Chapter

# GMSC: Updates of Advances on Its Therapy in Immunological Diseases

*Yuluan Hou and Song Guo Zheng*

## Abstract

Mesenchymal stem cells (MSCs) derived from various tissues are multi-potency of self-renewal and differentiation into multi-lineages, including chondrocytes, adipocytes and osteoblasts *in vitro* and *in vivo*. In addition, these cells also display potent immune regulatory roles that benefit the treatment of inflammatory and autoimmune diseases. We and others have previously identified that human gingival-derived mesenchymal stem cells (GMSCs) not only share similar biological features, but also display some potential advantages compared to other MSC populations. In the chapter, we have discussed the discovery, phenotypic and functional characteristics, as well as updated the advances of these cell therapies in immunological diseases.

**Keywords:** mesenchymal stem cells, gingival-derived mesenchymal stem cells, inflammatory and autoimmune diseases, immunomodulatory, cell therapy

## 1. Introduction

Mesenchymal stem cells (MSCs) are pluripotent stem cells derived from mesoderm with features of self-renewal and multi-lineage differentiation. These populations include MSCs that are primarily isolated from bone marrow (BMSCs) [1], fat [2], umbilical cord [3], dental pulp [4] and others [5, 6], particularly in most of adult tissues. Investigators have reported the successful differentiation of MSCs into mesenchymal-like cells, such as osteoblasts, chondrocytes, adipocytes [1–6], neural crest stem-like cells [7] and synoviocytes [8], and manifested that MSCs maintain immune homeostasis and prevent autoimmunity involving in the repair of impaired tissues and immunoregulation of autoimmune and inflammatory diseases [9, 10]. However, the occurrence and development of some autoimmune diseases are related to MSCs abnormality [11]. In addition, application of cell therapy using MSCs has weaknesses, like limited large-scale expansion *in vitro* and *vivo* [12], immunological rejection of allogeneic transplant and potential risk on tumorigenesis [13]. The availability of human gingival mesenchymal stem cells (GMSCs) together with their potent capacity of self-renewal, proliferation, multi-directional differentiation, inflammatory modulation and less tumorigenesis makes it as an ideal subtype of MSCs.

## 2. Discovery, development and biological characteristic of GMSCs

Gingiva is a unique oral tissue attached to the alveolar bone of tooth sockets, recognized as a biological mucosal barrier and a distinct component of oral mucosal immunity [14]. Wound healing within gingiva is characterized by rapid and fetal-like scarless healing, contrary to the common scar formation in skin [15]. Gingival tissue is easily assessable and gingival cells can be easily isolated and expanded from patients or healthy donors. Gingival fibroblast-like cells, including fibrocytes, myofibroblasts, pericytes and mesenchymal stem cells, a heterogeneous group of cells with distinct properties and functions, were named gingival fibroblasts before 2009, playing key roles in tissue development, maintenance and repair, as well as contributing to various pathologies [16]. Zhang et al. was the first to isolate and characterize a new population of precursor cells from human gingival tissues, termed GMSCs, which exhibit three unique stem cell-like properties as MSCs derived from bone marrow and other postnatal tissues [17]. Based on the minimal characterization criteria for human MSCs of the International Society for Cellular Therapy [18], the population of GMSCs shows: (1) *in vitro* proliferation as plastic-adherent cells with fibroblast-like morphology, colony-forming ability, (2) multipotent differentiation into different cell lineages, (3) positive expression of MSCs surface markers and stem cell-specific genes, negative of hemopoietic stem cell ones. Moreover, some studies reported that GMSCs manifested a higher expansion and telomerase activity and kept the features of MSCs, morphology and normal karyotype stable during cell expansion [19]. Recently, Gugliandolo et al. reported that most oncogenes of GMSCs at higher passengers were turned off, suggesting that long-term cultured GMSCs may be safer in the clinical setting [20].

| Advantages | GMSCs | Other MSCs | References |
|---|---|---|---|
| **Source** | Gingiva<br>a. Easily accessible and no invasive<br>b. Wound healing rapid and scarless | Bone marrow and other adult tissues<br>a. Invasive and rare from bone marrow and tendon<br>b. Wound healing with scar in skin | [15] |
| **Safty** | Oncogenes at higher passengers turned off<br>And no tumorigenic | Potential risk on tumorigenesis | [20] |
| **Basical characters** | Homogenous<br>Proliferatation faster and morphology stable<br>Normal karyotype and telomerase acticity in long-term cultures | Heterogenous<br>Variable morphology and replicative senescence in vitro serial propagation<br>Loose MSC characteristic at higher passages | [19] |
| **Regulation of immune** | Equal or even better immunoregulation in immunological diseases | Efficacy of the administration of MSCs for treatment of immune-related diseases has been confirmed in vivo studies. | [9], [10], [31], [53], [59], [63], |
| **Positive factors** | 3D spheroid culture<br>Hypoxic stimulation | No show in this chapter | [69],[74] |

**Table 1.**
*Advantages of GMSCs in the treatment of immunological diseases compared to other MSCs according to the updated studies.*

**Table 1** summarizes the advantages of GMSCs obtained from current studies in the treatment of immunological diseases.

## 3. Roles and mechanisms of GMSCs in treating immunological diseases

In response to the current challenges in the field of medicine on the efficacy and serious adverse effects of the current treatments, researchers are investigating the alternative therapies. In this regard, the use of MSCs represents a great promise for the treatment of a variety of immune-related diseases due to their potent properties of immunomodulatory ability [21, 22]. BMSCs and umbilical-cord MSCs (UC-MSCs) are widely studied because of their low immunogenicity [12, 23]. GMSCs, as a new subtype of MSCs, share strong abilities of immune regulation as MSCs from other tissues [24, 25]. As to update these advances of researches in GMSCs, we summarize the current recognition on the curative effects and mechanisms on immune and inflammation-related diseases (**Table 2**).

