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MINI-REVIEW ARTICLE

Mesenchymal Stem Cell-Mediated Immuno-Modulatory and Anti-Inflammatory Mechanisms in Immune and Allergic Disorders

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Abstract: ***Background***: Mesenchymal Stem Cells (MSCs) are present in almost all the tissues of the body and act as the backbone of the internal tissue homeostasis. Among their various characteristic features, immuno-modulatory and/ anti-inflammatory properties play an important role in therapeutics.

Objective: The current topic focuses on the characterization and immuno-modulatory and/ anti-inflammatory properties of MSCs. To present and discuss the current status of MSCs immuno-modulatory properties.

Methods: Available literature on MSCs properties and patents have been detailed, critically interpreted, and discussed based upon available literature. The main focus has been on their characteristic immuno-modulatory and anti-inflammatory properties though some of the basic characterization markers have also been detailed. The databases searched for the literature include PubMed, Med Line, PubMed Central, Science Direct and a few other scientific databases.

Results: MSCs are present in a very limited concentration in the tissues, and as such their culture expansion becomes imperative. MSCs immuno-modulatory and anti-inflammatory roles are achieved through direct cell-cell contact and / by the release of certain factors. Such properties are controlled by micro-environment upon which currently very limited control can be exerted. Besides, further insights in the xeno-protein free culture media as against the fetal bovine serum is required.

Conclusion: MSCs have been well-isolated, cultured and characterized from numerous tissues of the body. The majority of the studies have shown MSCs as immuno-compromised with immunomodulatory and / or anti-inflammatory properties except some of the latest studies that have failed to achieve the desired results and thus, demand further research. Further research is required in the area to translate the results into clinical application.

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1. INTRODUCTION

Stem cells are the specialized cells that can self renew, multiply, and differentiate into a wide variety of cells in the body [1-3]. As such endogenous stem cells have shown great potential in repair/healing in the living organism. The controlled application of such cells may be expected to do wonders in the field of therapeutics and regenerative medicine [2, 4-7]. However, limited understanding of the cellular physiology and effects of the microenvironment restricts their definitive therapeutic applications [8, 9]. Among various stem cell types, Mesenchymal Stem Cells (MSCs) are mostly considered for preclinical and/ or clinical trials [10-12]. Even MSCs have been genetically modified for particular therapeutic effects (Table **1**). These cells have accessible sources, simplicity of isolation protocol and can modulate immune responses and inflammation. Thus, these cells have the potential to regenerate damaged tissue without formation of any scar [13-15] (Zuk *et al.* 2001; Stewart and Stewart, 2011; Gugjoo *et al.* 2019). Furthermore, these cells carry minimal teratogenic risk and bear no ethical issues as are usually associated with pluripotent stem cells like human Embryonic Stem Cells (ESCs) and induced pluripotent stem cells (iPSCs) [13, 15, 16].

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2. DEVELOPMENT OF MSCs CONCEPT

The current concept of MSCs (a term coined later by Caplan), came into existence when bone marrow transplantation made into the heterotopic anatomical sites resulted in the de novo formation of ectopic bone and marrow [17, 18]. It was the Friedenstein and co-workers who showed that heterotopic bone formation post bone marrow transplantation is associated with minor sub-population of the cells. They could differentiate such cells from haematopoetic cells based on their specific features viz. plastic adherence and fibroblast-like appearance [19]. The fibroblast like appearance depicted their origin from the stromal compartment of the bone marrow. These cells upon seeding at clonal density had resulted in the establishment of discrete colonies initiated by single cells, known as colony-forming unit fibroblasts (CFU-Fs) [18, 19]. Mesenchymal Stem Cells (MSCs) originate from the pericyte as a consequence of assault to the tissue [20, 21]. It occurs as a part of the body's defense system as MSCs act as double-edged weapons. On the front side (facing towards blood vasculature), the cells impart immuno-modulatory and anti-inflammatory properties to prevent over-aggressive response of the body that may establish chronic autoimmune reaction (immuno-modulation or guardians of inflammation). From the back (towards damaged tissue) the cells secrete trophic factors for tissue regeneration [22-24]. The current topic focuses on the mesenchymal stem cell characteristics especially about their immuno-modulatory and/ anti-inflammatory properties.

