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Mesenchymal Stem Cell-Mediated T Cell Immunosuppression

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Abstract

Besides being a pool for stromal cells and connective tissues, the mesenchymal stem cells (MSCs) as well exert a potent immunosuppression against almost all types of immune cells, particularly T cells. Many in vitro and in vivo studies revealed that the reported regenerative property of MSCs is partially due to the immunosuppressive activity of MSCs where it creates an optimal microenvironment for the execution of reparative and restorative processes. To date, MSCs can interact with nearly all cells of the immune system, in a convoluted mechanism with the ability of inhibiting the activation, proliferation, and function of T cells. These characteristics showcase MSCs' candidature as a natural immunosuppressive agent in regenerative medicine, therapies for immune disorders and tissue engineering. In this review, the intricate mechanisms of MSC-mediated immunosuppression on T cells were briefly evaluated. The physical, paracrine and molecular interactions that being tools for delivering the immunosuppression were also highlighted.

Introduction

Mesenchymal stem cells or stromal cells (MSCs) are classically known as a group of the heterogeneous stromal cell populations with non-hematopoietic nature and, able differentiate into cells of connective tissues [1]. Upon an appropriate induction, MSCs are capable of giving rise to a diverse range of mesodermal lineage tissues, including bone, cartilage, adipose tissue, tendon, and muscle [2]. Besides being a reservoir for various mature cells as of any other type of stem cells, MSCs as well reported to possess a unique immunosuppressive activity which is mainly reflected in the form of anti-inflammatory activities [3].

Based on the immunosuppressive ability, MSCs have been utilised in various clinical applications since the 1990s [4]. Particularly, the laboratory-expanded MSCs were infused to ameliorate acute and chronic graft-versus-host disease (GVHD) in patients receiving allogeneic hematopoietic stem cell transplantation [5]. Subsequently, several clinical reports on the MSC-based treatment of various diseases were published, and as such, it has elicited excitement and promising therapeutic interventions for many degenerative and malignant diseases. These properties cumulate and establish MSCs as a widely accepted ideal candidate cell type in regenerative medicine and therapies for immune disorders and tissue engineering [6].

However, the key to improvement of the clinical application that exploits immunosuppressive function of MSCs is relying on a better understanding of the upstream and downstream intricate mechanisms. Most of the studies on investigating the immunosuppressive properties of MSCs had extensively focused on unravelling the molecular pathways geared towards exploring and modifying intermediate and cell signalling molecules [7]. This to improve the immunosuppressive characteristics of MSCs and resolve the immunosuppression versus immunogenicity issues raised by previous studies. Thus, in line with the current trend in this field, this review discusses the recent findings on the various mechanisms employed by MSCs, to suppress T cell-mediated immune response.

Immunosuppressive Properties of MSCs

In recent years, much attention has been given to the immunosuppressive property of MSCs. Although the exact mechanism that governs such immunosuppressive activity is still elusive, yet the outcome of MSCs treatment in numerous one-off clinical applications and clinical trials had shown a promising therapeutic benefit. Accordingly, Yanez et al. in 2006 showed that adipose tissue-derived MSCs could efficiently control the GvHD associated with allogeneic hematopoietic transplantation [8]. The observed immunosuppressive phenomenon is resultant of very intricate process where it involves the secretion of immunosuppressive molecules and various growth factors by MSCs [1]. Also, several studies have correlated these immunosuppressive molecules and growth factors with immune homeostasis, reparative and regenerative functions of MSCs [9,10].