### 3.1 Immunoregulatory properties of GMSCs on autoimmune diseases

Autoimmune diseases are caused by defects in immune tolerance, resulting in that the body immune system failing to identify cells from their own or the foreign accompanied by the cellular or tissue damage [26]. Autoimmune diseases are categorized into systemic or organ-specific types according to the extent of tissue involvements [27]. The pathogenesis of autoimmune diseases is still not well-understood as multifactorial factors may be involved in at least both genetic and environmental factors [28, 29]. Although the conventional and biological therapies can somehow ameliorate clinical symptoms and decrease the morbidity and mortality, the limited efficiency, bone marrow toxicity and other side effects including infection and tumor are problematic [30]. Therefore it is desirable to find new strategies that can cure autoimmune diseases with minimal side effects. The MSCs therapy has been demonstrated to be likely as a new alternative approach. As a subset of MSCs, current studies show that GMSCs have even strong and better immunoregulatory effects than MSCs derived from other sources, through cell-cell contacting or secreting molecules to modulate both innate and adaptive responses [31].

Type 1 Diabetes Mellitus (T1DM) is an autoimmune disorder resulted from T cell-mediated destruction of pancreatic β-cells [32]. Hu et al. reported a clinical trial that implantation of Wharton's jelly-derived mesenchymal stem cells (WJ-MSCs) from the umbilical cord for newly-onset T1DM restored the function of islet β-cells in a longer time by improving the level of HbA1c and C peptide without acute or chronic side effects, suggesting that the implantation of WJ-MSCs for the treatment of newly-onset T1DM is safe and effective [33]. Researches in experimental models of mice manifested that MSCs inhibited the expansion of Th1, Th17 cells and stimulated the proliferation of CD4+CD25+Foxp3+ T regulatory (Treg) cells by reducing the levels of pro-inflammatory cytokines such as TNF-α, IFN-γ, CCL2, IL-1β, IL-2 and IL-17 but increasing the expression of immunoregulatory cytokines such as IL-4, IL-10 and IL-13 [9]. Zhang et al. infused GMSCs to determine the therapeutic effect on T1DM model, just as other MSCs, showed that GMSCs administration, homing to pancreas lymph nodes and pancreas, could delay diabetes onset, ameliorate pathology in pancreas by regulating down IL-17 and IFN-γ of CD4+ and CD8+ T cell and induce the generation of induced regulatory T (iTreg) *in vivo* which may be regulated through CD39/CD73 signal pathway [34]. Treg cells are a crucial immune suppressor that maintains the immune tolerance and prevents

| Type of diseases | | Model | Laboratory effects | Proposed mechanisms | References |
|---|---|---|---|---|---|
| **Autoimmune diseases** | T1DM | Mice | ↓Diabetes onset<br>↓Pathology scores | ↓IL-17 in spleen and lymph node<br>↓IFN-γ in spleen and lymph node<br>↑CD4+Foxp3GFP+Tregs<br>↑Islet β-cells | [34] |
| | CIA | Mice | ↓Severity of arthritis<br>↓histopathology scores | ↓IL-17 in lymph node<br>↓TGF-α in lymph nodes<br>↓IFN-γ in lymph nodes<br>↓IL-2 in lymph nodes<br>↑CD4+CD39+FoxP3+ Treg<br>↑CD39/CD73 signal<br>↑T-cell apoptosis | [38] [41] |
| **Allo-GVHD** | | Mice | ↓weight loss<br>↓inflammation degrees<br>↓pathological changes | ↓T cell proliferation<br>↓IFN-γ, IL-4, IL-17<br>↑CD39/CD73 signal<br>↑IDO signal | [45] |
| | Inflammatory bowel | Mice | ↓diarrhea and weight loss<br>↓disease activity<br>↑restore injured mucosal tissues | ↓CD4+T infiltration<br>↑IDO, IL-10<br>↑Fas/FasL signal<br>↑Treg infiltration<br>↑T-cell apoptosis | [17], [49] |
| **Inflammatory diseases** | Atherosclerosis | Mice | ↓plaque size and lipid deposition | ↓recruitment of inflammatory macrophages<br>↓Inflammatory Ly-6Chi+monocytes<br>↓Macrophage Foam Cell Formation<br>↓M1 Macrophages<br>↓IFN-γ, IL-4 in spleen<br>↑M2 Macrophages | [51] |
| | Periodontitis | Dog<br>Pig | ↑cementum-like tissue<br>↑bone<br>↑sharpey fibers | ↑differentiation of osteoblasts, cementoblasts, PDL fibroblasts in vivo<br>↑histological attachment level<br>↑junctional epithelium length<br>↑connective tissue adhesion | [55], [56] |
| **Allergic diseases** | CHS | Mice | ↑desensitize<br>↑suppress CHS | ↓ dendritic cells, $CD8^+$ T, TH-17 and MCs in LN<br>↑PGE2–EP3 signaling | [60],[61] |
| **Wound healing** | | Mice | ↑regenerated epidermis, skin appendages and hair follicles | ↓M1 macrophages<br>↑M2 macrophages<br>↑re-epithelialization, collagen deposition and angiogenesis<br>↑TGF-β, CTGF,Tenascin-C<br>↑IL-1RA | [39],[40] [64],[65], |

