Chapter

Introductory Chapter: Update on Mesenchymal and Induced Pluripotent Stem Cells

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1. Introduction

Stem cells are a subset of biological cells in the human body that are capable of self-renewal, tissue repair, differentiation, and division into different cell lineages [1–3]. Based on their origin and potency, stem cells are divided into either (1) embryonic and adult (non-embryonic) stem cells or (2) unipotent, oligopotent, totipotent, multipotent, and pluripotent stem cells [1, 2, 4, 5]. Multipotent or adult stem cells include mesenchymal stem cells (MSCs), while pluripotent stem cells include embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs) [5].

2. MSCs

MSCs are heterogeneous, non-hematopoietic, adult multipotent stromal progenitor cells that are capable of self-renewal and differentiation into multiple lineages and various cell types [6–12]. They were first described in the 1960s by Alexander Friedenstein [7, 8, 10, 13]. They can be isolated from the bone marrow (BM), peripheral blood, umbilical cord blood, amniotic fluid, placenta, adipose tissue (AT), dental pulp, palatal tonsil, synovial fluid, salivary glands, as well as liver, lung, skin, and skeletal muscle tissues [6–13]. The main source of MSCs is the BM although MSCs constitute only a small fraction of the total number of cells populating the BM [7, 9–11].

MSCs have certain distinguishing features: being plastic adherent and ability of differentiation into osteoblasts, adipocytes, and chondrocytes, in addition to having characteristic surface markers [6–8, 10, 11, 13, 14]. On flow cytometry, they are characteristically positive for CD105, CD73, and CD90 and negative for CD45, CD34, CD11b, CD14, CD19, CD79a, and HLA-DR [6–8, 10, 11, 13]. However, several studies have shown that MSCs obtained from BM, AT, and other sources do express CD34 surface markers [9, 15–18]. MSCs can be seen in abundant numbers in the circulation under the following circumstances: stem cell mobilization with growth factors, tissue injuries, stroke, hypoxia, and inflammatory conditions [9, 19–24]. Despite the efforts made over the last five decades including identification of nine transcriptional factors, little is known about the molecular basis underlying the stemness of MSCs, and it is still unclear whether the recently discovered genes regulate stemness or only differentiation of MSCs [12].

MSCs have immunomodulatory and immunosuppressive properties that enable them to have several therapeutic and clinical applications, which include the enhancement of engraftment as well as prevention and treatment of graft versus

host disease (GVHD) in recipients of allogeneic hematopoietic stem cell transplantation (HSCT); treatment of several autoimmune disorders such as systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, type I diabetes mellitus, and Crohn's disease; role in regenerative medicine and tissue repair including treatment of myocardial ischemia, myocardial infarction, cardiac dysfunction, dilated cardiomyopathy, chronic non-healing wounds, critical limb ischemia, liver injury, spinal cord injuries, as well as macular degeneration, corneal reconstruction, and transplantation; neurological disorders such as multiple sclerosis and amyotrophic lateral sclerosis; bone and cartilage diseases such as osteogenesis imperfecta; and treatment of various infections and acute respiratory distress syndrome [6, 7, 11, 25–27].

MSCs are major constituents of hematopoietic stem cell niche which is a highly complex and dynamic microenvironment of the BM [28]. Leptin receptor (LepR) is a marker that enriches BM-MSCs, and LepR+ cells in the BM are a major source of bone, cartilage, and adipocytes [29]. The exosome secretome of BM-MSCs regulates stem cell maintenance and their regenerative potential, and this BM-derived secretome will be critical to the future development of therapeutic strategies for oncologic diseases and regenerative medicine [30]. Apparently, MSCs are the masters of survival and clonality as they communicate with diverse immune cells and interact with other cellular components of the BM microenvironment as well as with normal cells, leukemic stem cells, and progenitor cells [31]. The main functions of MSCs include formation of hematopoietic microenvironment, modulation of the activity of the immune system, and regulating cell trafficking [32]. When stimulated by specific signals, MSCs can be released from BM niche into circulation and can be recruited to the target tissues where they undergo in situ differentiation and contribute to tissue regeneration and homeostasis [33]. The efficacy of MSCs is linked to their immunosuppressive and anti-inflammatory properties primarily due to the release of soluble factors [34].