To start with a simple approach, the secretion of soluble factors and cell-to-cell contact are always the first level in the immunosuppressive cascade where the interaction of target immune cells with MSCs is initiated [11]. This interaction plays a vital part in determining the magnitude of immunosuppression. Although MSCs are known inherently immunosuppressive, in which the ability of MSCs to exert an immunosuppression is independent of activation triggered by primed T cells, however, some studies support the prerequisite of inflammation to 'licence' MSCs. The early work from Djouad et al. suggested that the immunosuppression mediated by MSCs was in response to inflammation as evidenced by the existence of TNF-α, IL-1α/β and IFN-γ [12]. Thus, in response to the inflammatory environment, many soluble factors, as well as immunosuppressive factors along with several chemokine and adhesion molecules, are produced by MSCs. These include interleukin (IL)-10, transforming growth factor (TGF)-β and IL-1 receptor antagonist (IL-1Ra), CXCR3 ligands, CCR5 ligands, intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1). The accumulation of these factors creates a suitable milieu where their concerted effect congregate with an amplified immunosuppression [13]. However, the ability of MSC's culture supernatant to substantially inhibit the proliferation of T cells indicate a certain degree of the inherent potential of MSCs to exert immunosuppression via soluble factors but enhanced with the existence of inflammation [14].

Mechanisms of T Cell Immunosuppression by MSCs

The MSC-mediated immunosuppression is facilitated by a convoluted mesh of interaction between target immune cells and MSCs through physical contact and secretion of soluble factors. Researchers have suggested that the end product of these interactions is the prevention of T-cell activation and inhibition of T cell proliferation leading to direct and indirect immunosuppression of T cells [15]. Nonetheless, the immunosuppression exerted by MSCs could be dependent on T cells activation where the byproducts of T cells activation needed to prime MSCs to be immunosuppressive. In other words, MSCs support the survival of quiescence T cell and only exert inhibition of proliferation when they are activated [16]. Upon co-culture with MSCs, the cell surface markers of T cell activation like CD25 [17], CD28 [18] and CD69 [19] are downregulated and as a result, the likelihood of antigenic activation of T cells by DCs and other APCs is greatly reduced. This leaves the T-cell population at the naïve or quiescent state [20].

Although the mechanisms of T cell suppression by MSCs can be studied closely by grouping them into two broad groups, i.e. the direct and the indirect mechanism, it is of utmost importance to carefully peruse the factors associated with these mechanisms at the molecular level.

Indirect Mechanism

The indirect mechanism of immunosuppression is one of the methods by which MSCs escape from immune response and modulate T cell proliferation. This achieved through paracrine interactions with other immune cells involving soluble factors, growth factors, growth inhibitors, chemoattractant as well as degradative enzymes. As a result, the normal metabolism and function of immune cells like DCs, Regulatory T Cells (Tregs) and naïve T cells are altered [21].

Factors such as PGE_2, IL-10, human leukocyte antigen-g5 (HLA-G5), heme oxygenase 1 (HO-1) and transforming growth factor beta (TGF-β) released by MSCs induce the generation and expansion of Tregs which in turn inhibits the proliferation of T cells [21]. The endocytosis as well as cell cycle progression from G_o to G_1 of precursors of DCs, CD34+ hematopoietic progenitors and monocytes are inhibited by MSCs through IL-6, PGE_2, and growth-regulated oncogene-gamma (GRO-γ). In such paracrine manner, the soluble factors secreted by MSCs leads to the impairment of differentiation, maturation, and function of DCs that leads T cell anergy/inactivation. Subsequently, the important cell surface molecules on DCs and the corresponding cytokines such as MHC class II, CD40, CD80, CD83, CD86, IFN-γ and IL-12 gets downregulated too. Finally, these impair DC functions by preventing the formation of a functional immune synapse with T cells, antigen presentation ability and hence activation/proliferation of T cells [21, 22].

The functional profile of DCs changes in the presence of MSCs where it induces the generation of tolerogenic DC. One of the potent cytokine secreted by MSCs that able to produce tolerogenic DCs is GRO-γ [22]. Tolerogenic DCs can induce T cell anergy, stimulate Tregs production and Th1 to Th2 phenotype switch. In lymph nodes, MSCs stimulates the downregulation of C-C

Motif Chemokine Receptor 7 (CCR-7) on DCs and chemotactic migration to C-C Motif Chemokine Ligand 12 And 19 (CCL-12 and CCL-19) on naïve T- cells. This interaction causes a subside in the migratory property of DCs to regions where naïve T cells are found thereby preventing their activation [23].

