened and deepened our horizon of multidimensional understanding about the pervasive cellular intercourse observed between stem and non-stem cells at the cellular, molecular and biochemical levels. Stem cells have immense potential of intracellular, such as autocrine and intercellular, such as paracrine, communications, as well as communications with the genetically, structurally and functionally distinct cell types located somewhere else in the body. In this work, we have tried to throw light upon such a structurally and functionally kaleidoscopic cell entity, with special emphasis on their spatio-temporal diversity and therapeutic relevance in ever changing disease dynamics at molecular and cellular levels.

Keywords: Stem cells, anatomical niche, paracrine, autocrine, cellular intercourse, spatio-temporal diversity, therapeutic relevance.

INTRODUCTION

Stem cells are cells with self-renewal, differentiation and trans-differentiation potentials, reported to be present in specific microenvironment-rich anatomical spaces across the multiple tissues and organs with unique molecular and gene profiles. Unlike somatic cells, stem cells have huge biological potential in terms of functional and structural plasticities and supports that are contingent upon the cellular niches and need of the organs, in particular and body, in general (Ogawa *et al*., 2015).

Microenvironment is very crucial for the long term self-renewal, proliferation, differentiation, cellular interaction and survival of all types of stem cells (Polisetti *et al*., 2016). Stem cells can occupy multiple anatomical spaces, such as interlobular space, branching sites of capillary and blood vessels, close proximity to the bone-marrow interface, intercellular spaces, basement membrane, body fluid etc. Self-renewal is one of the cellular characteristics of stem cells which help them maintain their cellular repertoire throughout the life with little decline and attrition. These cells have multiple regulations on nearby cells as well as cells and tissues located quite far away through secretion of myriad of growth factors, chemokines and other regulatory molecules. Furthermore, they show concentration gradient-guided cell mobility in order to reach to damage area(s) in the body, secrete on-site damage-revival factors and, if needed, can differentiate themselves into specialized cells lost as result of damage. Stem cells also help differentiate the remaining uninjured and partially damaged cells at the damage site so as to alleviate the extent of damage to the maximum extent possible. Such aspects of stem cells have made them very promising and one of the emerging novel therapeutic candidates for cell-based therapy and other kind of therapeutic applications (Hashemi and Kalalinia 2015). Therapeutic applications of stem cells have helped transcend multiple limitations encountered in the field of modern drugs and medications. Therefore, stem cell-based therapy, unlike modern drugs, has minimal side-effect on the one hand and multifactorial curative effect on diseased/degenerated tissues and organs on the other.

ORGANS AND THEIR STEM CELLS

Stem cells reside in multiple organs of the body with varying abundance and distinct molecular, immunophenotypic and genetic profiles. Followings are the concise descriptions of various organ-specific stem cells along with their probable potential applications.

Bone marrow and bone marrow resident stem cells

Bone marrow (BM) consists of dynamic loose connective tissues with diverse somatic cell populations, such as adipocytes, osteocytes, various blood cells among others. Besides, it also contains different types of stem cell populations, including hematopoietic and non-haematopoietic stem cells. Bone marrow provides two types of cellular niches for growth and nourishment of the bone marrow resident cells of both stem and non-stem cell types. For instances, "endosteal or osteoblastic niche" which encompasses the inner surface, 2-3 cell diameters from the bone marrow interface (Xie *et al*. 2009). Such niche has been shown to be preferably homed by pre-labelled Hematopoietic Stem Cells (HSCs) following transplantation, indicating appropriateness for HSCs localization and habitation (Fujisaki *et al*., 2011). Osteoblasts, progenitor bone-making cells, secret several HSCs supporting and maintaining growth factors, cytokines, chemokines and cell adhesion molecules, whose absence leads to decrease in the HSCs repertoire. Hematopoietic stem cells produce various types of blood cells, including B and T lymphocytes. The second category of cellular niches in bone marrow is "vascular or peri-vascular or endothelial niche," juxtaposed to the bone marrow endothelial sinuses (Kiel *et al*., 2005). Endothelial cells (ECs) express cell adhesion molecules, including endothelial selectin (E-selectin), to which haematopoietic stem and progenitor cells (HSPCs) adhere. The E-selectin, constitutively expressed protein, not only helps in adherence but also induces HSC proliferation and chemosensitivity (Winkler *et al*., 2012) through extracellular matrix-induced signalling.
On the other hand, mesenchymal stem cells (MSCs) (Radtke, *et al*., 2013), multipotent adult progenitor cells (MAPCs) (Jacobs *et al*., 2013) and very small embryonic-like (VSEL) stem cells (Wojakowski *et al*., 2009) collectively constitute non-hemopoietic stem cell population in the bone marrow. Among them, MSCs, integral part of various bone marrow niches, are subset of fibroblast like cells, which bear spindle-shape morphology, and possess colony formation and multilineage differentiation potentials. Moreover, MSCs, irrespective of locations, are known to have multiple regulations on the companion resident cells. HSCs and MSCs work together with mutual interaction and regulations so as to maintain healthy status of bone marrow cellular and non-cellular components. Owing to functional diversity, HSCs, MSCs and other stem cell populations of bone marrow have been quite