3. MESENCHYMAL STEM CELL SOURCES AND CHARACTERIZATION

MSCs have been isolated from almost all the body tissues, though with variable cell concentration. Tissues like bone marrow, adipose tissue, dental pulp, embryonic tissue, endometrium, gingiva, hair follicle, lungs, limbal epithelium, muscle, ovary, periodontal ligament, peripheral blood, periosteum, synovial fluid and membrane, umbilical cord, Wharton's Jelly, etc. have successfully been explored as MSC sources as reviewed by Gugjoo and co-workers [3, 7, 8, 12, 15]. However, bone marrow and adipose tissue are commonly employed sources for cell harvesting due to ease of harvesting and possessing a good number of cellular concentrations [25]. Among these two sources, adipose tissue carries higher cellular concentration as compared to the bone marrow [14, 26]. MSCs are characterized based on the recommendation of the International Society for Cell Therapy (ISCT) given initially for humans and later followed for animal species. This includes cellular plastic adherence, expression of surface receptors (CD105, CD90, CD73, CD90) and inability to express CD45, CD34, CD14 or CD11b, CD79a or CD19 and HLA-DR. The cells should at least differentiate into osteogenic, chondrogenic and adipogenic lineages in respective media [27-30]. There are various advanced protocols and media prepared that lead to the better and early differentiation of the cells [31-34] (Table **1**). Across species, MSCs generally meet the set criteria of plastic adherence and pluripotency [35-37] but lack established consensus on surface marker expression as reported for horse, goat, dog and others [36-40]. Variable expression of surface markers may be attributed to the differences in the type of cell tissue sources, harvesting methods and antibodies used [36, 37, 41, 42]. The detaching agent (e.g., trypsin) used in culture could lead to the impairment of certain cell surface receptor membrane proteins [36, 37] and not all the antibodies are reactive to specific molecules across species [42]. Further, MSCs immunophenotype, being dynamic that changes over the course of culturing, may impart alterations in their biological features [43, 44].

Culture type affects MSCs expression including their immune-modualtory effects. Usually, cells are cultured in DMEM medium with Fetal Bovine Serum (FBS) supplementation. However, FBS poses potential threats of disease transmission and may give variable cell behavior as it carries xenogenic proteins. In addition, ensuring the uniform cell culture samples are difficult to develop posing difficulty in clinical studies [45, 46]. Thus, serum-free medium culture techniques have been followed [47] (Table **1**). Though such an alternative has been successful to some extent in humans, further research is required in canines and equines [48]. Human MSCs under hypoxic conditions show improved immuno-modulatory effects besides, the cells have decreased differentiation capacity and carry higher expansion rate in comparison to MSCs cultured in normoxia [49-52]. Even MSCs from different sources may have significant heterogeneity in their differentiation capability [53]. However, the same is yet to be confirmed under *in vivo* studies [54].

4. IMMUNO-MODULATORY AND ANTI-INFLAMMATORY ROLE OF MSCs

Immuno-compromised MSCs are generally considered to decrease inflammation, protect tissues from hypoxia/tissue reperfusion injury, avoid allogeneic rejection, and suppress immune responses. The cells variably express Major Histocompatibility Complex (MHC) class I but mostly fail to express MHC class II or T-cell co-stimulatory molecules on their surface [55-58]. Equine MSCs express *STC-1* (blocks negative effects of reactive oxygen species), *TSG-6* (receptor antagonist of pro-inflammatory cytokine IL-1) and *IL1-Ra* (anti-inflammatory action and inhibitor of matrix metalloproteinases) that reduce inflammation and also prevent the hypoxia-induced tissue injury [59]. The immuno-modulatory actions are brought about by their ability to interact with various kinds of immune cells including the cells involved in innate immunity (Dendritic Cells (DCs), Natural Killer (NK) cells, neutrophils, and macrophages) and acquired immunity (B cells and T cells) [60-66].