The effector functions of T and B cells is mainly influenced helper T cells. The cytokines secreted by T helper cells will determine the polarity of immune response either inclines toward the cellular or humoral immunity. Besides the microenvironment, MSCs as well can affect the plasticity and differentiation of helper T cells [24, 25]. Upon stimulation, helper T cells are either converted to the proinflammatory Th1 cells (which secrete IFN-γ, IL-2 and TNF-α) [26] or the anti-inflammatory Th2 cells (which secretes IL-4, IL-5, IL-6, IL-9, IL-10, and IL-13) [27]. By impairing the generation of specific helper T cells, MSCs could tune down the cell-mediated immunity and inflammation. Similarly, the Th2 cells are also equally inhibited by MSCs through induction of Tregs [28, 29].

Direct Mechanism

The MSCs mediated immunosuppression can be achieved through a direct contact between MSCs and T cells. These interactions involve receptor-ligand interactions, binding of soluble factors to specific receptors, upregulation and downregulation of the expression of key receptors and ligands. The resultant effect is the direct inhibition of proliferation and prevention of activation of cytotoxic T cells as well as alteration of T helper differentiation [30, 31].

In the direct mechanism, the cell-cell contact is an instrument to deliver the required volume of suppression on T cells' functions. For instance, MSCs bind to T cells through CD200, a protein that expressed on T cell surface which correlates to the downregulation of T cell function [32]. The ligation between programme death ligand 1 (PDL1) on T cells binds to its receptor PD1 on MSCs to halt T-cell proliferation [33]. Furthermore, FAS and FASL interactions among these cells trigger the extrinsic pathway of apoptosis [34]. To date, approximately 30 different soluble factors were associated with mediating immunosuppressive activity of MSCs on T-lymphocyte activation and proliferation [35]. These include semaphorin-3A [36], hepatic growth factor (HGF) [37], PGE_2 [38], TGF-β [39], IDO [40], nitric oxide (NO) [41], IL-6 [42], IL-10 [43], and galectins [44]. These factors bind to specific receptors on T-cells to exert immunosuppressive effects.

Most of the studies had documented the anti-proliferative effect of MSCs on cell cycle of T cells [11, 45-47]. In acquired immunity, the expansion of antigen-specific T cells is vital, and it permits the amplification of T cell clones once activated to meet the demand of inflammation. Thus, targeting T cell proliferation would be an ideal way to disturb T cell function as a part of immunosuppression. The anti-proliferative activity of MSCs is generic where it halts the expansion of activated T cells by any modes of stimulations. It has been shown that the anti-proliferation is a consequence of cell cycle arrest in which the activated T cells failed to complete the S phase of cell cycle due to detention in G_1 phase [48]. However, a diverse range of mechanisms had been inflicted to cause this MSC-induced anti-proliferation that affects the signalling pathways of T cell proliferation.

Conclusion

Although the utilisation of MSCs to treat tissue degeneration, improve allograft tolerance and curtail inflammation has been shown to be safe and tolerated, yet results from other studies, have reported adverse clinical outcomes that could associate with therapeutic approaches [49]. Hence, this has prompted the need for a great understanding of the science involved in the interactions between MSCs and T cells. Despite an enormous amount of data are available, but careful and meticulous scrutiny of the source of MSCs, immunoregulatory mechanisms as well as the response of MSCs to different physiological and biochemical stimuli in both in vitro and in vivo environment is very necessary for the validation of its clinical applications. Although it will be hard to anticipate the mechanisms that mediate MSC-exerted immunosuppression due to many confounding factors such stem cell heterogeneity and variation of in vitro culture, yet identification of such mechanisms is important to delineate the potential adverse effects. Therefore, the exploration of molecular-based studies on the interaction of MSCs and T cells will enable the identification of potential adverse clinical outcome that may arise after MSCs-based therapy as well as the development of therapeutic interventions to address this challenge.

