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Editorial
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Mesenchymal Stem Cells Derived Paracrine Factors: An Alternative Approach in Regenerative Therapy

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Editorial

Stem cell transplant, an emerging approach in regenerative therapy followed globally and many on-going researches focused on clinical applications of Stem Cells (SC). Among different SC, Mesenchymal Stem Cells (MSC) attracted the scientists due to its characteristic features like non-immunogenic, self-differentiation and multipotent nature. The paracrine factors including, growth factors, chemokines, cytokines and exosomes derived from MSC are the principle molecules which plays vital role in regeneration of damaged tissue or organ. These paracrine factors has been secreted in the host as well as in the Condition Medium (CM) or spent medium harvested from cultured cells. Several cytokines were present in CM, these cytokines are classified into:

Growth factors

Vascular Endothelial Derived Growth Factor (VEGF), Platelet Derived Growth Factor (PDGF), Epidermal Growth Factor (EGF), Insulin like Growth Factor I&II (IGF-I&II), Hepatocyte Growth Factor (HGF), Fibroblast Growth Factor 2/basic Fibroblast Growth Factor (FGF-2/bFGF), Keratinocyte Growth Factor/Fibroblast Growth Factor 7 (KGF/FGF-7), Platelet Derived Endothelial cell Growth Factor (PDEGF), Heparin Binding Epidermal Growth Factor (HEGF), Placenta Growth Factor (PlGF), Neural Growth Factor (NGF) and Brain Derived Neurotrophic Factor (BDNF).

Proinflammatory cytokines

Interleukins (IL) like IL-8/CXCL-8, IL-9, and IL-1b.

Anti-inflammatory cytokines

TGFβ1, IL-6, IL-10, IL-27, IL-17E, IL-13, IL-12p70 and IL-1 receptor antagonist (IL-1ra).

Other cytokines

Leptin, angiogenin, Granulocyte Colony Stimulating Factor (GCSF), Granulocyte Macrophage CSF (GM-CSF), Macrophage CSF (MCSF), fractalkine, monocyte chemotactic protein (MCP-1), serpin E-1, endostatin/collegen XVIII, urokinase plasminogen activator, thrombospondins 1and 2, Tissue Inhibitor of Metalloproteinase-1 (TIMP-1), IGF Binding Protein (IGFBP), Stem Cell-Derived Factor 1 (SDF-1)/CXCL-12, Adrenomedullin (ADM), Dickkopf-1 (DKK-1), MCSF receptor (MCSFR) and PDGF receptor (PDGFR). These major cytokines present in CM are the principle substances plays role in regeneration mechanisms.

Available literatures strongly suggest the impact of paracrine factors in regenerative therapy and use of CM for therapy may become popular in the near future. Application of CM has been reported for successful outcome in pre-clinical studies, whereas limited reports are available on clinical application of CM. Clinical trial with CM from Adipose Derived Mesenchymal Stem Cells (ADMSC) showed regeneration of hair follicle and effective wound healing through the formation of new blood vessels (angiogenesis), regeneration of keratinocyte and migration of fibroblast. In a clinical study, intra-dermal injection of ADMSC-CM showed highly effective for alopecia, CM increases the number of hair and it may open a new avenue of therapy for hair regeneration. Katagiri et al., [1] reported alveolar bone regeneration by treatment with bone marrow derived (BM-MSC-CM) which has great osteogenic potential. In another clinical study, intrathecal administration of BM- MSC followed by ADMSC-CM in multiple sclerosis patients showed both BM-MSC and MSC-CM are safe with relative efficacy in stabilizing the disease and reverse the symptoms [2]. A recent case study (unpublished data) by our research demonstrates that ADMSC-CM ameliorate psoriasis vulgaris. The severity of psoriasis was completely reduced from Psoriasis Scalp Severity Index score 28 to 0. ADMSC-CM promotes the collagen synthesis, proliferation of keratinocytes and dermal

