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Role of mesenchymal stem cells in the regulation of immune response

Abstract: Mesenchymal stem cells are used due to their inherent immunoregulatory properties in the treatment of many immune diseases. Currently, mechanisms of their therapeutic effect are under active investigation, and for their proper application, an obvious understanding of the interaction of MSCs with immune cells is necessary.

This review is intended to examine the current progress in the mechanisms of interaction of MSCs with immune cells and how they correlate with the immune response in both animal models and in clinical trials.

Keywords: Mesenchymal stem cells, immunomodulation, immunosuppression, preclinical studies, clinical trials.

MSCs are a heterogeneous fibroblast-like cell population that can be isolated from nearly all human tissues and organs, such as bone marrow, adipose tissue, synovial membrane, skeletal muscle, umbilical cord, etc. MSCs are usually characterized by the presence of positive expression of such markers as CD29, CD44, CD54, CD73, CD90, CD105, CD166, and Stro-1, and the negative expression of specific antigens such as CD34, CD45, CD14 or CD11b, CD79 or CD19 and HLA- DR [4]. For the first time, a clonogenic potential of MSCs was identified by Friedenstein [2], and a first clinical trial using MSCs was completed in 1995. [3]. Since this decade, clinical applications of MSCs have been performed by many research groups, and currently, most of them are at the stage of studying a biocompatibility. A number of studies are characterizing the important advantages of MSCs, such as regenerative properties, easy cultivation, and high proliferation in *in vitro* culture. MSCs have attracted the attention of scientists and clinicians due to their multilineage differentiation potential, low immunogenicity and active participation in tissue repair and regeneration after migration to the site of tissue injury [17]. When stimulated by definite signals, MSCs are capable for differentiating into a number of specialized cell types, such as adipocytes, chondrocytes, osteoblasts, and, less frequently, endothelial cells and cardiomyocytes [18]. Moreover, recent studies have shown that MSCs possess strong immunosuppression and immunomodulatory properties that are mediating both by the cell to a cell contact and production of several signaling factors. Indeed, it has been shown that MSCs are able to inhibit the activation of DCs, pro-inflammatory M1-like macrophages, natural killers, T, and B cells, and induce the generation of immune cells with anti-inflammatory phenotypes [19]. It was found that the immunomodulatory effect of MSCs was realized through the production of growth factors, cytokines, and mediators of angiogenesis by a paracrine mechanism. Importantly, MSCs produce a transforming growth factor β (TGF-β), a hepatocyte growth factor (HGF), a prostaglandin E2 (PGE2), a soluble protein form HLA-G5, an indolamine-2,3-dioxygenase (IDO), an inducible nitric oxide synthase (iNOS), etc. [20]. These remarkable features of MSCs have attracted considerable interest for the future uses them for the treatment of autoimmune, inflammatory diseases and transplantation conditions. This paper focuses on how MSCs interact with immune cells and how it affected on the regulation of immune responses.

Mechanisms of interactions of MSCs with immune cells.A number of studies have examined various treatment approaches to the treatment of inflammation in the host organism, and the main problem was to find an effective way to eliminate the pathogen of inflammation and to reduce the consequences of the disease in order to prevent its further progression. As a rule, in the beginning, the innate immune system of the organism provides first protection in response to infection or trauma which caused damage to cells and tissues. In addition, depending on the nature of the damage, together with the innate immune response, the adaptive immune response is activated in the following stages.

In the first stage, after the cells and tissue were infected or damaged, cytokines are released by activated macrophages and mast cells, in particular, the colony-stimulating factor (CSF). These cytokines then promote the release of granulocytes and monocytes from the bone marrow. Along with this, under the influence of other types of cytokines with the function of increasing the expression of adhesion molecules, immune cells are localized near the endothelium of the site of infection/damage. At the same time, a structure, permeability and elasticity of vascular tone and integrity of the endothelial layer changes in response to cytokines, known as chemokines.

In the second stage, immune cells stimulate a phagocytosis (by opsonins) by recognizing specific receptors or by binding of the proteins of antibody or complement pathway to the site of the infection/damage. Then, after phagocytosis, infected or damaged cells can be degraded by the actions of defensins or antimicrobial enzymes of the cellular granules. In addition, high activity of immune cells in the anti-inflammatory reaction stimulates the formation of an oxidizing environment and production of reactive oxygen radicals, which are known to destroy normal cells. Thus, a cumulative interaction of the chemical and cellular responses of immune system forms an inflammatory response. It should be noted that the anti-inflammatory processes of the immune cells at the site of infection/damage are directly related to the kinin system (responsible for the perception of pain), with a cascade of coagulation and with a fibrinolytic pathway.