**Table 2.**
*List of studies in which the therapeutic potential of administration of GMSCs for the treatment of immunological diseases was obtained.*

the autoimmune responses [35–37]. It was also observed in rheumatoid arthritis animal model where GMSCs promoted Treg cell development to control autoimmune arthritis [38]. Some investigators also identified that high exocytotic fusion by secreting exosomes and cytokines is an alternative mechanism of GMSCs to promote the wound healing in diabetic patients, one of the most challenging complications in clinical medicine [39, 40].

The utilization of MSCs has reduced both the severity of disease and histopathology scores in rheumatoid arthritis models [9]. In collagen-induced arthritis (CIA) models, Chen et al. demonstrated that the adoptive transfer of GMSCs significantly delayed the onset of CIA and decreased the severity scores [38]. Histological and quantitative analysis of ankle joints demonstrated a significant decrease in synovitis, pannus formation and destruction of bone and cartilage in treated mice by increasing iTreg cells frequency while reducing percentages of Th1 and Th17 cells and relevant pro-inflammatory cytokines IFN-γ, IL-17, and TNF-α. Interestingly, Th2-type IL-4, IL-5 and IL-13 were not affected [38]. They found that GMSCs exerted the immune suppression functions indirectly *via* adenosine through CD39/CD73 signaling [38]. Recently, Gu et al. further supported this finding that GMSC ameliorated CIA and revealed that GMSC mediated T-cell apoptosis and influenced the polarization of the Th cells *via* a FasL/Fas pathway, resulting in immune tolerance and ameliorating the severity of CIA in mice [41].

### 3.2 Immunoregulation of GMSCs on graft-versus-host disease

Allogenic graft-versus-host disease (allo-GVHD) is a severe complication of organ or bone marrow transplantation related to the activation of alloreactive T cells or autoreactive mechanisms [42–44]. In clinical trials and experimental models, the administration of MSCs from bone marrow, adipose tissue and others decreased the severity of the symptoms and increased the survival. Most studies reported that MSCs inhibit reactive T cells trafficking and their proliferation. In addition, MSCs also stimulate cells differentiation into immunomodulatory cells such regulatory dendritic cells, Treg, Breg cells and M2 macrophages [9]. There is only a research of GMSCs for the treatment of allo-GVHD in mice model. Huang et al. revealed that GMSCs displayed the superior effect to BMSCs on suppressing xeno-GVHD according to the weight loss and inflammatory pathology in liver, lung, and intestine [45]. The underlying mechanism may be that GMSCs inhibited lymphocytes proliferation through CD39/CD73/adenosine and/or IDO signals without influencing CD4+Foxp3+ Treg cells [45].

### 3.3 Therapeutic progression of GMSCs in other inflammatory diseases

Inflammatory bowel disease characterized by dysfunction of the innate and adaptive immunity is a group of inflammatory conditions of the colon and small intestine [46–48]. The existing studies demonstrated administration of MSCs inhibited the proliferation and infiltration of inflammatory cells, for instance, significant inhibition in the expansion of Th1 and Th17 cells and opposite effect in the clonal expansion of Treg, by two main ways: direct cell-cell contact and the release of soluble factors [9]. In line with other tissues-derived MSCs, systemic infusion of GMSCs protected mice from colitis related tissue injuries and reduced the overall disease severity. Zhang et al. confirmed that GMSCs suppressed CD4+ T lymphocyte and promoted regulatory T cells infiltration to the colonic sites, which was accelerated by IFN-β-induced IDO and IL-10 [17]. While Yang et al. exhibited other actions of GMSCs in colitis that hydrogen sulfide upregulated the expression of

Fas/FasL in GMSCs coupling-induced T cells migration and T-cell apoptosis to maintain immunomodulation of GMSCs *in vivo* and *in vitro* [49].

Atherosclerosis is the major cause of cardiovascular diseases. Current evidences indicate that inflammation is involved in the pathogenesis of atherosclerosis and monocytes/macrophages are the major inflammatory cells [50]. Zhang et al. firstly indicated that GMSCs decreased inflammatory level, plaque size and lipid deposition in mice model *in vivo*, partly by inhibiting macrophage foam cell formation, suppressing the activation of M1 macrophages and promoting their development into the M2 phenotype *via* IDO and CD73 signals [51].