4.1. *In Vitro* Studies

MSCs immuno-modulatory effects are achieved either through cell-cell contact and/ by the release of soluble factors. In cell-cell-mediated immuno-suppression, the cells secrete immune-modulatory factors after activation of certain receptors. The activated receptors include Toll-Like Receptors (TLRs), galectin-1, Intracellular Adhesion Molecule 1 (ICAM-1), and Vascular Cell Adhesion Molecule 1 (VCAM-1) on the surface of MSC and FAS-ligand-dependent interactions are considered to play an important role [67-71]. Apart from direct cell-cell contact, canine MSCs in transwell assays have been demonstrated to secrete factors that inhibit lymphocyte proliferation [62, 64, 72]. Furthermore, the MSCs preconditioned media too favors the inhibition of

lymphocyte proliferation [62]. However, immuno-suppression by cell-cell contact interaction is considered to be stronger than by paracrine action [73].

MSCs from different sources reduce inflammation by decreasing production of tumor necrosis factor-α (TNF-α) and Interferon-γ (IFN-γ) and increasing Prostaglandin (PGE2) and Interleukin-6 (IL-6) secretion [74-76]. However, the potential to express different immune-modulatory factors especially NO, TGF-β1, Indoleamine 2,3 Dioxygenase (IDO) and IL-6 may vary among the cells of different sources [64, 75, 77] and in different species [56]. The cells from various sources, though may have different immuno-modulatory/anti-inflammatory mechanisms but an overall comparable effect may be produced in an inflammatory environment [77, 78]. In relation to allogeneic and autologous cell sources, MSCs ability to suppress T-cell proliferation and IFN-γ production seem comparable [76].

Unlike immune cells, MSCs lack direct cytotoxic or humoral defense activity as these cells do not secrete granzymes or perforins and are unable to produce antibodies. However, MSCs can phagocytize apoptotic cells [79]. In general, the central role of MSCs in maintaining homeostasis (immuno-modulation and anti-inflammatory activities) occurs by interacting with immune cells and is mediated through cytokines, chemokines, cell surface molecules and metabolic pathways [7, 15]. MSCs suppress T-cell proliferation, cytokine secretion and cytotoxicity [80]. B Cell viability though is maintained by MSCs but may inhibit their proliferation, secretion of antibodies, and production of co-stimulatory molecules and also arrest the cell cycle [81]. On Dendritic Cells (DCs), MSCs produce immunosuppressive effects by restricting their maturation (differentiation from monocyte), cell surface expression (e.g., MHC-II, CD86, CD83, CD40 and CD1-*α*), migration potential and by depressing their pro-inflammatory capacity [66, 82-85]. NK cells that produce pro-inflammatory cytokines and carry cytolytic activity [86] are inhibited by MSCs. MSCs immuno-suppressive secretory factors that inhibit the effects of NK cells are PGE2, TGF-*β*, sHLA-G, IDO and PGE-2 [87, 88]. The direct cell-cell contact occurs by expression of Toll-Like Receptor- (TLR-) 4 on MSCs [89].

4.2. Factors Affecting MSCs Immuno-Modulatory Effects

MSCs immuno-regulation is critically under the control of the available micro-environment that may either induce their immuno-regulatory effects or evoke inflammation. *In vitro* confirmation of their immuno-modulation effects is done by their pre-treatment with IFNγ and TNF-α, usually secreted by T lymphocytes and thereby largely seen in inflammatory environments. Such primed cells show an increased potential to decrease lymphocyte proliferation and monocyte-derived Dendritic Cell (DC) activation [55, 66, 90, 91]. Although, the concentration of such factors as well plays an important role in MSCs expression. The lower concentration of IFN-γ guides them towards efficient Antigen-Presenting Cells (APCs) [92] while higher concentrations put an inhibitory response [55]. The Priming of MSCs with pro-inflammatory cytokines increases their expression of cell adhesion molecules like galectin-1, Vascular Cell Adhesion Molecule-1 (VCAM-1), chemokines ligands of C-C Chemokine Receptor Type (CCR)-5 and C-X-C chemokine Receptor type (CXCR)-3. This increases the cell-cell contact [70, 93] and thereby leads to immunosuppression. Further, pro-inflammatory cytokines also induce MSCs to express certain chemokine ligands like CXCL-9, CXCL10, and CCL2 that attract effector T cells [94]. Such cells upon contact with MSCs lead to immuno-modulation of T cells and is induced through NO or FAS ligand-induced apoptosis [71, 94].