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fibroblasts which leads the healing of psoriasis. The *in-vitro* and *in-vivo* preclinical studies in experimental animal models with CM show significant outcomes on various diseases viz., hind limb ischemia, wound healing, myocardial infarction, liver disorders, cerebral injury/stroke, spinal cord injury, lung fibrosis and bone defects. CM of embryonic stem cells derived endothelial precursor cells accelerates wound healing and increase the tensile strength of wounds after topical treatment and subcutaneous injection. Furthermore, human umbilical cord blood derived UCBMSC-CM inhibit melanogenesis by regulating Microphthalmia-associated Transcription Factor (MITF) expression *via* the ERK signaling pathway [3]. Studies show that ADMSC-CM promotes proliferation and migration of alveolar epithelial cells under septic conditions. This repair process depends on the activation of JNK and P38 MAPK pathways. Farahmand et al. [4] reported the up-regulation of anti-apoptotic and proliferative genes when breast tumor cells were co-cultured with ADMSC-CM and correlated with tumor progression and poor prognosis. Interestingly, CM from Dental Pulp Stem Cell (DPSC) enhances vasculogenesis, migration and differentiation of endogenous neuronal progenitor cells in ischemic brain injury in a rat model. In addition, ADMSC-CM promotes the recovery of skin burn wound in rat through the acceleration of wound closure, greater numbers of fibroblasts and blood vessels and high density of collagen fibers [5]. In another study, rats treated with paracrine factors from ADMSC-CM showed significant recovery against radiation burn. ADMSC-CM also evokes activation of angiogenic signals and *in vivo* angiogenesis, arteriogenesis and improves local blood flow recovery in ischemic hind limbs. In another study, cell-free lysates from MSC showed positive effect on wound closure and rapid re-epithelialisation. *In vitro* and *in vivo* studies indicated that CM derived from human gingival MSC play vital role in osteogenic process in bone regeneration. Chen et al. [6] reported that concentrated ADMSC-CM showed great potential for ADMSC-based therapy for osteoarthritis, reduce the inflammation of chondrocytes and down regulate the inflammation associated free radicles, TNF-α, IL-1β, IL-6 and iNOS. Similarly, Induced Pluripotent Stem Cell derived Conditioned Medium (iPSC-CM) attenuates acute kidney injury by down-regulating the oxidative stress-related pathway in ischemia. In addition, proliferation and migration of dermal fibroblasts were promoted by the paracrine factors present in iPSC-CM and it also attenuates the light-induced photo damaged retina in rats. In addition to cytokines, SC release extra cellular vesicles in the CM which is known as exosomes. Exosomes are small cells (30 nm to 120 nm in diameter), membrane-enclosed vesicles. It contains proteins, lipids, and microRNAs of parent cells. Being smaller than SC, exosomes easily circulate through the body and reach sites of injury. It has been documented that exosomes play a key role in stem cell therapy, acting through the paracrine mechanism. Exosomes derived from BMSC exerts immunoregulatory effect in different autoimmune related disorders, attenuate tissue injury and promote tissue repair. BMSC-derived exosomes also attenuate inflammation and demyelination of the central nervous system in experimental autoimmune encephalomyelitis rat model by regulating the polarization of microglia [7]. Studies also showed that intravenous/subcutaneous administration of human ADMSC derived exosomes ameliorate atopic dermatitis in mouse model. There are several factors which influence the release of paracrine factors in CM such as, culture medium and supplement, cell number, different type of stem cells, culture duration and culture condition (hypoxia or normoxia). Stem cell secretome, Collected Form (CM), is getting more attention not only from researchers, but also from industries for commercialization. In addition to therapeutic applications, CM has been used in many anti-aging and skin care cosmetics products. Growing evidences suggests that CM derived from SC could be a promising alternative to cell-based therapy and could avoid the problems associated with cell-based therapy like teratoma formation.

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