attractive candidates for therapeutic implications and applications, and in fact, are being used in various pre-clinical and clinical trials across the world with varying success, and are likely to emerge as most promising therapeutic candidate of 21st Century.

Brain stem cells

Brain stem cells are located in the multiple neuro-anatomical locations in the brain of multicellular organisms. They have immense biological potential and distinct molecular profile with normal cell turnover under potentially dynamic physiological condition. Brain stem cells, also referred as neural progenitor/stem cells (NSCs), unlike the previous belief, have capability of brain regeneration by producing different neuronal and non-neuronal cells, such as neurons, oligodendrocytes, astrocytes etc. The process of stem-cell based/induced neurogenesis has been observed as one of the recent biological phenomena in several regions such as subventricular zone, dentate gyrus of the hippocampus (Patel and Sun., 2016), and is thought to be dependent on various factors, including, age, sex, path-physiological conditions, life style etc. The neural stem cells (NSCs) have brain repairing and regenerating capability either through secretion of proteinaceous factors such as Wnt3-a, triggering Wnt/β-catenin signaling pathway in hippocampal neurons/neurogenesis (Zhao *et al*., 2016) or directly differentiating into lost/damaged neuronal/non-neuronal cells. The perivascular niche (small blood vessels area) in human adult brain has been shown to be potential site for occurrence of stem cells, particularly mesenchymal stem cell, which can differentiate into neuroectodermal progeny. These cells showed two types of cell surface markers; CD13 and CD105 (mesenchymal cell type surface markers) and PDGFR-β (pericyte-specific marker). Though observed at several locations with varying cellular density and preponderance, branching sites of blood capillaries were found one of the most preferred locations (Ozen *et al*., 2012). Endogenous Stem cells in brain could help alleviate brain damage, including traumatic brain injury (TBI) with concurrent increase in neurocognitive functions and overall neuronal health (Patel and Sun., 2016).

Mouth (intraoral tissue, dental pulp, apical papilla, periodontal ligament)-derived stem cells

Researchers across the world have come up with different anatomical orofacial tissue-derived stem cells, including msenchymal stem cells. These orofacial tissues include apical papilla, dental pulp, gingival tissue, periodontal ligament, exfoliated deciduous teeth, and stem cells present in the orofacial tissues are given different names depending on their tissue-specific locations such as dental pulp stem cells (DPSCs), root apical papilla-derived stem cells from apical papilla (SCAP), periodontal ligament stem cells (PDLSCs), gingival mesenchymal stem cells (GMSCs), and stem cells from human exfoliated deciduous teeth (SHED) (Jiang *et al*., 2012; Akiyama *et al*., 2012; El-Sayed *et al*., 2015). The pulp tissue of permanent adult human teeth was first used to isolate DPSCs which were found to be capable of high proliferation rate and multi-lineage differentiation into adipocytes, osteoblast, and neuronal cells. On comparison, Stem cells from exfoliated deciduous teeth (SHED) showed higher proliferation rate compared to DPSCs. Furthermore, isolation and collection of SHEDs are easier, less invasive, and could be a desirable source for regeneration and therapeutic implication in the context of oral tissue regeneration. Stem cells, located in different anatomical intraoral tissues differ from each other in terms of abundance and various biological processes. For instance, SCAP reported to be around three-fold higher proliferations than those in the pulp in organ culture experiment. Stem cells of oral origin are being used for regenerative therapy, such as pulp-dentin regeneration (Cao *et al*., 2015) regenerative endodontics (Short., 2015), in context of teeth and craniofacial tissues reconstruction etc (Zhao and Chai., 2015).