Periodontitis is a widespread bacterially induced immune-inflammatory disorder of the periodontium, featured with a progressive destruction of the tooth-supporting structures [52]. The milieu of bacterial biofilms challenges and activates host innate and adoptive immune systems to produce pro-inflammatory cytokines and chemokines for inflammatory cells recruitment, striking the balance of osteoblast and osteoclast [53]. MSCs from bone marrow, adipose, dental pulp and periodontal ligament have been testified to, *in vivo*, newly form periodontal bones, collagen fibers, periodontal ligament-like tissue and cementoid tissue indicating periodontium regeneration [54]. GMSCs also were proved to generate new cementum-like tissue, bone and sharpey fibers in dog and pig model of periodontitis [55, 56].

### 3.4 The contribution of GMSCs to contact hypersensitivity

Murine contact hypersensitivity (CHS) as a model similar to human allergic contact is caused by delayed-type hypersensitivity responses to antigens that come into contact with the skin [57]. The pathological process consists of sensitization phase, the elicitation or challenge phase, and resolution/regulation phase [58]. In this process, allergen-specific effector T cells and various types of innate immune cells are involved [59]. In 2011, Su et al. investigated the immunoregulatory role of GMSCs and for first time found that *i.v.* injection of GMSC significantly attenuated the CHS appearance at different phases of CHS, and showed that GMSCs-derived PGE2 played a crucial role in their inhibitory effect on dendritic cells and mast cells [60]. Li et al. further testified that PGE2–EP3 signaling played an important role in the immunomodulatory functions of GMSCs in murine CHS [61].

### 3.5 Wound healing

Cutaneous wound healing involves in three phases: inflammation, tissue formation, and remodeling [62]. Studies have demonstrated that systemically injected MSCs can home to injury sites accelerating wound repair [63]. Because of the rapid and fetal-like healing of gingival trauma, researchers have focused on the effect and mechanism of GMSCs. Experiments *in vitro* suggested that GMSCs were capable of switching macrophages from classical activation or proinflammatory M1 phenotype to an anti-inflammatory profile of M2 macrophages by soluble factors such IL-6, COX-2 and GM-CSF [64]. *In vivo* mice model suggested that enhancement of wound healing by systemic infusion of GMSCs related to enhanced re-epithelialization, collagen deposition and angiogenesis [64]. Compared with BMSCs, Linard et al. reported that gingival fibroblasts (GFs) intradermally injected in irradiated skin induced earlier development of thick, fully regenerated epidermis, skin appendages and hair follicles [65]. GFs also modified expression of ECM-related gene, ECM components (tenascin-C and a-smooth muscle actin) and wound healing-related factors, like TGF-β1 and CTGF [65]. While the influence to macrophage recruitment and differentiation of GFs was in accordance with Zhang et al., other studies presented that GMSC-derived exosomes accelerated wound healing in

a diabetic rat skin defect model [39, 40]. Kou et al. indicated that TNF-α-Fas/Fap-1 *via* the NF-κB pathway enhancing IL-1RA release in GMSCs participated in healing progress [40].

## 4. Analysis of factors influencing the function of GMSC

Only well preserved the comprehensive and stable features, GMSCs can be an alternative cell therapy to autoimmune and inflammation-related diseases. Many factors can disturb the functions of GMSCs. Su et al. reported disturbed oral microbiome weakened the wound healing of GMSCs through miR-21/Sp1/telomerase reverse transcriptase pathway [66]. The physical condition of donors is a key factor to properties of GMSCs. Assem et al. revealed that GMSCs exhibited a greater proliferation rate and higher surviving in normal individuals than the diabetic patients [67]. Moreover, GMSCs exosome from diabetic mice showed reduced IL-1RA and decreased Fas expression when compared to WT GMSCs [40]. Different culture techniques of GMSCs have a profound effect on their biological functions. Subbarayan et al. showed that GMSCs derived spheroids enhanced abilities of viability, pluripotency and multi-lineages and maintained the properties of stem cells convincingly than conventional culture methods [68]. Zhang et al. have confirmed that spheroid-derived GMSCs possessed better therapeutic efficacy than their adherent counterpart [69]. The spheroid-derived GMSCs also had a greater homing ability to mucositis sites and underwent a higher mesenchymal-epithelial transformation compared to conventional culture GMSC in murine model of chemotherapy-induced oral mucositis [69]. Although normal and inflammatory GMSCs similarly expressed mesenchymal stem cells markers and proliferation ability, inflammatory microenvironments indeed reduced differentiation potentials of GMSCs [70]. Zhang et al. demonstrated that initial inflammatory stimuli of IL-1 and TNF-α appeared essential for GMSCs proliferation and tissue regeneration, while with inflammatory persistence, this effect turned to osteogenesis followed by a short-term stimulatory [71]. However, Apatzidou et al. demonstrated that GMSCs from periodontal granulation tissue possessed similar immunophenotype and regeneration feature to those in healthy periodontal tissue [72]. Many studies have also demonstrated that other elements also affect the biological characteristics of GMSCs, for instance, Lee et al. reported that dexamethasone accelerated the aging of GMSCs through downregulating SIRT1 and IL6 and upregulating EDN1 genes *via* the AGE/RAGE pathway [73]. In addition, hypoxic enhanced the suppressive effects of GMSCs on peripheral blood mononuclear cells and inhibited the local inflammation of injured skin by suppressing the inflammatory cells, accompanying with reduction of TNF-α and increase of IL-10 [74].