4.3. *In Vivo* Studies

Mesenchymal Stem Cells (MSCs) may be implanted through various routes including local injection, intravenous, or intra-lymphatic. The therapeutic injection via parenteral routes is given based on their homing property [8]. Even a patent has been registered for adipose-derived mesenchymal stem cells for intra-lymphatic administration in autoimmune and inflammatory diseases [95] (Table **1**). Upon *in vivo* application, MSCs, whether allogenic or autologous, are considered to survive for long periods (90 days) but not indefinitely in the horse [35, 96]. As such the cells may not be removed actively but their indefinite self-renewal properties are not maintained [97]. In most of the studies, allogeneic MSCs implantation has failed to elicit any auto-immune reaction [7, 15]. Even repeated intra-articular implantation of allogeneic MSCs in horse and dog appears to be safe and devoid of any kind of hypersensitivity reaction [98, 99].

The immunomodulatory effect of MSCs has been demonstrated in numerous animal models. In a lab animal model that studied the effect of MSCs on allergen challenged mice, it was shown that MSCs have suppressive effects on airway hyper-responsiveness, airway inflammation, and goblet cell metaplasia. This was comparable irrespective of whether the cells were given prior to challenge or after the challenge except that the Broncho-Alveolar Lavage Fluid (BALF) was more prominent in mice that received MSC prior to allergen challenge as compared to the mice that received MSC later. It was shown that MSCs recruit CCR2+ monocytes to suppress allergic airway inflammation as inhibition of the same (CCR2 antagonist) tended to suppressive MSCs effects [100]. In another bleomycin-induced lung injury murine model, MSCs inhibited inflammation and fibrosis within the lungs of mice. The further evaluation confirmed that MSC transcriptome revealed Interleukin 1 Receptor Antagonist (IL1RN) as a potential mediator of this effect [101]. In lipopolysaccharide-induced acute lung injury murine model, MSCs attenuated lung injury by decreasing protein level and neutrophil recruitment into the Broncho-Alveolar Lavage Fluid (BALF) and improving the histologic change, also decreased the protein levels of pro-inflammatory cytokines including IL-1β, IL-6, and TNF-α, but had little effect on the protein expression of PCNA, caspase-3, and caspase-9 [102].

In an acute myocarditis rat model, intravenous administration of BM-MSCs suppressed immune reaction by reducing levels of monocyte chemotactic protein-1 and improved angiogenesis. This has led to an improved overall myocardial function [103]. Comparing the effect of BM-MSCs to that of fibroblasts in a hepato-toxicity model, the former cells reduced serum biomarkers of liver damage, reduced leukocyte infiltration to the liver and improved animal survival in comparison to the latter. Real-time monitoring of leukocyte trafficking to

the liver by single-photon emission computed tomography showed BM-MSCs actively prevented leukocyte homing and infiltration at the site of injury [104]. Similarly, in a renal model, implantation of MSCs could reduce levels of IL-1β, a pro-inflammatory cytokine and increased levels of IL-4, an anti-inflammatory cytokine in renal tissue [105]. In a murine and canine cutaneous model, MSCs enhanced wound repair. The cells were able to decrease IL-2 and INF-γ [106, 107]. Also preliminary data on Graft Versus Host Disease (GVHD) patients transplanted with bone marrow, MSCs were able to protect against the disease [108]. In acute spinal cord injury in dogs, MSCs prevented further damage through enhancement of anti-oxidative and anti-inflammatory mechanisms, without inducing adverse effects. The cells in combination with methylprednisolone sodium succinate were able to reduce 3-nitrotyrosine, 4-hydroxynenonal and cyclooxygenase-2 levels, and interleukin-6, tumor necrosis factor-α, and phosphorylated-signal transducer and activator transcription 3 levels [109]. In an induced chronic Inflammatory Bowel Disease (IBD) mice model, an improvement in clinical symptoms (bloody and watery stool), weight loss and histopathological profile were reported in MSCs treated group as compared to the control group [110]. In a similar way, in colitis, an improvement in clinical symptoms and histopathological findings was reported post-MSCs parenteral implantation [111].

