Annals of Stem Cell Research & Therapy

Review Article
Published: 21 May, 2018

Immune Properties of Human Dental Pulp Stem Cells and Interactions with the Immune System

*Hamada Attoumani[1], Michel Drancourt[1] and Eric Ghigo[2]**

[1]Department of Emerging Infectious and Tropical Diseases, Aix-Marseille University, France

[2]Department of Emerging Infectious and Tropical Diseases, Scientific Research National Center, France

Abstract

Dental Pulp Stem Cells (DPSCs) are mesenchymal stem cells well known by the scientific community thanks to the studies about their regenerative properties. This regenerative capacity is mainly due to their ability to differentiate into multi-lined cells and their self-renewal. Since their isolation by Gronthos in 2000, their regenerative capacity has been intensively studied in relation to immunity. Thus, several studies have reported about the immune properties of DPSCs. Nevertheless, little is known about the mechanism of action that DPSCs exert in their micro-environment and their interactions with immune cells. The purpose of this review is to summarize the set of knowledge on the immune properties of DPSCs and their interactions with immune cells.

Keywords: Dental pulp stem cells (DPSC); Immunity; Immunomodulatory; TLRs; NF-kb

General Presentation

Characterization

Dental Pulp Stem Cells (DPSCs) were first isolated by Gronthos et al. [1] in 2000 from a permanent tooth pulp of the third molar. Morphologically, they are fusiform, tapered with a central nucleus and a bulky cytoplasm. In comparison with Bone Marrow Stem Cells (BMSCs), they are highly proliferative and have a high potential for clonogenicity [2]. They represent a large and accessible stock of post-natal stem cells. The basic physiological properties of DPSCs are based on their multipotence. DPSCs are able to self-renew and to differentiate into multi-lineage cells, they are responsible for the maintenance and repair of periodontal tissues. They also have the ability to differentiate into different cell types such as odontonblasts, chondrocytes, adipocytes and neuronal cells according to appropriate induction conditions [1,3-5]. In homeostatic conditions, they are in a quiescent state, but after stimulation (i.e. mechanical or bacterial aggression, when tooth decay occurs), the DPSCs can be activated, resulting in a proliferation and migration into the damaged tissues where they differentiate into periodontal cells and form a repaired dentin. According to the criteria required by the International Society for Cellular Therapy ISCT, DPSCs are mesenchymal stromal cells [6]. They adhere to the plastic when they are maintained under standard culture conditions, proliferate by forming colonies and express mesenchymal antigen markers (CD13, CD29, CD44, CD73, CD90 and CD105) but lack hematopoietic markers (CD34 and CD45) [7]. Interestingly, this type of cell does not differentiate into immune cells.

Isolation of the dental pulp stem cells

Avulsion is performed for orthodontic reasons. Starting from the tooth, there are basically two methods for isolating DPSCs: an enzymatic method and an outgrowth method [8]. After extraction, the tooth surface is cleaned, disinfected and mechanically fractured around the cement-enamel junction. Then the pulp tissue is gently recovered in a standard medium and minced with a scalpel in cubes of 2 mm^2. This first part is common to both techniques. The enzymatic method consists in digesting the pulp by using an enzyme cocktail (dispase or collagenase) to obtain a monocellular suspension that is seeded in a medium with a plastic-adherent container. The outgrowth method is based on the direct culturing of pulp tissue fragments in a standard culture medium with a plastic-adherent container, with the stem cells budding around the explants. The proliferation medium is supplemented with penicillin or streptomycin antibiotics and antifungal amphotericin B. After cell proliferation, a washing and purification step by flow cytometry will follow which will eliminate contaminant cells such as monocytes, fibroblasts and hematopoietic stem cells.

OPEN ACCESS

Correspondence:
Eric Ghigo, Department of Emerging Infectious and Tropical Diseases, Scientific Research National Center, Mediterranean-Infection University Hospital Institute, 19-21 Bd Jean Moulin, CEDEX 05, 13385 Marseille, France,
E-mail: Eric.ghigo@gmail.com

Received Date: *23 Mar 2018*
Accepted Date: *18 May 2018*
Published Date: *21 May 2018*

Citation:
Attoumani H, Drancourt M, Ghigo E. Immune Properties of Human Dental Pulp Stem Cells and Interactions with the Immune System. Ann Stem Cell Res Ther. 2018; 2(3): 1018.