## 5. Conclusion

The existing studies have documented that GMSCs have self-renewal, multi-lineage differentiation potential, and immunomodulatory properties. These properties make GMSCs an alternative cell-based therapy of autoimmune and inflammation-related diseases. Plenty of internal and external factors may affect their functions of renewal, regeneration and immunoregulation. Moreover, the specific mechanisms and clinical efficacies are indistinct. Future studies and clinical trials should be implemented to elaborate mechanisms and therapeutic effects of immunomodulatory properties in detail on various inflammatory and immunological diseases.

## Author details

Yuluan Hou[1] and Song Guo Zheng[2]*

1 Department of Clinical Immunology, Third Affiliated Hospital, Sun Yat-sen University, Guangzhou, China

2 Department of Internal Medicine, Ohio State University College of Medicine, Columbus, OH, USA

*Address all correspondence to: songguo.zheng@osumc.edu

IntechOpen

## References

[1] Caplan AI. Mesenchymal stem cells. Journal of Orthopaedic Research. 1991; **9**(5):641-650. DOI: 10.1002/jor.1100090504

[2] Zuk PA, Zhu M, Mizuno H. Multilineage cells from human adipose tissue: implications for cell-based therapies. Tissue Engineering. 2001; **7**(2):211-228. DOI: 10.1089/107632701300062859

[3] Wang H-S, Hung S-C, Peng S-T, et al. Mesenchymal stem cells in the Wharton's jelly of the human umbilical cord. Stem Cells. 2004;**22**(7):1330-1337. DOI: 10.1634/stemcells.2004-0013

[4] Gronthos S, Brahim J, Li W, et al. Stem cell properties of human dental pulp stem cells. Journal of Dental Research. 2002;**81**(8):531-535. DOI: 10.1177/154405910208100806

[5] In't Anker PS, Scherjon SA, Kleijburg-van der Keur C, et al. Isolation of mesenchymal stem cells of fetal or maternal origin from human placenta. Stem Cells. 2004;**22**(7):1338-1345. DOI: 10.1634/stemcells.2004-0058

[6] Salingcarnboriboon R, Yoshitake H, Tsuji K, et al. Establishment of tendon-derived cell lines exhibiting pluripotent mesenchymal stem cell-like property. Experimental Cell Research. 2003; **287**(2):289-300

[7] Zhang Q, Nguyen PD, Shi S, et al. Neural crest stem-like cells non-genetically induced from human gingiva-derived mesenchymal stem cells promote facial nerve regeneration in rats. Molecular Neurobiology. 2018; **55**(8):6965-6983. DOI: 10.1007/s12035-018-0913-3

[8] Ferre FC, Larjava H, Loison-Robert LS, et al. Formation of cartilage and synovial tissue by human gingival stem cells. Stem Cells and Development. 2014;**23**(23):2895-2907. DOI: 10.1089/scd.2013.0547

[9] Leyendecker A Jr, Pinheiro CCG, Amano MT, et al. The use of human mesenchymal stem cells as therapeutic agents for the in vivo treatment of immune-related diseases: A systematic review. Frontiers in Immunology. 2018; **9**:2056. DOI: 10.3389/fimmu.2018.02056

[10] Ng J, Hynes K, White G, et al. Immunomodulatory properties of induced pluripotent stem cell-derived mesenchymal cells. Journal of Cellular Biochemistry. 2016;**117**(12):2844-2853. DOI: 10.1002/jcb.25596

[11] Sun LY, Zhang HY, Feng XB, et al. Abnormality of bone marrow-derived mesenchymal stem cells in patients with systemic lupus erythematosus. Lupus. 2007;**16**(2):121-128. DOI: 10.1177/0961203306075793

[12] Xu J, Wang D, Liu D, et al. Allogeneic mesenchymal stem cell treatment alleviates experimental and clinical Sjogren syndrome. Blood. 2012; **120**(15):3142-3151. DOI: 10.1182/blood-2011-11-391144

[13] Wang Y, Huso DL, Harrington J, et al. Outgrowth of a transformed cell population derived from normal human BM mesenchymal stem cell culture. Cytotherapy. 2005;**7**(6):509-519. DOI: 10.1080/14653240500363216

[14] Palmer R, Lubbock M. The soft connective tissues of the gingiva and periodontal ligament: Are they unique. Oral Diseases. 1995;**1**(4):230-237

[15] Mak K, Manji A, Gallant-Behm C, et al. Scarless healing of oral mucosa is characterized by faster resolution of inflammation and control of myofibroblast action compared to skin wounds in the red Duroc pig model.