After the impact of the innate immune response which limits the first phase of infection or damage in cells and tissues, an adaptive immunity of the organism begin to mediate their response functions. Their importance consists in the specific recognition of the pathogen, and its destruction. At the same time, T and B lymphocytes memory cells provide a rapid and significant immune response when the initial antigen or pathogen will be re-exposed. The main feature of adaptive immunity is the specific recognition of pathogens occurs due to the basic histocompatibility complex of genes (MHC) on the cell membranes [75].

Reviewing subsequent and more recent literature have considered that MSCs are able to exert their immunosuppression potential by the cell to a cell contact mechanism, by a condition of a local microenvironment [69] and by paracrine action on immunocompetent cells [6].

An increasing number of studies have supported that *the cell to a cell contact* mechanism involved in the interaction of MSCs with immune cells. According to literature data, there were identified next mechanisms of the cell to a cell contact of the interaction of MSCs with immune cells: Fas/FasL ligand-dependent pathway [70], PD-1/PD-L1 [71], notch pathway activation [72], CD73, TLR4 [73]. In the presence of proinflammatory factors, MSCs are able to secrete IDO and PGE2, known as immunosuppression cytokines. Indeed, MSCs have generated CD4+/ $CD25^{high}$ FoxP3+/Tregs (T regulatory cells) when were cultured with human peripheral blood mononuclear cells, which mechanism was partially mediated by the interaction of CC chemokine ligand-1 (CCL1) of MSCs with its receptors on T cells, namely CC-8 chemokine (CCR8) [44].

In another study, the phagocytic activity of neutrophils was stimulated by MSCs through the production of chemotactic cytokines: IL-6, IL-8, GM-CSF, and MIF (macrophage migration inhibitory factor). Unexpectedly, after infusion MSCs have migrated to the lymphoid organs at organism-recipient and demonstrated the significant immunomodulatory effect in organs or tissues. Referring with this data, Momynaliev et al. have suggested a concept that direct interaction of MSCs with immune cells at inductive and effectors sites have resulted to antigen-specific T cells priming, antibody synthesis by B lymphocytes and cytokine production by T lymphocytes, natural killer cells, and macrophages. These preclinical studies proved that MSCs can be used as an alternative therapeutic instrument for preventing the rejection of transplanted donor organs and tissues [48]. Evidence of this statement was found in studies on the use of MSCs for leukemia and liver [49], and kidney [50] transplantations at humans, in which there was observed the low incidence of episodes of acute graft rejection and reduction in the risk of opportunistic infections and faster recovery of organ transplant functions. It needs to note that some data examined that in limited cases there was an impairment of kidney function, due to the activation of pro-inflammatory mediators [51-53].

The next component of the immune system, known as natural killer cells, which usually kills both virus-infected, and tumor cells and play an important role in GVHD (graft and host diseases). Petri et al. argues that the interaction of MSCs with natural killer cells occurs in two stages: first, MSCs

are producing type 1 interferon to activate an effector function of NK cells and after a time interval the TGF-b and IL-6, which attracted to inflammation site, are inhibiting the inflammatory processes by inducing the polarization of regulatory phenotype NK [67].

According to the literature, activation of Th1 cells occurs by CD4+ T cells in the presence of IL-12, IFN-γ, IL-27. It is well known that the efferent functions of Th1 cells included the recruitment of proinflammatory macrophages into the inflammatory region and the induction of synthesis of immunoglobulin (Ig) G2a by B cells. In fact, the autoimmune conditions associated with Th1 cells are type 1 diabetes and Crohn's disease. Duffy et al. suggested that MSCs directly or indirectly suppress disease-related Th1, Th2, and Th17 cells, as well as cytotoxic T lymphocytes [56]. The author reported that both *in vitro* and *in vivo* studies demonstrated examples of immunosuppression with MSCs at cutaneous delayed-type hypersensitivity [57], experimental colitis [58] mice, and autoimmune Mellitus diabetes in rats, which are associated with deregulation of Th1 cells. Moreover, the mechanisms of this effect were associated with the modulation of antigen-presenting DCs and promotion of naturally occurring or induced FOXP3-Tregs. Tang et al. showed that ICAM-1highMSCs, after retroviral transfection, have inhibited the maturation of DCs and T cells and differentiation of Th1 cells, together with an increase of the number of Tregs, as was observed in the attempts of the treatment of GVHD [63].