References

1. Uccelli A, V Pistoia, L Moretta (2007) Mesenchymal stem cells: a new strategy for immunosuppression? Trends in immunology 28: 219-226.
2. Pittenger, M.F, Mackay AM, Beck SC, Jaiswal RK, Douglas R, et al. (1999) Multilineage potential of adult human mesenchymal stem cells. Science 284: 143-147.
3. Klinker, MW, Marklein RA, Lo Surdo JL, Wei CH, Bauer SR, et al. (2017) Morphological features of IFN-γ–stimulated mesenchymal stromal cells predict overall immunosuppressive capacity. Proceedings of the National Academy of Sciences 114: 2598-2607
4. Bruder SP, DJ Fink, AI Caplan (1994) Mesenchymal stem cells in bone development, bone repair, and skeletal regenaration therapy. Journal of cellular biochemistry 56: 283-294.
5. Takahashi I, Sato K, Mera H, Wakitani S, Takagi M, et al. (2016) Effects of agitation rate on aggregation during beads-to-beads subcultivation of microcarrier culture of human mesenchymal stem cells. Cytotechnology 69: 503-509.
6. Murphy MB, K Moncivais, AI Caplan (2013) Mesenchymal stem cells: environmentally responsive therapeutics for regenerative medicine. Experimental & molecular medicine 45: 54.

7. Ramasamy R, Lam EW, Soeiro I, Tisato V, Bonnet D, Dazzi F, et al. (2007) Mesenchymal stem cells inhibit proliferation and apoptosis of tumor cells: impact on in vivo tumor growth. Leukemia 21: 304-310.

8. Yanez R, Lamana ML, García-Castro J, Colmenero I, Ramírez M, et al. (2006) Adipose Tissue-Derived Mesenchymal Stem Cells Have In Vivo Immunosuppressive Properties Applicable for the Control of the Graft-Versus-Host Disease. Stem cells 24: 2582-2591.

9. Kode JA (2009) Mesenchymal stem cells: immunobiology and role in immunomodulation and tissue regeneration. Cytotherapy 11: 377-391.

10. Du WJ, Reppel L, Leger L, Schenowitz C, Huselstein C, et al. (2016) Mesenchymal Stem Cells Derived from Human Bone Marrow and Adipose Tissue Maintain Their Immunosuppressive Properties After Chondrogenic Differentiation: Role of HLA-G. Stem Cells and Development 25: 1454-1469.

11. Ramasamy R, Tong CK, Seow HF, Vidyadaran S, Dazzi F, et al. (2008) The immunosuppressive effects of human bone marrow-derived mesenchymal stem cells target T cell proliferation but not its effector function. Cellular Immunology 251: 131-136.

12. Djouad F, Fritz V, Apparailly F, Louis-Plence P, Bony C, et al. (2005) Reversal of the immunosuppressive properties of mesenchymal stem cells by tumor necrosis factor α in collagen□induced arthritis. Arthritis & Rheumatology 52: 1595-1603.

13. Ren G, Zhang L, Zhao X, Xu G, Zhang Y, et al. (2008) Mesenchymal stem cell-mediated immunosuppression occurs via concerted action of chemokines and nitric oxide. Cell stem cell 2: 141-150.

14. Ramasamy R, Fazekasova H, Lam EW, Soeiro I, Lombardi G, et al. (2007) Mesenchymal stem cells inhibit dendritic cell differentiation and function by preventing entry into the cell cycle. Transplantation 83: 71-76.

15. Di Nicola M, Carlo-Stella C, Magni M, Milanesi M, Longoni PD, et al. (2002) Human bone marrow stromal cells suppress T-lymphocyte proliferation induced by cellular or nonspecific mitogenic stimuli. Blood 99: 3838-3843.

16. Benvenuto F, Ferrari S, Gerdoni E, Gualandi F, Frassoni F, et al. (2007) Human Mesenchymal Stem Cells Promote Survival of T Cells in a Quiescent State. Stem Cells 25: 1753-1760.

17. Yoo HS, Lee K, Na K, Zhang YX, Lim HJ, et al. (2017) Mesenchymal stromal cells inhibit CD25 expression via the mTOR pathway to potentiate T-cell suppression. Cell death & disease 8: 2632.