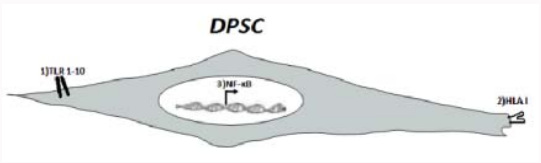

Figure 1: Immune characteristics of Dental Pulp Stem Cells (DPSC). DPSC are equipped with TLR 1-10, HLA-1 and produce NF-kB.

Immune Properties of Human Dental Pulp Stem Cells

TLR expression

The dental pulp is a richly vascularized and innervated tissue, containing different cell populations, such as fibroblasts, odontoblasts, immune cells (dendritic cells, macrophages and lymphocytes) and DPSCs [9-11]. This set constitutes a dynamic complex forming a functional unit conferring to the dental pulp its nutrition and repair functions as well as a primordial role in the response to aggressions. This activation is the consequence of the commitment of TLRs expressed on the cell surface by pathogens. Toll-like receptors are type I transmembrane glycoproteins with an extracellular domain Rich in Leucine Repeats (LRR) that is responsible for the recognition of PAMPs (Pathogens Associated Molecular Patterns) and a transmembrane and intracellular domain named Toll-Interleukin 1 cytoplasmic domain (TIR), that is required for downstream signaling [12]. TLRs are known to be expressed primarily in innate and adaptive immune cells, however, some studies have shown their expression on other cell types such as mesenchymal stromal cells [13]. Indeed, in 2012 Fawy El Sayed et al. [14] have shown for the first time that DPSCs express TLR 1-10 (Figure 1). In addition, the data showed that according to the inflammatory environment of the DPSCs, TLRs are expressed in different ways. Thus, in an inflammatory environment, TLR 2,3,4,5 and 8 are over-expressed while TLR 1,7, 9 and 10 are under-expressed, with an abolished TLR 6 expression [14].

Immunogenic profile

DPSCs are immuno-privileged cells also hypo immunogenic. As shown in Figure 1, they express on their surface the MHC I constitutively as all the nucleated cells and do not express MHC II [15]. Although DPSCs are not direct immune effectors and do not express MHC II, they may act indirectly in initiating the immune response by activating immune cells by a signalling cascade [16]. It has been shown that human Mesenchymal Stromal Cells (MSCs) have the ability to express MHC II in inflammatory conditions and present antigens, an important characteristic of immune cells [17-19]. It is therefore suggested that DPSCs under inflammatory or stress conditions could also express MHC II and become immunogenic.

NF-KB roles

Discovered in 1986 by Sen and Baltimore, NF-KB is a key transcription factor for the transcription of light chain kappa immunoglobulin genes. NF-KB's activity was first demonstrated in a murine model [20]. Soon after, it was found that its expression is ubiquitous, and present in almost all cells, including dental pulp stem cells (Figure 1). Numerous works have shown that NF-KB plays a central role in immunity through the production and the regulation of pro-inflammatory cytokines such as TNF-α, IL-8, chemokines (MCP-1), adhesion molecules (ICAM-1, VCAM-1, E-selectin), growth factors and antimicrobial peptides [21]. In 2005, Chang et al. [22] showed for the first time the expression of NF-KB in stem cells derived from the dental pulp and its implication in their immunomodulatory properties. DPSCs stimulated with both TNF and LPS induce the activation of NF-KB, leading to the production of pro-inflammatory cytokines such as IL-8. In addition, another study consolidates the idea that DPSCs possess an NF-KB dependent immune activity by reporting that *lipopolysaccharide* (LPS) induces IL-8 production via the TLR-4, MyD88 and NF-KB pathways [23]. NF-KB is also involved in the migration of DPSCs; indeed, the migration of DPSCs is important in the process of dentin repair during an attack of the tooth by an infectious agent during cariogenesis [24]. The pro-inflammatory cytokine IFN-γ has been shown to promote the proliferation as well as the migration of DPSCs depending on the activation of NF-KB [16]. Migration and immunity are indivisible processes, thus, the ability of cells to migrate is essential for tissue repair and immune response. In this same study, the authors also showed that NF-KB plays a role in the adhesion of DPSCs. The DPSCs stimulated by LPS activate the expression of NF-KB inducing an increase of the expression of IFN-γ, ICAM-1, integrin-β1 and VEGF and enhancing the adhesion of DPSCs [16]. In addition, NF-KB plays also a role in the process of cell differentiation. It has been shown that NF-KB is involved in the differentiation of mesenchymal stem cells. TNF-α promotes osteogenic differentiation of human mesenchymal stem cells via the NF-KB signaling pathway [25]. In agreement with mesenchymal stem cells, DPSCs stimulated by TNF-α also differentiate into osteogenic cells via NF-KB factor as shown in Figure 1 [26].

