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The Future Role of Mesenchymal Stem Cells in Tissue Repair and Medical Therapeutics: Realities and Expectations

Khalid A Al-Anazi^{1*}

¹Consultant Hemato-Oncologist and Chairman, Department of Hematology and Hematopoietic Stem Cell Transplantation, Oncology Center, King Fahad Specialist Hospital, Saudi Arabia

***Corresponding Author:** Khalid Ahmed Al-Anazi, Consultant Hemato-Oncologist and Chairman, Department of Hematology and Hematopoietic Stem Cell Transplantation, Oncology Center, King Fahad Specialist Hospital, P.O. Box: 15215, Dammam 31444, Saudi Arabia; Email: kaa_alanazi@yahoo.com

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Editorial

Mesenchymal Stem Cells (MSCs); which were first described by Alexander Fridenstein in the 1960s; are heterogeneous, non-hematopoietic, adult multipotent stromal progenitor cells that are capable of self-renewal and differentiation into various cell types [1-8]. They can be isolated from various sources including: Bone Marrow (BM) which is the main source, peripheral blood, umbilical cord blood, amniotic fluid, placenta, Adipose Tissue (AT), dental pulp, synovial fluid, salivary glands, liver, lung, skin and skeletal muscles [1-10]. MSCs have the following distinguishing features: adherence to the plastic vessel; capacity to differentiate into osteoblasts, adipocytes and chondrocytes; and being characteristically positive for CD105, CD73, and CD90 and characteristically negative for CD45, CD34, CD11b, CD14, CD19, CD79a, and human leukocyte antigen (HLA)-DR on flow cytometry [1,3,4,11-16]. However, under certain circumstances, MSCs obtained from BM, AT, and other sources may express CD34 surface markers [5-8,17]. Additionally, MSCs do not express significant histocompatibility complexes and immune stimulating molecules. Consequently, they escape immune surveillance and their clinical utilization in transplantation is not associated with graft rejection [10].

MSCs have immunomodulatory, immunosuppressive, and antimicrobial properties that enable them to have several therapeutic and clinical applications including: treatment of several autoimmune disorders such as systemic lupus erythematosus, rheumatoid arthritis, systemic

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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; treatment of bone and cartilage diseases such as osteogenesis imperfecta; enhancement of engraftment in addition to prevention and treatment of graft versus host disease in recipients of allogeneic Hematopoietic Stem Cell (HSC) transplantation; treatment of neurological disorders including multiple sclerosis, and amyotrophic lateral sclerosis; and treatment of various infections and their complications including: viral pneumonia, bacterial sepsis, Acute Respiratory Distress Syndrome (ARDS), multidrug-resistant tuberculosis, and Chagas disease [1,9-12,18-21]. Recently, MSCs and their secretomes have been successfully used in the treatment of certain complications of coronavirus disease 2019 (COVID-19) such as pneumonia, ARDS, acute lung injury, and the associated cytokine storm [22-24]. The therapeutic potential of MSCs in the treatment of cancer is still controversial. Hence, efforts to understand when MSCs promote or suppress tumor development are sustained [21,25]. Worldwide, > 1000 clinical trials on the clinical utilization of MSCs enrolling approximately 48,000 patients have been registered at www.clinicaltrials.gov and www.celltrials.org since the year 2011 [16,26].

MSCs are major constituents of the BM microenvironment or HSC niche [27]. The exosome of BM-MSCs regulates stem cell maintenance and regeneration and is critical to the development of therapeutic strategies for oncologic diseases and regenerative medicine [28]. MSCs are the masters of survival and clonality as they interact with diverse immune cells and other cellular components of the BM microenvironment to: form the hematopoietic microenvironment, modulate the activity of immune system, and regulate cell trafficking [29,30]. They 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 [31]. The efficacy of MSCs, their differentiation capacity, as well as the anti-inflammatory, immunomodulatory, anti-fibrogenic, antimicrobial, and trophic functions are closely linked to the release of cytokines, growth factors, microvesicles, and biomolecules, and micro-RNAs; referred to as secretomes; that enable MSCs to become ideal delivery platforms for cellular and gene therapies [9,10,26,32-34]. MSCs promote tissue repair through their paracrine activity by secretion of proteins and other substances; and transfer of mitochondria, exosomes, or microvesicles containing RNA and other molecules [10, 35]. The combination of MSCs and tissue engineering strategies can enhance the immunoregulatory properties of MSCs and expand their utilization in medical therapeutics and tissue regeneration [36-38]. Despite the remarkable progress in MSC therapies, several challenges need to be overcome before the full utility of specific types of MSCs in medical therapies and tissue engineering and these include: characterization of specific MSCs available for therapeutic use; patient selection; use of autologous versus allogeneic MSCs; preparation and expansion of human MSCs; dosing regimens, delivery methods, routes of administration, and biodistribution of MSCs; engraftment of transplanted cells; banking of harvested MSCs; bioengineering methods used

to enhance their homing and survival; and the remaining gaps in our knowledge on the biology as well as therapeutic efficacy of MSCs [26,39-45].

Several studies have shown safety and efficacy of MSCs. However, optimizing the bioprocess to generate human MSCs and their products as well as improving the cultural environment of MSCs and selecting the appropriate scaffolds and induction factors will further improve the safety, efficacy, and outcome of MSC medical therapies and MSC-based tissue engineering [9,41,42,46]. Thus, MSCs may reshape the future of medical therapeutics and eventually become curative for several chronic and intractable medical illnesses provided the remaining obstacles are corrected.

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