Journal of Dermatological Science. 2009;**56**(3):168-180. DOI: 10.1016/j.jdermsci.2009.09.005

[16] Hakkinen L, Larjava H, Fournier BP. Distinct phenotype and therapeutic potential of gingival fibroblasts. Cytotherapy. 2014;**16**(9):1171-1186. DOI: 10.1016/j.jcyt.2014.04.004

[17] Zhang Q, Shi S, Liu Y, et al. Mesenchymal stem cells derived from human gingiva are capable of immunomodulatory functions and ameliorate inflammation-related tissue destruction in experimental colitis. Journal of Immunology. 2009;**183**(12): 7787-7798. DOI: 10.4049/jimmunol.0902318

[18] Dominici M, Le Blanc K, Mueller I, et al. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Cytotherapy. 2006;**8**(4):315-317. DOI: 10.1080/14653240600855905

[19] Tomar GB, Srivastava RK, Gupta N, et al. Human gingiva-derived mesenchymal stem cells are superior to bone marrow-derived mesenchymal stem cells for cell therapy in regenerative medicine. Biochemical and Biophysical Research Communications. 2010;**393**(3):377-383. DOI: 10.1016/j.bbrc.2010.01.126

[20] Gugliandolo A, Rajan TS, Scionti D, et al. Reprogramming of oncogene expression in gingival mesenchymal stem cells following long-term culture in vitro. Cellular Reprogramming. 2017; **19**(3):159-170. DOI: 10.1089/cell.2016.0056

[21] Tanaka Y. Human mesenchymal stem cells as a tool for joint repair in rheumatoid arthritis. Clinical and Experimental Rheumatology. 2015;**33** (Suppl. 92):S58-S62

[22] Hynes K, Bright R, Proudman S, et al. Immunomodulatory properties of mesenchymal stem cell in experimental arthritis in rat and mouse models: A systematic review. Seminars in Arthritis and Rheumatism. 2016;**46**(1): 1-19. DOI: 10.1016/j.semarthrit.2016.02.008

[23] Tsai PC, Fu TW, Chen YM, et al. The therapeutic potential of human umbilical mesenchymal stem cells from Wharton's jelly in the treatment of rat liver fibrosis. Liver Transplantation. 2009;**15**(5):484-495. DOI: 10.1002/lt.21715

[24] Fournier BP, Larjava H, Hakkinen L. Gingiva as a source of stem cells with therapeutic potential. Stem Cells and Development. 2013; **22**(24):3157-3177. DOI: 10.1089/scd.2013.0015

[25] Liu J, Yu F, Sun Y, et al. Concise reviews: Characteristics and potential applications of human dental tissue-derived mesenchymal stem cells. Stem Cells. 2015;**33**(3):627-638. DOI: 10.1002/stem.1909

[26] Ludwig RJ, Vanhoorelbeke K, Leypoldt F, et al. Mechanisms of autoantibody-induced pathology. Frontiers in Immunology. 2017;**8**: 603. DOI: 10.3389/fimmu.2017.00603

[27] Marrack P, Kappler J, Kotzin BL. Autoimmune disease: Why and where it occurs. Nature Medicine. 2001;**7**(8): 899-905. DOI: 10.1038/90935

[28] Edwards M, Dai R, Ahmed SA. Our environment shapes us: The importance of environment and sex differences in regulation of autoantibody production. Frontiers in Immunology. 2018;**9**:478. DOI: 10.3389/fimmu.2018.00478

[29] Ruocco V, Ruocco E, Lo Schiavo A, et al. Pemphigus: Etiology, pathogenesis, and inducing or triggering factors: Facts and controversies. Clinics in Dermatology. 2013;**31**(4):374-381. DOI: 10.1016/j.clindermatol.2013.01.004

[30] Liu Y, Pan YF, Xue YQ, et al. uPAR promotes tumor-like biologic behaviors of fibroblast-like synoviocytes through PI3K/Akt signaling pathway in patients with rheumatoid arthritis. Cellular & Molecular Immunology. 2018;**15**(2): 171-181. DOI: 10.1038/cmi.2016.60

[31] Huang F, Liu ZM, Zheng SG. Updates on GMSCs treatment for autoimmune diseases. Current Stem Cell Research & Therapy. 2018;**13**(5): 345-349. DOI: 10.2174/1574888X13666180220141114

[32] American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2009;**32** (Supp. 1):S62-S67. DOI: 10.2337/dc09-S062

[33] Hu J, Yu X, Wang Z, et al. Long term effects of the implantation of Wharton's jelly-derived mesenchymal stem cells from the umbilical cord for newly-onset typ. 1 diabetes mellitus. Endocrine Journal. 2013;**60**(3):347-357

[34] Zhang W, Zhou L, Dang J, et al. Human gingiva-derived mesenchymal stem cells ameliorate streptozoticin-induced T1DM in mice via suppression of T effector cells and up-regulating Treg subsets. Scientific Reports. 2017; **7**(1):15249. DOI: 10.1038/s41598-017-14979-5

[35] Liu ZM, Wang KP, Ma J, et al. The role of all-trans retinoic acid in the biology of Foxp3+ regulatory T cells. Cellular & Molecular Immunology. 2015;**12**(5):553-557. DOI: 10.1038/cmi.2014.133

[36] Li B, Zheng SG. How regulatory T cells sense and adapt to inflammation. Cellular & Molecular Immunology. 2015;**12**(5):519-520. DOI: 10.1038/cmi.2015.65