Immunomodulatory activity

In addition to multipotency and clonogenicity, DPSCs have been reported to regulate the immune response in many diseases and thus play an important role in immunity. Immunomodulation is the capacity of a substance to modify the immune responses by increasing (immuno-stimulator) or decreasing it (immuno-suppressor) to maintain homeostasis. Pierdomenico et al. [26] in 2005 have shown that DPSCs have immunoregulatory characteristics. Compared with BM-SCs, DPSCs are more immunosuppressive and the inhibition of Phyto-Hem -Agglutinin (PHA) stimulated T cell proliferation is more marked in the co-culture of DPSCs-T lymphocytes than of MSC-T lymphocytes [27]. The underlying mechanisms of these immunosuppressive properties of DPSCs have been discovered in 2011. This study shows that DPSCs suppressed the proliferation of Peripheral Blood Mononuclear Cells (PBMCs) by the production of Transforming Growth Factor (TGF), and this expression is correlated with the increased expression of TLR-4 and TLR-3 [28]. A recent study has shown that co-culture between naive T lymphocytes CD4+ and DPSCs induces an increase in Treg cells CD4+ and FOXP3+. This activation is the consequence of a strong TGF-β and IL-10 anti-inflammatory cytokines production [29]. Thus, this process confers immunotolerance to DPSCs. The molecular and cellular mechanisms underlying immunomodulatory properties rely heavily on the production of TGF-β, being the main soluble factor inhibiting hyper immune reactions. TGF-β is a pleiotropic cytokine known for its role in immune suppression. Several studies have shown its direct or indirect involvement in this process trough its link with the Treg, allowing the induction of the FOXP3 transcription factor, the master regulator of Treg naive cells. The master transcriptional factor of Treg cells is responsible for the suppression of pro-inflammatory T cells, inhibits the secretion of pro-inflammatory cytokines such as IL-2, IFN-γ, IL-4, IL-17 and enhances anti-inflammatory cytokine like IL -10 [30,31]. Others studies have also demonstrated the