Liver stem cells

The liver is one of the most important organs with metabolically diverse functions. It has amazing capability of regeneration throughout the life (Michalopoulos *et al*., 2007), and even after repeated hepatectomy major portion could be intrinsically restored. So where does this potential come from? This question has led researches in this direction, which attributes such potential to the resident progenitor stem cells. Hepatic stem cells, originally referred as alpha-fetoprotein (AFP) positive hepatobast are precursor to hepatoblast (Schmelzer *et al*., 2006). Liver stem cells could be cultured up to 100 population doublings; with 46 h average doubling time as well as they differentiates not only in liver cells but cells/tissues of various lineages. Liver stem cells, isolated from adult human livers showed myriad of markers similar to the hepatic and mesenchymal cells like AFP, CD29, CD73, CD44, CD90, vimentin, and nestin, CK8 and CK18 (Herrera *et al*., 2006). These cells are found to be highly proliferative and differentiation and trans-differentiation potentials which are being looked into for various therapeutic applications to find possible cure for various liver pathology and diseases (Yang *et al*., 2016).

Lung stem cells

Lung is one of the several non-hematopoietic organs, wherein presence and the types of stem cells are under lots of debate. However, several works have shown the presence of cells in the normal bronchial tissue from human and murine lungs, resembling MSCs phenotype, and under appropriate inducible conditions *in vitro* they could differentiate into cells of mesodermal lineage (Martin *et al*., 2008). Later, similar cells, following study, were isolated from bronchoalveolar fluid from human lung allografts. Bronchial tissue-derived stem cells predominantly showed expression of antigens similar to those present on ordinary adult tissue fibroblast, including vimentin, CD90, collagen prolyl 4-hydroxylase, and fibronectin. Human fetal lung has also shown presence of mesenchymal stem cells (Hua *et al*., 2009). Recently, MSCs isolated from human lung were shown to be able to differentiate into epithelial cells following *in vitro* treatment with retinoic acid (RA). Multiple other laboratories around the world have also differentiated lung resident stem cells, particularly MSCs, into multilineage cell types, including myofibroblasts, displayed paracrine anti-inflammatory properties, and T cell proliferation suppression (Jun *et al*., 2011). It is more likely that lung-resident stems cells, including MSCs are involved in the maintenance and repair of injured tissues and may be needed for various functions of lungs. There are also chances that any kind of alteration in these stem cell populations might lead to compromised pulmonary functioning as well as lung diseases, including chronic pulmonary pulmonary disease (COPD), resulting into significant morbidity and mortality. Further study of lung resident stem cells and their roles could be very important in context of lung biology as well as in understanding their underlying importance in lung diseases.