The health status of an individual may affect the MSCs immuno-modulatory properties. In the case of acute GVHD and Systemic Lupus Erythematosus (SLE), MSCs decrease the Th1 response [112, 113]. Contrarily, in the case of allergic inflammatory diseases of airway (allergic rhinitis and asthma), BM-MSCs favour the shift from Th2 to Th1 responses [114-119]. Even inflammatory conditions tend to change MSCs immuno-modulatory gene expression. This leads to an enhanced immunosuppressive response [70, 120, 121]. Thus, it is important to consider the health status of an individual before one opts for MSCs therapy.

An overview of the self-renewal, differentiation and immunomodulatory properties of mesenchymal stem cells is depicted in Fig. (**1**).

5. CONFLICTING RESEARCH REPORTS

Although the literature is full of studies that favor MSCs immuno-modulatory effects but many studies have failed to see immuno-privileged and/ immuno-modulatory effects of the cells [3, 9, 15, 122]. Many studies have shown that MSCs carry a number of receptors that can interact with T-cells. These include MHC-I, a variety of adhesion molecules and other integrins that have their counterpart ligands on T-cells like Lymphocyte Functional Antigen-3 (LFA3; CD58) [123]. Even several other studies have shown that MSCs may contain intracellular deposits or may express MHC-II alloantigen under inflammatory environment (IFN-γ) [77, 124-126]. Some reports showed allo-MSC antibodies were generated against the allogenic MSCs [127, 128]. Also, MHC-mismatched MSCs activated complement-dependent cytotoxicity that led to their targeted death [128].

Despite numerous *in vivo* studies that showed favorable healing effects of MSCs, various studies, however, have failed to get desired results [129-131]. In equine osteoarthri-

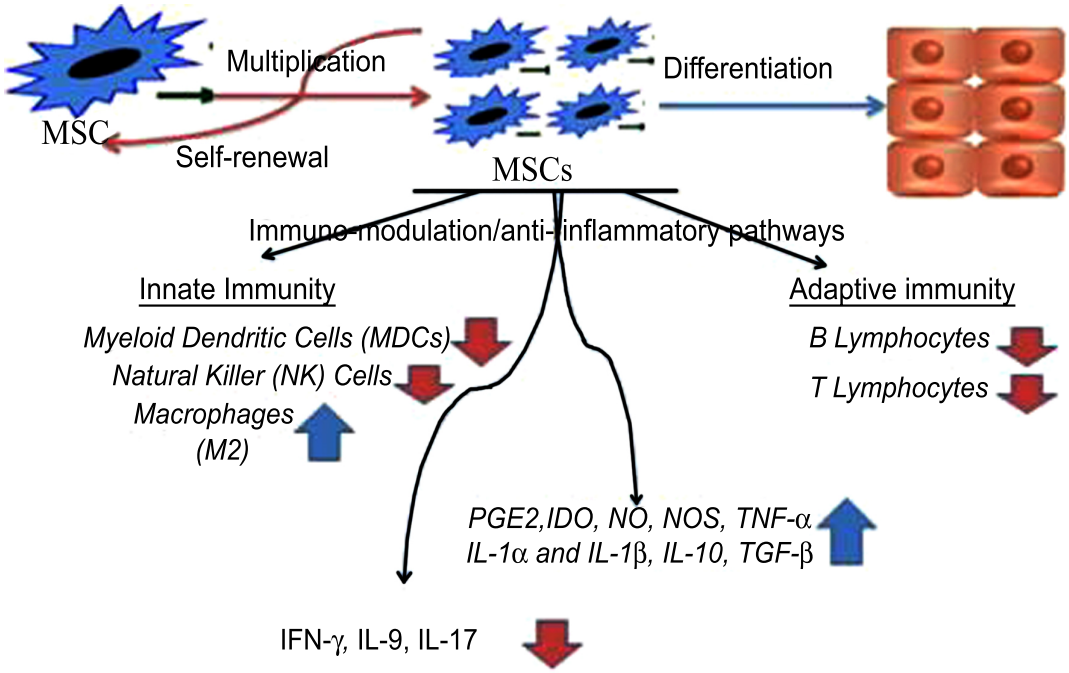

Fig. (1). Mesenchymal stem cell self-renewal, differentiation and immuno-modulatory properties. MSCs mechanisms of immune-modulation: Suppression of T- and B- cells; PGE2 secreted by MSCs suppress T-cell proliferation and their cytokine production; IDO degrades tryptophan and thereby inhibits lympho-proliferation; MSCs increase the levels of NO and NOS that inhibits TCR induced T-cells proliferation and cytokine production; MSCs secrete anti-inflammatory IL10, IL-α and IL-16; Allogeneic MSCs reduce IFN-ϒ and IL-17, and increase in TNF-α, IL1α and IL1β that aid in immunosuppression.