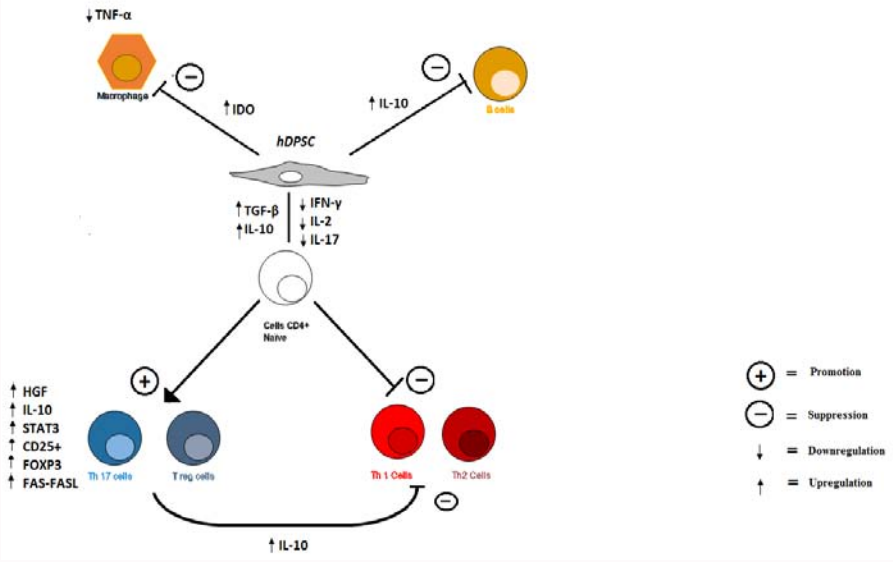

Figure 2: Immunosuppressive activity of Dental Pulp Stem Cells (DPSC). DPSC suppress Peripheral Blood Mononuclear Cell (PBMC) by producing immunosuppressive molecules such as Transforming Growth Factor beta (TGF- β) and interleukin 10. DPSC inhibit the function of macrophages and the production of B cells by producing respectively Indoleamine 2,3-Dioxygenase (IDO) and IL-10. DPSC induce a differentiation of CD4+ naïve cells to Treg cells and TH17 cells that activate STAT3, FOXP3, FAS-FASL, CD25+ produce also solubles factor IL-10 and Hepatocyte Growth Factor (HGF). Additionally DPSC inhibit the production of proinflammatory cytokine such as IL-2, IL-17 and IFN- to suppress Th1 and Th2 cells.

immunomodulatory properties of DPSCs in contact with immune cells, such as lymphocytes. Cell-cell contact of DPSCs and T lymphocytes induces the expression of FAS to induce their apoptosis [32]. FAS are a transmembrane cellular receptor inducing the death of cells expressing the Tumor Necrosis Factor (TNF6) receptor super family. The FAS / FASL interaction induces apoptotic cell death [33].

Interaction between Dpscs and Immune Cells

In teeth, dental pulp stem cells are found at the anatomical location of apical dental pulp. The microenvironment of this niche is composed of type I and III collagenic proteins, fibronectin, tenascin and other non-collagenous Extra Cellular Matrix (ECM) proteins. Cells such as fibroblasts, endothelial cells, pericytes and lymphatic vessels are also found, all of these elements constitute a functional unit. The main role of this complex is to regulate the homeostatic state of the dental pulp stem cells involved in the maintenance and repair of the pulp. In addition to their putative function, the DPSCs possess a role in immune defense based on a close relationship with defensive cells. Defensive cells such as inflammatory and immuno competent cells, namely dendritic cells, macrophages, lymphocytes and endothelial cells are also found, these cells are present in the dental pulp [34]. DPSCs interact with the cells of innate and adaptive immunity *via* direct cell-cell interactions or through the set of immunomodulatory molecules secreted (Figure 2).

Interaction between DPSCS and macrophages

Several researchers have already evidenced the presence of macrophages in healthy dental pulp, found in different morphological forms: round, oval, short-spindle, and dendritic [35]. Macrophages are the most predominant immune cells present in the dental pulp, with a sentinel role [10]. Macrophages play an important role in immunity and defense (acting mainly as trapping cells) thanks to their main function, the phagocytosis of foreign components, including infectious microorganisms. They also have the ability to communicate with other immune cells through the production of substances such as cytokines such as IL-1, IL-6, Tumor Necrosis Factor (TNF), antimicrobial peptides and Reactive Oxygen Species (ROS) as well as Growth Factors of Fibroblasts (FGF) and Endothelial Cells (EGF) that promote wound repair [36]. Recent studies have shown the interaction between dental pulp stem cells and macrophages. DPSCs are also able to modulate the immune system through their interaction with macrophages. A report has shown that DPSCs suppress macrophage activity via the TNF/IDO axis [37]. Moreover, DPSCs suppress the secretion of TNF produced by macrophages stimulated by LPS [37]. IDO is a cytosolic enzyme involved in the catabolism of tryptophan via the kynurenine degradation pathway. The products of tryptophan degradation are known to have immunoregulatory functions on immune cells, such as macrophages, they are also known for their strong immunosuppressive activity [38]. It was also reported that there are monocytes circulating in the dental pulp. Monocytes have a protective effect on DPSCs against cytotoxicity and cell-mediated NK cell lysis [39].