Heart stem cells

The heart, a muscular organ involved in continuous pumping of blood through the circulatory system to the entire body parts, mainly consists of cardiomyocytes (CMs), endothelial cells (ECs), and smooth muscles cells (SMCs) (Martin-Puig *et al*., 2008). Study has shown that during embryonic development, multipotent cardiovascular progenitors (MCPs) with an additional support and contribution by neural crest cells are involved in heart tissue formation (Buckingham *et al*., 2010). MCPs specifically express various receptor such as *Brachyury* (*Bry*)/or *Isl1* and Flk1 (vascular endothelial growth factor receptor 2), and can also differentiate into ECs, CMs, and SMCs. Cardiac stem cells (CSCs) are isolated and obtained by several methods, including antigenic panning or culturing cardiac tissue to make "cardiospheres"(Smith *et al*., 2007). Though bone marrow-derived and cardiac tissue-derived MSCs display similar morphological and cell surface marker characteristics, but CSCs have higher cardiomyogenic potential. CSCs have shown quite promising result in terms of generation of new heart cells and blood vessel in several trials around the world. This gives a ray of hope for the heart patients in therapeutic usages of stem cells which could either be taken from patient's own heart, enriched and infused or other organ-specific stem cells which have cardiac repair potential through growth factor secretion or trans-differentiation and cellular integration at infracted/ischemic site.

Uterus/endometrial tissue-derived stem cells

Studies over several decades have shown rich presence of various kinds of stem cells, including mesenchymal stem cells in menstrual blood, the fallopian tubes, the endometrium and associated tissues. Such findings have encouraged stem cells researchers to embark on journey leading to discovery of their potential applications in cell-based therapy. These stem cell populations, owing to dynamic biology of such tissues, are most likely to be involved in regeneration of endometrium following menstruation, postpartum, uterine curettage, endometrial ablation etc, (Jazedje *et al*., 2009; Gargett *et al*., 2007). Moreover, these progenitor cells have colonogenic and self-renewal and shown to be multipotent. Exposure of estrogen to seemingly quiescent stem cells results into proliferation and hence reepithelialisation of endometrium, suggesting responsiveness of these stem cell population to estrogen and similar molecules (Kaitu'u-Lino *et al*., 2010). Such results could be a ray of hope for patients with damaged endometrium as a result of injury or diseases, which, if not intervened medically, eventually results in female impotency and infertility and imposing huge socio-cultural burden on such patients.

Skin stem cells

Skin is the soft outer covering, consisting of two prominent sheets of cell layers, epidermis and dermis. Skin is the largest organ of the body. Epidermis and dermis layers show constant renewal process, and contain various cell populations that originate from both mesoderm and ectoderm. Such processes are very important in cyclic development of hair follicles which is dependent on precursor cells that reside in the dermal papillae and the bulge. Skin resident stem cells also involved the process of repair and healing and thereby help maintain and restore adult skin homeostasis as well as hair regeneration . An empirical look out for stem cells has revealed the cellular stratification in the different layers of skin with different molecular profile. For example, epidermal stem cells present in epidermis and dermal stem cells, and melanocytes stem cells in dermal layer or beneath (Al-Nbaheen *et al*., 2013; Steingrimsson *et al*., 2005). These adult skin stem cells display overlapping features, including morphology, expression of immunophenotypic markers and multilineage differentiation with other kind of stem cells. Research into the functional aspects of skin stem cells could be of immense help in case of diseases affecting skin. For example, skin stem cells could be used in diabetic patient in which wound healing capacity is compromised (Zgheib *et al*., 2016), or burn where skin cells either loses its stem cell population or have very few such cells with severely compromised biology. Similar approach could also be adopted in finding out the stem cell-based therapy for other kind of skin patients through research and experimentation. In addition, skin stem cells are also being used for drug testing and gene therapy.

