Short Communication

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Journal of Stem Cell Biology and Transplantation
ISSN : 2575-7725

2021
Vol. 5 ISS. 2 : sc 52

DOI : 10.21767/2575-7725.5.2.52

Novel techniques of improving the efficiency of stem cell treatment in regenerative medicine

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Abstract:

Analysis of numerous clinical trial results in regenerative medicine generally shows low level of efficacy with stem cells due to which very few trials actually reach culmination. This is due to the fact that most researchers do not take into account the importance of stem cell microenvironments in the treatment design, use an insufficient number or type of stem cells, and/or ignore the possibility of using exosomes in the complex therapy of patients. Proliferation, differentiation and engraftment of stem cells (SCs) require a specific, pre-defined microenvironment called 'stem cell niche'. For in vivo modulation of organ-specific niches during SCs transplantation, appropriate tissue based growth factors (including Placental tissue extracts - PTEs and Fetal Tissue extracts - FTEs) can improve outcomes significantly. Mesenchymal stem cell (MSC) and especially hematopoietic stem cell (HSC) culture, enumeration and amplification provide adequate number of cells for optimum results. Additionally growth factors and exosomes can induce the phenotypic modifications of SCs. We investigated the content of growth factors in FTEs and PTEs; studied the efficacy of adding these in patients who did not respond well to conventional SC treatment and optimized results considerably. We showed impact of PTEs/FTEs for remodeling the SC niche in treatment of liver cirrhosis and non-healing wounds and ulcers in patients. Transplantation of SCs with PTEs/ FTEs showed efficacy in 75% cases of liver cirrhosis, characterized by significant decrease of liver fibrosis, portal hypertension, ascites, and biochemical markers of liver damage. In patients with chronic non-healing wounds, administration of PTEs/FTEs activated the wound epithelialization resulting in complete wound healing. Total wound closure observed with conservative treatment was in 4% of patients; with autologous bone marrow stem cells treatment in 59% of patients; and by remodeling the stem cell niche (stem cells + PTEs + FTEs) was seen in a significant 75% of patients. Death from cardiovascular causes observed was in 31, 11, and 1% patients respectively. We also created a novel Rejuvenation (anti-aging) Program, which included infusion with SCs and exosomes of cord blood plasma. Global Aesthetic Improvement Scale after this Rejuvenation Program showed optimal cosmetic improvement of 78.9% and significant reduction of biological age and Frailty Index.

Mesenchymal stem cells are undifferentiated cells able to acquire different phenotypes under specific stimuli. In vitro manipulation of these cells is focused on understanding stem cell behavior, proliferation and pluripotency. Latest advances in the field of stem cells concern epigenetics and its role in maintaining self-renewal and differentiation capabilities. Chemical and physical stimuli can modulate cell commitment, acting on gene expression of Oct-4, Sox-2 and Nanog, the main stemness markers, and tissue-lineage specific genes. This activation or repression is related to the activity of chromatin-remodeling factors and epigenetic regulators, new targets of many cell therapies. The aim of this review is to afford a view of the current state of in vitro and in vivo stem cell applications, highlighting the strategies used to influence stem cell commitment for current and future cell therapies. Identifying the molecular mechanisms controlling stem cell fate could open up novel strategies for tissue repairing processes and other clinical applications.

Stem cells are known for their self-renewal and their capability to differentiate into various lineages, participating in tissue regeneration after damage. Since human embryonic stem cells (ESCs) are isolated from the inner cell mass of the blastocyst their application in vitro and in vivo is burdened by ethical issues, causing researchers to turn their interests toward other sources. Mesenchymal stem cells, defined by other authors as mesenchymal stromal cells, have shown a high proliferative potential in vitro, being identified as the elements that maintain the bone marrow microenvironment, improve hematopoiesis and give rise to various cell lineages. The most common source for human mesenchymal stem cells (hMSCs) is the bone marrow, usually obtained from the iliac crest of adult patients. Bone marrow-derived stem cells (BM-MSCs) can be separated from the tissue by centrifugation in a density gradient media and, once placed in culture, they can be easily induced to differentiate towards different phenotypes. MSCs are found in many other adult tissues, including the dental pulp, adipose tissue (ASCs), umbilical cord blood and Wharton's jelly of umbilical cord12]. Despite some differences in terms of growth kinetics and pluripotency, donor age- and -gender-related features, MSCs can differentiate .

Electromagnetic fields can interact with cells, tissues and biological systems in general and are able to influence phenotypic features, gene expression patterns and differentiation in MSCs, acting in a dose and time-dependent manner. It has been shown that 7 d of MSC growth on an electroconductive polymeric substrate was sufficient to promote Nestin and β-3 Tubulin upregulation and the appearance of neural-like morphological extensions. MSCs can be employed to improve cartilage regen-

eration. Synthetic scaffolds and biopolymers are incorporated in stem cell cultures to induce their growth, mimicking the stem cell niche. Biomaterials provide a physical environment that can control cell function.

Epigenetics refers to the range of heritable changes in the structure of chromatin able to affect gene expression and represents the molecular reaction to all the environmental changes. These chromatin modifications are orchestrated by different kind of enzymes, such as DNA methyltransferases (DNMTs), or enzymes controlling post-translational histone modification, as Histone deacetylase (HDACs) and histone acetyltransferases. Epigenetic mechanisms are involved in the progression from the undifferentiated to differentiated state, through silencing of self-renewal genes and activation of differentiation markers. The onset of these specific gene expression patterns is stimulated by developmental and environmental stimuli, causing changes in the chromatin structure, thus allowing a specific transcriptional program, with a mechanism not fully clarified yet. Therefore, epigenetics has a central role not only during embryogenesis but also in maintaining tissue homeostasis and controlling the regenerative potential through adulthood. Wang et ademonstrated that HDAC6 takes part in dental MSC differentiation and osteoblast maturation by maintaining dental and periodontal tissue homeostasis. Exposure of human amniotic fluid stem cells to DNMT inhibitors induces cardiomyogenic differentiation via chromatin remodeling, upregulation of cardiac-related genes and repression of HDAC1 expression. In addition, a combination of DNMT and HDAC inhibitors counteracts cancer stem cell growth, reducing the tumor mass in mouse mammary tumor models, thus increasing mice survival, and unfolding novel epigenetic-based therapies for drug-resistant breast cancer. DNA methylation plays a key role in maintaining the undifferentiated state in stem cells by silencing the differentiation genes, and it is also implicated in somatic cell reprogramming. All of these classes of enzymes promote changes in chromatin structure, exerting a crucial role in regulating the balance between pluripotency and differentiation. On the whole, continuous efforts to unravel epigenetic regulation holds promise for continuous innovation in strategies aimed at controlling stem cell pluripotency and tissue homeostasis. MicroRNAs (miRNAs), small non-coding RNAs, have been discovered as regulators of different signaling pathways, stem cell pluripotency and somatic cell reprogramming

Note : This work is partly presented at Joint Event On 6th World Congress On Natural Product & Synthetic Chemistry & 3rd Annual Cell Congress (June 24-25, 2019| New York, USA