Interaction between DPSCs and T lymphocytes

In 1987, Jontel et al. [40] were the first to show the presence of CD8+ and CD4+ T lymphocytes in a healthy human dental pulp. This result was confirmed later by Hahn et al. [41]. Moreover, they demonstrate that the proportion of CD8+ is higher than that of CD4+ in normal teeth, establishing a CD4+/CD8+ ratio equal to 0.26 for normal pulp and 1.14 for pathological pulp. Gang Ding et al. [42] showed that DPSCs adopt an anti-inflammatory and immunosuppressive behavior when they are co-cultured with PBMC. DPSCs failed to stimulate the proliferation of allogene T cell and suppressed T cell proliferation and B cells by TGF-β secreting. In the same work, they also reported that DPSCs up-regulate IL-10, an anti-inflammatory cytokine and down-regulate the production of IL-2, IL-17 and IFN-gamma, pro-inflammatory cytokines, associated with an increase of Treg and Th 17 [43]. Moreover, according to the discovering of a perinatal murine model, DPSCs are capable of suppressing cell proliferation, inducing activated cell activation and ameliorating the inflammatory response. This process is associated with the expression

of FAS-FASL [32]. In addition, similar expressions of DPSC with other kinds of T cells have been reported. Recently Hong et al. [29] showed that co-cultured CD4+ T cells with DPSCs increase the number of CD4+, CD25+ and FOXP3+ regulatory T cell, trough the expression of TGF-β and IL-10. Thus, DPSCs can modulate immune tolerance by producing Treg. It has also been reported that DPSCs have an immunosuppressive activity on helper T cells, Th1 and Th2 subsets of CD4+ lymphocytes, and in parallel they stimulate Th17, a subset of Treg. A strong expression of Hepatocyte Growth Factor (HGF) is required to stimulate the production of Stat3 in Th17 cells, thus allowing for an inflammatory switch of pro-inflammatory Th17 in immunosuppressant Th17 [44].

Interaction between DPSC and B lymphocyte

The studies by Pulver et al. in 1977, Pekovic and Frillery in 1984 with immuno histochemistry or Jontel et al. in 1987 with monoclonal antibodies against B lymphocytes showed no evidence of the presence of B cells in a healthy human dental pulp. In 1989, thanks to the work done by Hahn et al., the presence of B lymphocytes in a healthy human dental pulp was evidenced. However, other teams have shown that there are a lot of antibodies in an inflamed pulp compared to a healthy pulp [10]. This presence of antibodies therefore suggests that there are B lymphocyte in the inflamed pulp [45,46]. This observation was confirmed by the work of Chin-Lo Hahn et al. [46] who they reported the presence of B lymphocytes in an infected pulp.

Conclusion

DPSCs possess immunological properties based on their hypo-immunogenicity and their secretome. These secretory activities enable them to interact with immune cells through the production of the identified soluble factors. Although there has been a major interest in their immune properties over the past decades, research has focused only on paracrine activity by analogy with mesenchymal cells in general. Other types of immune properties, like those found in professional immune cells, such as phagocytosis and the production of antimicrobial compounds could be studied in years to come.

Acknowledgment

This review was financially supported by the «Conseil departmental de Mayotte» and we would like to take this opportunity to thank Cedric Torre most sincerely for his reflection to improve this review.