The putative roles of BM-MSCs during infection are detection of pathogens; activation of host immune response; elimination of pathogens; induction of proinflammatory gradients; and modulation of proinflammatory host immune response [6, 7]. Examples of the immunoregulatory properties of MSCs include inhibition of differentiation of monocytes to dendritic cells (DCs), alteration of cytokine profile of DCs, induction of tolerant phenotypes of naïve and effector T cells, inhibition of antibody production by B cells, and suppression of natural killer (NK) cell proliferation and NK-mediated cytotoxicity [35]. BM-MSCs may augment antimicrobial responses, abridge proinflammatory and damage responses, and ameliorate injury caused by the host defense to the pathogen [6, 7]. BM-MSCs appear to function as a critical fulcrum providing balance by promoting pathogen clearance during the initial inflammatory response and suppressing inflammation to preserve host integrity and facilitate tissue repair [6].

MSCs could potentially be involved at multiple levels in host defense by mobilizing immune effector cells and modulation of proinflammatory immune responses so as to minimize the tissue damage induced by inflammation [6, 36]. The immunomodulatory properties of MSCs are mediated by both: cell to cell interaction and the secreted cytokines [36, 37]. BM-MSCs may protect against infectious challenge either by direct effects on the pathogens or through indirect effects on the host [6]. On the other hand, certain types of MSCs, particularly placenta-derived MSCs and fetal membrane-derived MSCs, are highly susceptible to herpes viruses including varicella zoster virus [7, 38].

Studies have shown that several types of stem cells including BM-MSCs and neural stem cells can cross the blood brain barrier and reach tumors localized in

the brain such as glioblastoma multiforme as well as ischemic areas and injured sites in the brain and engraft there. Hence, MSCs can be used as means of cellular carriers or Trojan horses to deliver cytotoxic genes or therapeutic agents for brain tumors, and they can be used to exert their therapeutic and regenerative effects in the brain [39–43]. In cancer, MSCs are a double-edged sword as they can exert stimulatory effects on tumor development, while they can have inhibitory effects on cancer cell growth and metastases [44]. MSCs have anticancer properties, and they can be engineered or modified to become carriers of suicide genes, employed as carriers of anti-angiogenesis factors, and utilized to target cancer stem cells [45–47]. MSCs have recently been engineered to express antiproliferative, anti-apoptotic, and antiangiogenic agents that specifically target different types of solid tumors [45].

The capacity of MSCs to proliferate and differentiate into other cells in addition to their ability to release biomolecules such as cytokines, growth factors, and microvesicles that have anti-inflammatory, immunomodulatory, anti-fibrogenic, and trophic functions make MSCs ideal candidates to function as delivery platform for cellular and gene therapies [48, 49]. Consequently, clinical trials incorporating the utilization of MSCs in the treatment of immune-related diseases have rapidly evolved after reports from preclinical studies confirming their safety and efficacy [49]. Recently, scientists have established several strategies to generate highly functional AT-derived MSCs and these include preconditioning of AT-MSCs with various stimulants and inflammatory agents; genetic manipulation of AT-MSCs; modification of culture conditions with three-dimensional aggregate formation and hypoxic culture; and proper utilization of exosome and extracellular vesicles (ECVs) that are secreted by AT-MSCs [50, 51]. Also, the main focus has recently shifted from studying differentiation of MSCs to studying their paracrine properties such as the release of ECVs that contain numerous micro-RNAs (miRNAs) including regulatory miRNAs and the production of multiple bioactive proteins and compounds that regulate MSC differentiation [52]. Hence, soluble elements derived from MSCs including ECVs have recently been proposed as a cell-free alternative for various therapies on the clinical side [51].

The combination of MSCs and tissue engineering technology can enhance the immunoregulatory properties of MSCs, and this will ultimately lead to further expansion of their utilization in regenerative medicine [53]. Tissue engineering strategies such as the use of various types of stem cells, scaffolds, medical devices, gene therapy, and nanotopography have resulted in progressing the translation of basic research towards clinical therapeutics [54, 55]. Despite the remarkable progress in MSC therapies, sufficient data on the biodistribution of MSCs, cellular and molecular structures of their target cells, and mechanisms by which MSCs reach these targets are still lacking [56]. Also, several obstacles need to be overcome before the utilization of specific types of MSCs in tissue engineering becomes a routine practice in the clinical arena [57]. Currently, human MSCs are generated through conventional static adherent cultures in the presence of fetal bovine serum or human-sourced supplements. Unfortunately, these methods are not ideal procedures to meet the future expectations of quality-assured human MSCs for clinical therapies in humans [58]. Additionally, having substantial gaps in our knowledge of the biology and therapeutic efficacy of MSCs presents major challenge to their sustainable implementation in clinical medicine [59]. Thus, optimizing the bioprocess to generate human MSCs and their products will improve efficacy and safety of stem cell therapies [58]. Also, improving the cultural environment of MSCs and selecting the appropriate scaffolds and induction factors are essential in improving the outcome of MSC-based tissue engineering [60].