tis cases, MSCs showed reduced production of glycosaminoglycans [132], and in addition, the cellular expression was more of adhesion molecule and less of migration-related molecules [133, 134]. Besides, exposure to the pro-inflammatory cytokines (IL-1β and TNF-α) decreased MSCs expression levels of articular cartilage-specific matrix, though their proliferation potential remained unaffected [132]. The decreased expression of factors like SOX-9, TGF-β1 and of matrices like aggrecan, collagen II galactin expression was recorded [132, 135]. An *in vivo* equine study reported an undesirable clinical response upon repeated intra-articular implantations of the allogeneic equine BM-MSCs [136]. Thus, it is worth mentioning that allogenic implantation of MSCs may develop some potential adverse effects, besides, expected therapeutic efficacy may not be achieved [137]. Even a study on Graft-Versus-Host Disease (GVHD) in mice, allogenic MSCs failed to protect against GVHD [130]. MSCs therapy on GVHD considered useful in preliminary studies that have failed to be considered as the optimal therapy to prevent the immune reaction.

An overview of the recent methods patented for culture, differentiation and application of mesenchymal stem cells is presented in Table **1**. [31-34, 47, 95, 138-149].

Table 1. Patents for Culture, Differentiation, and Application of Mesenchymal Stem Cell.

S. No.	Title of Patent	Patent No. Assigned	Year of Grant / Application	Current Status	References
1	Method for differentiating pluripotent stem cell-induced from a mesenchymal stem cell into osteoblasts	US10053669	2013	Application granted	Fisk, N.M., Wolvetang, E.J. [31]
2	Improved differentiation of mesenchymal stem cells into osteoblasts	EP2899266	2015	Application active	Munoz, C.J.R., Diaz, T.J.M., Herenci, B.C., Rodriguez, O.M.E., Montes, D.G.A.R., Martinez-Moreno, J.M., Pena, Y.A., Portillo, M.R., Garcia, P.A., Gundlach, K., Büchel, P.M.J., Steppan, S., Passlick-Deetjen, J. [32]
3	One neural stem cell cryopreservation solution and method of use	CN104542576	2015	Application granted	Zhiyuan, L., Sihao, D., Wenyu, C., Dahua, L., Yang, X. [33]
4.	Species for early predict mesenchymal stem cell osteogenic differentiation potential gene detection kit	CN107475402	2017	Application granted	Henghui, Z., Bo, D., Haibo, W., Dandan, Z., Yong, Y., Ping, F. [34]
5.	Serum-free medium for human umbilical cord mesenchymal stem cells and preparation method thereof	CN105112365	2018	Application granted	Yifei, W., Xiaofeng, L., Qiaoli, W., Qiuying, L. [47]
6	Adipose-derived mesenchymal stem cells for intra-lymphatic administration in autoimmune and inflammatory diseases	KR101900664	2018	Granted	Dalemans, W., Lombardo, E. [95]
7	Mesenchymal stem cells for oral inflammation treatment	US20160199414	2016	Application active	Arzi, B., Borjesson, D.L., Verstraete, F.J.M. [138]
8	Encapsulated stem cells for the treatment of inflammatory disease	WO2016086020	2016	Application active	Weiss, M., Grumet, M.H. [139]
9	Stem cell carrier and method for bone regeneration with 3D customized CAD/CAM using the carrier	EP3034102	2016	Application active	Lee, J.J. [140]
10	Hypoxia-cultured mesenchymal stem cells for treating atherosclerotic lesions	US20160113968	2016	Application active	Hung, S.C. [141]
11	Externally used gel preparation containing human umbilical cord mesenchymal stem cell extract as well as preparation method and application of externally used gel preparation	CN106474155	2019	Application granted	Han, H.Q., Lu, Z.Y., Zhang, B.J., Qin, Z., Xiong, L., Liu, J.J., Xu, Y., Huang, W.J. [142]

Table (1) contd….