18. Liu M (2015) Study of immunomodulatory function of exosomes derived from human umbilical cord mesenchymal stem cells. Zhonghua yi xue za zhi 95: 2630-2633.

19. Arutyunyan I, Elchaninov A, Bolshakova G, Glinkina V, Goldshtein D, et al. (2015) Elimination of allogeneic multipotent stromal cells by host macrophages in different models of regeneration. International journal of clinical and experimental pathology 8: 4469-4480.

20. Beyth, S, Borovsky Z, Mevorach D, Liebergall M, Gazit Z, et al. (2005) Human mesenchymal stem cells alter antigen-presenting cell maturation and induce T-cell unresponsiveness. Blood 105: 2214-2219.

21. Haddad, RF Saldanha-Araujo (2014) Mechanisms of T-cell immunosuppression by mesenchymal stromal cells: what do we know so far? BioMed research international.

22. Vellasamy S, Tong CK, Azhar NA, Kodiappan R, Chan SC, et al. (2016). Human mesenchymal stromal cells modulate T-cell immune response via transcriptomic regulation. Cytotherapy 18: 1270-1283.

23. Laranjeira, P, Monia Pedrosa, Susana Pedreiro, Joana Gomes, Antonio Martinho, et al. (2015) Effect of human bone marrow mesenchymal stromal cells on cytokine production by peripheral blood naive, memory, and effector T cells. Stem cell research & therapy 6: 3.

24. Duffy M.M (2011) Mesenchymal stem cell effects on T-cell effector pathways. Stem cell research & therapy 2: 34.

25. Wang Y (2014) Plasticity of mesenchymal stem cells in immunomodulation: pathological and therapeutic implications. Nature immunology 15: 1009-1016.

26. Pianta S (2015) Amniotic membrane mesenchymal cells-derived factors skew T cell polarization toward Treg and downregulate Th1 and Th17 cells subsets. Stem Cell Reviews and Reports 11: 394-407.

27. Batten P, Sarathchandra P, Antoniw JW, Tay SS, Lowdell MW, et al. (2006) Human mesenchymal stem cells induce T cell anergy and downregulate T cell allo-responses via the TH2 pathway: relevance to tissue engineering human heart valves. Tissue engineering 12: 2263-2273.

28. Renner P (2009) Mesenchymal stem cells require a sufficient, ongoing immune response to exert their immunosuppressive function. Transplantation proceedings Elsevier 41: 2607-2611.

29. Dave S, A Vanikar, H Trivedi (2017) Mesenchymal Stem Cells Induced In Vitro Generated Regulatory-T Cells: Potential Soldiers of Transplantation Biology. Current Biotechnology 6: 26-32.

30. Abumaree M, Abomaray FM, Alshabibi MA, AlAskar AS, Kalionis B, et al. (2017) Immunomodulatory properties of human placental mesenchymal stem/stromal cells. Placenta 59:87-95.

31. Uccelli A, NK Rosbo (2015) The immunomodulatory function of mesenchymal stem cells: mode of action and pathways. Annals of the New York Academy of Sciences 1351: 114-126.

32. Loibl M, Andreas Binder, Marietta Herrmann, Fabian Duttenhoefer, R. Geoff Richards, et al. (2014) Direct cell-cell contact between mesenchymal stem cells and endothelial progenitor cells induces a pericyte-like phenotype in vitro. BioMed research international

33. Dezutter-Dambuyant C, Durand I, Alberti L, Bendriss-Vermare N, Valladeau-Guilemond J, et al. (2016) A novel regulation of PD-1 ligands on mesenchymal stromal cells through MMP-mediated proteolytic cleavage. Oncoimmunology 5: 1091146.

34. Nishizawa K, R Seki (2016) Mechanisms of immunosuppression by mesenchymal stromal cells: a review with a focus on molecules. Biomed Res Clin Prac 1: 116.