3. iPSCs

Human iPSCs resemble human ESCs in many aspects including morphology, proliferation, differentiation potential, and pluripotency markers, but the epigenetic characteristics of human iPSCs are rather distinct [1, 2, 5, 61]. Although the utilization of iPSCs can avoid the obstacles and ethical concerns that limit the use of human ESCs, clinical application of human iPSCs still has a number of disadvantages that include chromosomal instability and tumorigenic potential, thus raising questions about the safety of their clinical utilization, and low reprogramming efficiency in addition to other concerns about their reproducibility for laboratory applications in disease modelling and drug screening [1, 3, 5, 61, 62].

In 2006, Takahashi and Yamanaka were the first scientists to generate mouse iPSCs from dermal fibroblasts through retroviral-mediated ectopic expression of the four genes: OCT4, SOX2, KLF4, and c-MYC [1, 3, 4, 63]. Since this discovery, iPSCs have been used in many research and clinical trials, including disease modelling; drug toxicity as well as drug discovery; and regenerative medicine [3–5]. Reprogramming of iPSCs should have the following crucial requirements: species such as human or mouse; cell type such as blood cell or fibroblast; factor, drug, chemical, or other protein molecules such as miRNA, DNA modifying agent, NANOG, or LIN28; vector such as retrovirus or lentivirus; and disease with specific genetic mutation [1, 4, 5, 64].

Human iPSCs have revolutionized the field of human disease modelling with an enormous potential to serve as paradigm shifting platforms for preclinical trials, personalized clinical diagnosis, and personalized drug therapy [65]. During the last 13 years, significant developments and remarkable progress have been achieved in enhancing reprogramming techniques and their efficacy, increasing safety of derived iPSCs, and developing different delivery methods [61, 62]. The ability to generate iPSCs from human somatic cells provides tremendous promises and opportunities in basic research and regenerative medicine and can provide a wide range of applications including cell-based therapies, drug screening, and disease modelling [61, 66].

The capacity of human iPSCs to retain patient-specific genomic, transcriptomic, proteomic, metabolomic, and other visualized big data information makes it possible to extend their applications beyond disease modelling into the field of personalized medicine which encompasses the adoption of novel prevention and treatment strategies based on individual variability [65]. The emergence of modern iPSC technology, with the capacity of these stem cells to undergo unlimited self-renewal and differentiation into any type of cell, has a great potential to advance translational applications including stem cell therapies and the generation of large-scale collections of cell lines for research purposes [67]. Recently, genomic editing technologies have been applied to correct the mutations in disease-specific iPSCs to create gene-corrected iPSCs that can be utilized in autologous stem cell-based therapies [64]. Nowadays, patient-specific iPSCs can be obtained by reprogramming of adult somatic cells by ectopic expression of pluripotency-associated transcription factors including OCT4, SOX2, KLF4, and c-MYC [64]. The availability of precisely generated iPSC-derived functional cells to replace or repair damaged tissues or organs will likely affect therapies of hematopoietic disorders and facilitate treatment of neurological, cardiovascular, hepatic, and retinal diseases and possibly diabetes mellitus [67]. Additionally, patient-specific iPSCs can bypass certain limitations of ESCs such as ethical concerns and immunological rejection [64]. The first clinical trial on cell-based therapy using iPSCs derived from patients to treat blindness started in Japan in September 2014 [67].

4. iPSC-MSCs and conclusion

MSCs derived from iPSCs (iPSC-MSCs) exhibit higher proliferation rate and less senescence than BM-MSCs, and thus the former cells are emerging as an attractive therapeutic option for obtaining a substantial population of stem cells in a sustained manner for applications in regenerative medicine [68, 69]. Several studies using human iPSC-MSCs and their exosomes in human and animal studies have shown that transplantation of these cells can produce protection of the liver against hepatic ischemia; reduction in the volume of brain infarction and preservation of neurological function after acute intracranial hemorrhage; prevention of osteonecrosis of femoral head by promotion of local angiogenesis and prevention of bone loss; facilitation of cutaneous wound healing by promotion of collagen synthesis and angiogenesis; and modulation of differentiation and function of DCs in order to support their clinical application in DC-mediated immune disorders [69–73]. Thus, MSCs and iPSCs may reshape the future of medical therapeutics and may eventually become curative for several chronic and intractable medical illnesses [2, 4, 5].

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