S. No.	Title of Patent	Patent No. Assigned	Year of Grant / Application	Current Status	References
12	Genetically modified mesenchymal stem cells expressing alpha-1 antitrypsin (AAT)	EP3242933	2016	Active application	Günther, C., Geiger- Schredelseker, S., Hermann, F., Huss, R., Forster, D.L. [143]
13	Genetically modified mesenchymal stem cells expressing an immune response-stimulating cytokine to attract and/or activate immune cells	WO2016026854	2016	Application active	Günther, C., Theoharis, S., Hermann, F., Huss, R. [144]
14	Mesenchymal stem cells for the treatment of CNS diseases	US9474787	2016	Application Granted	Kadouri, A., Bar-Ilan, A., Melamed, E., Offen, D., Sadan, O., Bahat-Stromza, M. [145]
15	Activated mesenchymal stem cells for wound healing and impaired tissue regeneration	US9011840	2015	Application granted	Bartholomew, A., Lee, S., Szilagyi, E. [146]
16	Management of osteoarthritis using pooled allogeneic mesenchymal stem cells	WO2015022670	2015	Application active	Gupta, P.K., House, A.C., Das, A.K., Majumdar, A.S., Raj, S.S., Balasubramanian, S., Rengasamy, M. [147]
17	Human-derived mesenchymal stem cell factor, and preparation method and application thereof	CN105543313	2015	Application granted	Yingying, R., Baihua, J., Jinqiong, H., Rong, W., Yuntao, D. [148]
18	Mesenchymal stem cell compositions for the treatment of microbial infections	US20140134140	2013	Application pending	Caplan, A.I., Bonfield, T.L. [149]

CONCLUSION

MSCs have been extensively studied stem cells due to their immunomodulatory effects, in addition, to their self-renewal and trans-differentiation properties. The cells have been well harvested, isolated and characterized by almost all the adult and fetal tissues in various species. Among various properties, immuno-modulatory properties of the cells are considered as an important mechanism to bring about the therapeutic effects. Numerous *in vitro* and *in vivo* studies have been conducted to show their immuno-modulatory and / anti-inflammatory activities. This helps to bring the allogenic therapy into the action. However, some of the studies have failed to get the desired results and even have shown the opposite effects. Thus, further studies are required to accumulate more data to translate the therapy into clinical cases.

CURRENT & FUTURE DEVELOPMENTS

There is a need to investigate the effects of micro-environment on the MSCs cellular physiology. The cells have to be cultured in a uniform environment for effective comparative studies. The *in vitro* and *in vivo* studies need to be definitive conducted simultaneously for better understanding and thereby clinical applications.

LIST OF ABBREVIATIONS

MSCs = Mesenchymal Stem Cells

CFU-Fs = Colony Forming Unit Fibroblasts

CD = Cluster of Differentiation

ISCT = International Society for Cellular Therapy

FBS = Fetal Bovine Serum

MHC = Major Histocompatibility Complex

STC-1 = Stanniocalcin

STG-6 = Tumor Necrosis Factor-stimulated Gene-6

IL1-Ra = Interleukin 1 Receptor Antagonist

DCs = Dendritic Cells

NK = Natural Killer

TLRs = Toll-Like Receptors

ICAM-1 = Intracellular Adhesion Molecule 1

VCAM-1 = Vascular Cell Adhesion Molecule 1

TNF- α = Tumor Necrosis Factor-α (TNF-)

IFN-γ = Interferon-γ

PGE2 = Prostaglandin E2

IL-6 = Interleukin-6

NO = Nitrous Oxide

TGF-β1 = Transforming Growth Factor β

IDO	=	Indoleamine 2,3 Dioxygenase
sHLA-G	=	Soluble Human Leukocyte Antigen-G
APCs	=	Antigen Presenting Cells
CXCR	=	Chemokine Receptor Type
CXCL-9	=	C-X-C- Motif Chemokine Ligand
BALF	=	Broncheo-Alveolar Lavage Fluid
IL1RN	=	Interleukin 1 Receptor Antagonist
PCNA	=	Proliferating Cell Nuclear Antigen
GVHD	=	Graft Versus Host Disease
IBD	=	Inflammatory Bowel Disease
LFA3	=	Lymphocyte Functional Antigen-3

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No Animals/Humans were used for studies that are base of this research.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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