[37] Lan Q, Fan H, Quesniaux V, et al. Induced Foxp3(+) regulatory T cells: A potential new weapon to treat autoimmune and inflammatory diseases? Journal of Molecular Cell Biology. 2012;**4**(1):22-28. DOI: 10.1093/jmcb/mjr039

[38] Chen M, Su W, Lin X, et al. Adoptive transfer of human gingiva-derived mesenchymal stem cells ameliorates collagen-induced arthritis via suppression of Th1 and Th17 cells and enhancement of regulatory T cell differentiation. Arthritis and Rheumatism. 2013;**65**(5):1181-1193. DOI: 10.1002/art.37894

[39] Shi Q, Qian Z, Liu D, et al. GMSC-derived exosomes combined with a chitosan/silk hydrogel sponge accelerates wound healing in a diabetic rat skin defect model. Frontiers in Physiology. 2017;**8**:904. DOI: 10.3389/fphys.2017.00904

[40] Kou X, Xu X, Chen C. The Fas_Fap-1_Cav-1 complex regulates IL-1RA secretion in mesenchymal stem cells to accelerate wound healing. Science Translational Medicine. 2018;**10**(432): eaai8524

[41] Gu Y, Shi S. Transplantation of gingiva-derived mesenchymal stem cells ameliorates collagen-induced arthritis. Arthritis Research & Therapy. 2016; **18**(1):262. DOI: 10.1186/s13075-016-1160-5

[42] Chakraverty R, Sykes M. The role of antigen-presenting cells in triggering graft-versus-host disease and graft-versus-leukemia. Blood. 2007;**110**(1): 9-17. DOI: 10.1182/blood-2006-12-022038

[43] Huang F, Cao FL, Zheng SG. Update of humanized animal disease models in studying graft-versus-host disease. Human Vaccines & Immunotherapeutics. 2018;**14**(11):2618-2623. DOI: 10.1080/21645515.2018.1512454

[44] Lu L, Lan Q, Li Z, et al. Critical role of all-trans retinoic acid in stabilizing human natural regulatory T cells under inflammatory conditions. Proceedings

of the National Academy of Sciences of the United States of America. 2014; **111**(33):E3432-E3440. DOI: 10.1073/pnas.1408780111

[45] Huang F, Chen M, Chen W, et al. Human gingiva-derived mesenchymal stem cells inhibit xeno-graft-versus-host disease via CD39-CD73-adenosine and IDO signals. Frontiers in Immunology. 2017;**8**:68. DOI: 10.3389/fimmu.2017.00068

[46] Xavier RJ, Podolsky DK. Unravelling the pathogenesis of inflammatory bowel disease. Nature. 2007;**448**(7152):427-434. DOI: 10.1038/nature06005

[47] Gao Y, Tang J, Chen W, et al. Inflammation negatively regulates FOXP3 and regulatory T-cell function via DBC1. Proceedings of the National Academy of Sciences of the United States of America. 2015;**112**(25):E3246-E3254. DOI: 10.1073/pnas.1421463112

[48] Ramalingam R, Larmonier CB, Thurston RD, et al. Dendritic cell-specific disruption of TGF-β receptor II leads to altered regulatory T cell phenotype and spontaneous multiorgan autoimmunity. Journal of Immunology. 2012;**189**(8):3878-3893. DOI: 10.4049/jimmunol.1201029

[49] Yang R, Yu T, Liu D, et al. Hydrogen sulfide promotes immunomodulation of gingiva-derived mesenchymal stem cells via the Fas/FasL coupling pathway. Stem Cell Research & Therapy. 2018;**9**(1):62. DOI: 10.1186/s13287-018-0804-6

[50] Libby P. Inflammation in atherosclerosis. Nature. 2002; **420**(6917):868-874. DOI: 10.1038/nature01323

[51] Zhang X, Huang F, Li W, et al. Human gingiva-derived mesenchymal stem cells modulate monocytes/macrophages and alleviate atherosclerosis. Frontiers in Immunology. 2018;**9**:878. DOI: 10.3389/fimmu.2018.00878

[52] Page RC, Offenbacher S, Schroeder HE, et al. Advances in the pathogenesis of periodontitis: Summary of developments, clinical implications and future directions. Periodontology 2000. 1997;**14**:216-248

[53] Hajishengallis G. Periodontitis: From microbial immune subversion to systemic inflammation. Nature Reviews Immunology. 2015;**15**(1):30-44. DOI: 10.1038/nri3785

[54] Racz GZ, Kadar K, Foldes A, et al. Immunomodulatory and potential therapeutic role of mesenchymal stem cells in periodontitis. Journal of Physiology and Pharmacology. 2014; **65**(3):327-339

[55] Fawzy El-Sayed KM, Paris S, Becker ST, et al. Periodontal regeneration employing gingival margin-derived stem/progenitor cells: An animal study. Journal of Clinical Periodontology. 2012; **39**(9):861-870. DOI: 10.1111/j.1600-051X.2012.01904.x