References

1. Gronthos S, Mankani M, Brahim J, Robey PG, Shi S. Postnatal human dental pulp stem cells (DPSCs) in vitro and in vivo. Proc Natl Acad Sci USA. 2000;97(25):13625-30.
2. Alge DL, Zhou D, Adams LL, Wyss BK, Shadday MD, Woods EJ, et al. Donor-matched comparison of dental pulp stem cells and bone marrow-derived mesenchymal stem cells in a rat model. J Tissue Eng Regen Med. 2010;4(1):73-81.
3. Nemeth CL, Janebodin K, Yuan AE, Dennis JE, Reyes M, Kim DH. Enhanced chondrogenic differentiation of dental pulp stem cells using nanopatterned PEG-GelMA-HA hydrogels. Tissue Eng Part A. 2014;20(21-22):2817-29.
4. Jo YY, Lee HJ, Kook SY, Choung HW, Park JY, Chung JH, et al. Isolation and characterization of postnatal stem cells from human dental tissues. Tissue Eng. 2007;13(4):767-73.
5. El-Sayed KF, Dörfer C, Fändrich F, Gieseler F, Moustafa MH, Ungefroren H. Adult Mesenchymal Stem Cells Explored in the Dental Field. In Mesenchymal Stem Cells - Basics Clin Appl II. 2012;89-103. Berlin, Springer, Berlin, Heidelberg.
6. Dominici M, Le Blanc K, Mueller I, Slaper-Cortenbach I, Marini F, Krause D, et al. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Cytotherapy. 2006;8(4):315-7.
7. Chalisserry EP, Nam SY, Park SH, Anil S. Therapeutic potential of dental stem cells. J Tissue Eng. 2017;8:2041731417702531.
8. Karamzadeh R, Eslaminejad MB, Aflatoonian R. Isolation, characterization and comparative differentiation of human dental pulp stem cells derived from permanent teeth by using two different methods. J Vis Exp. 2012;(69):4372.
9. Rombouts C, Giraud T, Jeanneau C, About I. Pulp Vascularization during Tooth Development, Regeneration, and Therapy. J Dent Res. 2017;96(2):137-44.
10. Jontell M, Okiji T, Dahlgren U, Bergenholtz G. Immune defense mechanisms of the dental pulp. Crit Rev Oral Biol Med. 1998;9(2):179-200.
11. Farges JC, Alliot-Licht B, Renard E, Ducret M, Gaudin A, Smith AJ, et al. Dental Pulp Defence and Repair Mechanisms in Dental Caries. Mediators Inflamm. 2015;2015:230251.
12. Leulier F, Lemaitre B. Toll-like receptors--taking an evolutionary approach. Nat Rev Genet. 2008;9(3):165-78.
13. Ledesma-Martínez E, Mendoza-Núñez VM, Santiago-Osorio E. Mesenchymal Stem Cells Derived from Dental Pulp: A Review. Stem Cells Int. 2016;2016:4709572.
14. Fawzy El-Sayed KM, Klingebiel P, Dörfer CE. Toll-like Receptor Expression Profile of Human Dental Pulp Stem/Progenitor Cells. J Endod. 2016;42(3):413-7.
15. Collart-Dutilleul P-Y, Chaubron F, De Vos J, Cuisinier FJ. Allogenic banking of dental pulp stem cells for innovative therapeutics. World J Stem Cells. 2015;7(7):1010-21.
16. He X, Jiang W, Luo Z, Qu T, Wang Z, Liu N, et al. IFN-γ regulates human dental pulp stem cells behavior via NF-κB and MAPK signaling. Sci Rep. 2017;7:40681.
17. Romieu-Mourez R, François M, Boivin M-N, Stagg J, Galipeau J. Regulation of MHC Class II Expression and Antigen Processing in Murine and Human Mesenchymal Stromal Cells by IFN-γ, TGF-β, and Cell Density. J Immunol. 2007;179(30):1549-58.
18. Chan JL, Tang KC, Patel AP, Bonilla LM, Pierobon N, Ponzio NM, et al. Antigen-presenting property of mesenchymal stem cells occurs during a narrow window at low levels of interferon-γ. Blood. 2006;107(12):4817-24.
19. Stagg J, Pommey S, Eliopoulos N, Galipeau J. Interferon-gamma-stimulated marrow stromal cells: a new type of nonhematopoietic antigen-presenting cell. Blood. 2006;107(6):2570-7.
20. Sen R, Baltimore D. Multiple nuclear factors interact with the immunoglobulin enhancer sequences. Cell. 1986;46(5):705-16.
21. Baldwin AS. Series Introduction: The transcription factor NF-κB and human disease. J Clin Invest. 2001;107(1):3-6.
22. Chang J, Zhang C, Tani-Ishii N, Shi S, Wang CY. NF-κB Activation in Human Dental Pulp Stem Cells by TNF and LPS. J Dent Res. 2005;84(11):994-8.
23. He W, Qu T, Yu Q, Wang Z, Lv H, Zhang J, et al. LPS induces IL-8 expression through TLR4, MyD88, NF-kappaB and MAPK pathways in human dental pulp stem cells. Int Endod J. 2013;46(2):128-36.
24. Gunzer M. Migration, cell-cell interaction and adhesion in the immune system. Ernst Schering Found Symp Proc. 2007;(3);97-137.
25. Hess K, Ushmorov A, Fiedler J, Brenner RE, Wirth T. TNFα promotes

osteogenic differentiation of human mesenchymal stem cells by triggering the NF-κB signaling pathway. Bone. 2009;45(2):367-76.