35. La Rocca G, Lo Iacono M, Corsello T, Corrao S, Farina F, et al. (2013) Human Wharton's jelly mesenchymal stem cells maintain the expression of key immunomodulatory molecules when subjected to osteogenic adipogenic and chondrogenic differentiation in vitro: new perspectives for cellular therapy. Current Stem Cell Research & Therapy 8: 100-113.

36. Lepelletier Y, Lecourt S, Renand A, Arnulf B, Vanneaux V, et al. (2009) Galectin-1 and semaphorin-3A are two soluble factors conferring T-cell immunosuppression to bone marrow mesenchymal stem cell. Stem cells and development 19: 1075-1079.

37. Chen S, Chen X, Wu X, Wei S, Han W, et al. (2017) Hepatocyte growth factor-modified mesenchymal stem cells improve ischemia/reperfusion-induced acute lung injury in rats. Gene therapy 24: 3-11.

38. Feigenson M, Eliseev RA, Jonason JH, Mills BN, O'Keefe RJ, et al. (2017) PGE2 Receptor Subtype 1 (EP1) Regulates Mesenchymal Stromal Cell Osteogenic Differentiation by Modulating Cellular Energy Metabolism. Journal of Cellular Biochemistry 118: 4383-4393.

39. Daneshmandi S, MH Karimi, AA Pourfathollah (2017) TGF-B1 Transduced Mesenchymal Stem Cells Have Profound Modulatory Effects on DCs and T Cells. Iranian Journal of Immunology 14: 13.

40. Lotfi R, L Steppe, R Hang, M Rojewski, B Jahrsdörfer, et al. (2017) ATP promotes immunosuppressive MSCs inhibiting lymphocyte proliferation and expressing indoleamine dioxygenase. European Journal of Cancer 72: 98.

41. Sato K, Ozaki K, Oh I, Meguro A, Hatanaka K, et al. (2007) Nitric oxide plays a critical role in suppression of T-cell proliferation by mesenchymal stem cells. Blood 109: 228-234.

42. Najar M, Rouas R, Raicevic G, Boufker HI, Lewalle P, et al. (2009) Mesenchymal stromal cells promote or suppress the proliferation of T lymphocytes from cord blood and peripheral blood the importance of low cell ratio and role of interleukin-6. Cytotherapy 11: 570-583.

43. Meng X, Li J, Yu M, Yang J, Zheng M, et al. (2017) Transplantation of mesenchymal stem cells overexpressing IL10 attenuates cardiac impairments in rats with myocardial infarction. Journal of Cellular Physiology 233: 587-595.

44. Gieseke F, Böhringer J, Bussolari R, Dominici M, Handgretinger R, et al. (2010) Human multipotent mesenchymal stromal cells use galectin-1 to inhibit immune effector cells. Blood 116: 3770-3779.

45. Tong CK, HF Seow, R Ramasamy (2008) Cord blood-derived mesenchymal stem cell does not stimulate nor inhibits T lymphocytes activation. Med J Malaysia 63: 77-8.

46. Vellasamy S, Pratheep Sandrasaigaran, Sharmili Vidyadaran, Maha Abdullah, Elizabeth George, et al. (2013) Mesenchymal stem cells of human placenta and umbilical cord suppress T-cell proliferation at G0 phase of cell cycle. Cell Biology International 37: 250-256.

47. Vellasamy S, Tong CK, Azhar NA, Kodiappan R, Chan SC, et al. (2016) Human mesenchymal stromal cells modulate T-cell immune response via transcriptomic regulation. Cytotherapy 18: 1270-83.

48. Glennie, S, Soeiro I, Dyson PJ, Lam EW, Dazzi F, et al. (2005) Bone marrow mesenchymal stem cells induce division arrest anergy of activated T cells. Blood 105: 2821-2827.

49. Hartleif S, Michael Schumm, Michaela Döring, Markus Mezger, Peter Lang, et al. (2017) Safety and Tolerance of Donor-derived Mesenchymal Stem Cells in Pediatric Living-donor Liver Transplantation: The Mystep1 Study. Stem Cells International 2017: 1-11.