[56] Yu X, Ge S, Chen S, et al. Human gingiva-derived mesenchymal stromal cells contribute to periodontal regeneration in beagle dogs. Cells, Tissues, Organs. 2013;**198**(6):428-437. DOI: 10.1159/000360276

[57] Honda T, Egawa G, Grabbe S, et al. Update of immune events in the murine contact hypersensitivity model: Toward the understanding of allergic contact dermatitis. The Journal of Investigative Dermatology. 2013;**133**(2):303-315. DOI: 10.1038/jid.2012.284

[58] Vocanson M, Hennino A, Rozieres A, et al. Effector and regulatory mechanisms in allergic contact dermatitis. Allergy. 2009;**64**(12): 1699-1714. DOI: 10.1111/j.1398-9995.2009.02082.x

[59] Silvestre MC, Sato MN, Reis V. Innate immunity and effector and regulatory mechanisms involved in allergic contact dermatitis. Anais Brasileiros de Dermatologia. 2018;**93**(2): 242-250. DOI: 10.1590/abd1806-4841.20186340

[60] Su WR, Zhang QZ, Shi SH, et al. Human gingiva-derived mesenchymal stromal cells attenuate contact hypersensitivity via prostaglandin E2-dependent mechanisms. Stem Cells. 2011;**29**(11):1849-1860. DOI: 10.1002/stem.738

[61] Li P, Zhao Y, Ge L. Therapeutic effects of human gingiva-derived mesenchymal stromal cells on murine contact hypersensitivity via prostaglandin E2-EP3 signaling. Stem Cell Research & Therapy. 2016;**7**(1): 103. DOI: 10.1186/s13287-016-0361-9

[62] Gurtner GC, Werner S, Barrandon Y, et al. Wound repair and regeneration. Nature. 2008;**453**(7193):314-321. DOI: 10.1038/nature07039

[63] Agay D, Scherthan H, Forcheron F, et al. Multipotent mesenchymal stem cell grafting to treat cutaneous radiation syndrome: Development of a new minipig model. Experimental Hematology. 2010;**38**(10):945-956. DOI: 10.1016/j.exphem.2010.06.008

[64] Zhang QZ, Su WR, Shi SH, et al. Human gingiva-derived mesenchymal stem cells elicit polarization of m2 macrophages and enhance cutaneous wound healing. Stem Cells. 2010; **28**(10):1856-1868. DOI: 10.1002/stem.503

[65] Linard C, Tissedre F, Busson E, et al. Therapeutic potential of gingival fibroblasts for cutaneous radiation syndrome: Comparison to bone marrow-mesenchymal stem cell grafts. Stem Cells and Development. 2015; **24**(10):1182-1193. DOI: 10.1089/scd.2014.0486

[66] Su Y, Chen C, Guo L, et al. Ecological balance of oral microbiota is required to maintain oral mesenchymal stem cell homeostasis. Stem Cells. 2018; **36**(4):551-561. DOI: 10.1002/stem.2762

[67] Assem M, Kamal S, Sabry D, et al. Preclinical assessment of the proliferation capacity of gingival and periodontal ligament stem cells from diabetic patients. Open access Macedonian journal of medical sciences. 2018;**6**(2):254-259. DOI: 10.3889/oamjms.2018.076

[68] Subbarayan R, Murugan Girija D, Ranga Rao S. Gingival spheroids possess multilineage differentiation potential. Journal of Cellular Physiology. 2018; **233**(3):1952-1958. DOI: 10.1002/jcp.25894

[69] Zhang Q, Nguyen AL, Shi S, et al. Three-dimensional spheroid culture of human gingiva-derived mesenchymal stem cells enhances mitigation of chemotherapy-induced oral mucositis. Stem Cells and Development. 2012; **21**(6):937-947. DOI: 10.1089/scd.2011.0252

[70] Li N, Liu N, Zhou J, et al. Inflammatory environment induces gingival tissue-specific mesenchymal stem cells to differentiate towards a pro-fibrotic phenotype. Biology of the Cell. 2013;**105**(6):261-275. DOI: 10.1111/boc.201200064

[71] Zhang F, Si M, Wang H, et al. IL-1/TNF-alpha inflammatory and anti-inflammatory synchronization affects gingival stem/progenitor cells' regenerative attributes. Stem Cells International. 2017;**2017**:1349481. DOI: 10.1155/2017/1349481

[72] Apatzidou DA, Nile C, Bakopoulou A, et al. Stem cell-like populations and immunoregulatory molecules in periodontal granulation tissue. Journal of Periodontal Research. 2018;**53**(4): 610-621. DOI: 10.1111/jre.12551

[73] Lee H, Kim M, Park YH, et al. Dexamethasone downregulates SIRT1 and IL6 and upregulates EDN1 genes in stem cells derived from gingivae via the AGE/RAGE pathway. Biotechnology Letters. 2018;**40**(3):509-519. DOI: 10.1007/s10529-017-2493-0

[74] Jiang CM, Liu J, Zhao JY, et al. Effects of hypoxia on the immunomodulatory properties of human gingiva-derived mesenchymal stem cells. Journal of Dental Research. 2015;**94**(1):69-77. DOI: 10.1177/0022034514557671