26. Feng X, Feng G, Xing J, Shen B, Li L, Tan W, et al. TNF-α triggers osteogenic differentiation of human dental pulp stem cells via the NF-κB signalling pathway. Cell Biol Int. 2013;37(12):1267-75.
27. Pierdomenico L, Bonsi L, Calvitti M, Rondelli D, Arpinati M, Chirumbolo G, et al. Multipotent mesenchymal stem cells with immunosuppressive activity can be easily isolated from dental pulp. Transplantation. 2005;80(6):836-42.
28. Tomic S, Djokic J, Vasilijic S, Vucevic D, Todorovic V, Supic G, et al. Immunomodulatory properties of mesenchymal stem cells derived from dental pulp and dental follicle are susceptible to activation by toll-like receptor agonists. Stem Cells Dev. 2011;20(4):695-708.
29. Hong JW, Lim JH, Chung CJ, Kang TJ, Kim TY, Kim YS, et al. Immune Tolerance of Human Dental Pulp-Derived Mesenchymal Stem Cells Mediated by CD4+CD25+FoxP3+ Regulatory T-Cells and Induced by TGF-β1 and IL-10. Yonsei Med J. 2017;58(5):1031-9.
30. Haiqi H, Yong Z, Yi L. Transcriptional regulation of Foxp3 in regulatory T cells. Immunobiology. 2011;216(6):678-85.
31. Mantel P-Y, Schmidt-Weber CB. Transforming growth factor-beta: recent advances on its role in immune tolerance. Methods Mol Biol Clifton NJ. 2011;677:303-38.
32. Zhao Y, Wang L, Jin Y, Shi S. Fas Ligand Regulates the Immunomodulatory Properties of Dental Pulp Stem Cells. J Dent Res. 2012;91(10):948-54.
33. Waring P, Müllbacher A. Cell death induced by the Fas/Fas ligand pathway and its role in pathology. Immunol Cell Biol. 1999;77(4):312-7.
34. Goldberg M, Hirata A. The Dental Pulp: Composition, Properties and Functions. JSM. 2017;5(1):1079.
35. Orban BJ, Bhaskar SN. Orban's Oral Histology and Embryology. Mosby.1976.
36. Elhelu MA. The Role of Macrophages in Immunology. J Natl Med Assoc. 1983;75(3):314-7.
37. Lee S, Zhang QZ, Karabucak B, Le AD. DPSCs from Inflamed Pulp Modulate Macrophage Function via the TNF-α/IDO Axis. J Dent Res. 2016;95(11):1274-81.
38. Mbongue JC, Nicholas DA, Torrez TW, Kim N-S, Firek AF, Langridge WH. The Role of Indoleamine 2, 3-Dioxygenase in Immune Suppression and Autoimmunity. Vaccines (Basel). 2015;3(3):703-29.
39. Jewett A, Arasteh A, Tseng H-C, Behel A, Arasteh H, Yang W, et al. Strategies to Rescue Mesenchymal Stem Cells (MSCs) and Dental Pulp Stem Cells (DPSCs) from NK Cell Mediated Cytotoxicity. PLoS One. 2010;5(3):e9874.
40. Jontell M, Gunraj MN, Bergenholtz G. Immunocompetent Cells in the Normal Dental Pulp. J Dent Res. 1987;66(6):1149-53.
41. Hahn CL, Falkler WA, Siegel MA. A study of T and B cells in pulpal pathosis. J Endod. 1989;15(1):20-6.
42. Durutürk L, Sarı Ş, Şengül A. Immunocompetent cell level as a diagnostic reference for pulpal pathosis of primary teeth. Arch Oral Biol. 2013;58(10):1517-22.
43. Ding G, Niu J, Liu Y. Dental pulp stem cells suppress the proliferation of lymphocytes via transforming growth factor-β1. Hum Cell. 2015;28(2):81-90.
44. Özdemir AT, Özgül Özdemir RB, Kırmaz C, Sarıboyacı AE, Ünal Halbutoğlları ZS, Özel C, et al. The paracrine immunomodulatory interactions between the human dental pulp derived mesenchymal stem cells and CD4 T cell subsets. Cell Immunol. 2016;310:108-15.
45. Baumgartner JC, Falkler WA Jr, Bernie RS, Suzuki JB. Serum IgG reactive with oral anaerobic microorganisms associated with infections of endodontic origin. Oral Microbiol Immunol. 1992;7(2):106-10.
46. Hahn C-L, Falkler WA, Siegel MA. A study of T and B cells in pulpal pathosis. J Endod. 1989;15(1):20-6.