Induced pluripotent stem cells (iPSCs)-derived stem cells

Stem cells of various types not only can be obtained from the various organs but also be made *in vitro* with the help of molecular induction/reprogramming process discovered over a decade ago. Induced pluripotent stem cells (iPSCs) are special type of stem cells generally made out of non-stem cell or somatic cell populations by the process known as molecular induction or cellular reprogramming (Takahashi *et al*., 2006). Owing to the high level of biological similarity with embryonic stem cells (ESCs), induced-pluripotent stem cells are held in very high regard by the researchers and clinicians alike. The foundational stone in this direction was most probably laid down by Gurdon and co-workers who empirically showed that nuclear transplantation from differentiating cells can lead to the formation of different cell types (Gurdon, 1962). Following such lead, somatic cell reprogramming was successfully achieved by transferring their nuclear contents into enucleated oocytes (Wilmut *et al*., 1997). This clearly indicates presence of potential biomolecules/factors, in egg cells which can reverse cellular machinery to embryonic stage, thereby conferring pluripotency to adult somatic cells. Eventually, Takahashi and Yamanaka showed successful molecular induction/nuclear reprogramming by introducing four predominantly embryonic-stage specific transcription factors, Oct3/4, Sox2, c-Myc and Klf4 into mouse adult fibroblast, and showed its conversion into pluripotent stem cells, under embryonic stem cell culture conditions (Gurdon, 1962). Upon experimental verification, these reprogrammed cells resembled embryonic stem cells (ESCs) on account of various parameters, including pluripotency-associated marker expression, teratoma formation, chimerism, and three germ-line contribution. Later on, such cellular reprogramming of somatic cells has been accomplished using a single polycistronic vector (Carey *et al*., 2009), recombinant Oct3/4, Sox2, c-Myc and Klf4 proteins (Zhou *et al*., 2009), polyarginine peptide, which acts as cell penetrating peptides (CPP), and acquired human iPSCs, named PiPS (Protein-produced iPS), derived from human newborn fibroblasts (HNF) using Oct4, Sox2, Klf4, and c-Myc reprogramming proteins for the first time (Kim *et al*., 2009). Yakubov *et al*., proceeding on the same molecular path, showed reprogramming of human fore-skin fibroblast (hFF) by introducing *in vitro*-produced mRNA encoding for Oct4, Lin28, Sox2 and Nanog, and obtained RiPS (RNA-produced iPS) cell (Yakubov *et al*., 2010; Warren *et al*., 2012). Moving a step ahead, Warren *et al*. by incorporating 5'-guanine cap to mRNA encoding for Oct4, Sox2, and Nanog showed efficient reprogramming of somatic cells (Warren, L *et al*., 2010). Apart from this, several small organic molecules could also help in efficient cellular reprogramming. For instance, non-steroid anti-inflammatory drug, Nabumetone, and the anticancer drug, 4-hydroxytamoxifen, can generate iPSCs without Sox2, and without compromising self-renewal and any aspect of pluripotency (Nie *et al*., 2012; Yang *et al*., 2011).

CONCLUSION

Stem cells are undifferentiated cells, mainly present in multicellular organisms, and are appropriated and stored in organ–specific niche during embryonic and post-embryonic development as per organs' functional need. Stem cells isolated from various organs differ in terms of morphology, immunphenotype, molecular profiles and differentiation. Furthermore, these cells have immense potential of self-renewal as well as differentiation and trans-differentiation. Self-renewal is one of the characteristics of stem cells whereby they maintain their cellular repertoire over period of time. These cells undergo age-dependent quantitative and qualitative attrition and could explain why aged individuals do not show high intrinsic damage-repair capability following disease and injury? Important molecular processes like cellular differentiation and trans-differentiation makes them capable of producing cells of specific type needed in wake of physiological damage, injury and degenerative diseases, thereby maintaining long-term tissue homeostasis (Klimczack and Kozlowska., 2016). Research findings have proven their universal occurrence with respect to various tissues and organs. These organs have allocated specific anatomical spaces for them to live in, and in turn, stem cells help recover these organs in the hour of need either by secreting growth factors or by cellular differentiation, compensating cellular loss. Stem cells of a particular organs show similarity as well as dissimilarity on accounts of cellular divisions and proliferation, differentiation/trans-differentiation, secretion of regulatory factors/secretome (konala *et al*., 2016), immunomodulation (Gao *et al*., 2016), life-span and curative potential. Recent methodology of cellular reprogramming through various means (Gene, RNA, small molecules) have added new dimension to the therapeutic applications of stem cell for treating various cellular damages and tissue degenerations, including, arthritis, neurodegeneration etc. Stem cells have been proving very promising means for cellular therapy of various kinds of diseases, such as cancer, neurodegeneration, infertility, cognitive disorder, immunological challenges/inflammation/autoimmune disorders and injury, including traumatic brain injury (Pati *et al*., 2016) and so on.

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