In some studies, researchers have used MSCs as a tool for priming the cells of immune system. Indeed, Gazdic et al. found that administration of MSCs-primed Tregs significantly inhibited α-galactosylceramide-induced acute hepatic failure at mouse model. This MSCs-mediated effect was explained by the presence of elevated levels of IDO and kynurenine (intermediate product of enzymatic decomposition of tryptophan and biosynthesis of nicotinic acid), which have induced apoptosis of effector T cells by Fas/FasL ligand-dependent pathway [66] but activated the expression of transcription factor FoxP3, which determine Tregs [65].

In recent literature data, it was revealed that a *local microenvironment* of inflamed cells and tissues considerably impacted on the immunosuppression effects of MSCs. A number of preclinical and clinical studies have recently been carried out taking into account the specific immunomodulatory as well as immunosuppression effects of MSCs. The presence of soluble factors secreted by MSCs, such as TGF-β1, PGE2, HGF, IDO, nitrogen oxide (NO) and interleukin-10 (IL-10) in the inflammation area has been reported by many scientists [5]. Referring to this, Andreeva et al. have noted that there is a third factor which impacted in the interaction of MSCs with the immune system, namely the local microenvironment with a low concentration of oxygen and being existed in a normal or inflammatory condition [69]. It has also been found that MSCs can exert their immunosuppression effects on both innate and adaptive immune responses. In addition to the published data about the potential use of MSCs, the understanding of the mechanisms of immunomodulation of MSCs is still unclear. As reviewed by Rozenberg and colleagues, MSCs can modulate the immune responses of Th17 cells while limiting Th1 cell responses, which were shown on the model of multiple sclerosis [68]. As it was suggested, that immunosuppression function was mediated through the PGE2 activity which has enhanced the Th17 level and has created the regulatory balance between Th1 и Th17 responses in the presence of myeloid cells. Thus, many studies supported that condition or state of the local microenvironment of inflamed cells and tissues may importantly affect on the consequence of MSCs-immune interactions [68]. According to preliminary studies on MSCs, it is possible to assume that changes in the expression of immunomodulatory genes of MSCs are occurring in the area of inflamed or damaged tissue, leading to their enhanced immunosuppression response. In this regard, Zhang et al. reported that increase of the secretion of anti-inflammatory cytokine - IL-10 by MSCs have modulated the lipid metabolism and have protected vessels against atherogenesis. Indeed, studies on the effects of BM-MSCs which were conducted *in vitro* and at ApoE-KO mice have demonstrated that MSCs are able to inhibit the formation of foam cells in atherosclerosis by down-regulation of CD36 and SRA mutant receptors in response to the infusion of MSCs [26].

A number of studies have immunomodulatory effects by means of paracrine actions of MSCs. Brown et.al showed that administrated bone-marrow mesenchymal stem cells (BM-MSCs) have eliminated allergic inflammation in a model of passive cutaneous anaphylaxis by inhibiting the MCs' degranulation, pro-inflammatory cytokine production, chemokinesis, and chemotaxis. Moreover, this

study has revealed that suppression effects were mediated through a COX2-dependent mechanism where up-regulation of the COX2 factor in BM-MSCs have been promoted activation of EP4 receptors on MCs [76]. These data were confirmed by a number of preclinical studies for the treatment of allergic asthma conditions, rheumatoid arthritis [5, 76]. It should be noted that umbilical cord blood mesenchymal stem cells (UCB-MSCs) and BM-MSCs are currently using in preclinical and clinical studies of this disease. The mechanism of the suppression by MSCs was potentially depended on the cell to a cell contact and secretion of IDO, PGE2, TGF β 1, HLA-G5, and activin A factors [7, 8]. It was noted that the effect of MSCs on dendritic cells (DCs) which normally regulate both the innate and adaptive immune system can be mediated by inhibiting the maturation of monocytes, CD34+ precursor cells and promoting the secretion of PGE2, IL-6, tumor necrosis factor-inducible gene 6 (TSG-6), M-CSF through Jagged-2 signaling mechanism [9,10,11].

Several authors have attempted to define the impact of MSCs on Th2 cell-associated diseases. Genз et al. reported about the suppression of CD4+ T helper cells by dental-derived MSCs in patients with asthma disease and concluded that the mechanism of Th2 cell polarization toward Th1 cells was mediated through IDO and TGF- β pathways [60]. Chan et al. demonstrated that the injection of human UCB-MSCs to asthmatic mice have significantly suppressed the asthmatic symptoms by Th2 cells pathway [61]. In another study, Luz-Crawford et al. in the mouse model of autoimmune diseases encephalomyelitis showed that infused MSCs have suppressed the proliferation and differentiation of CD4+ T cells on the high level, and also have promoted the differentiation into Th1 and Th17 cells. In addition, the authors have indicated that the positive effect of MSCs was associated with an increase of the number of functionally active CD4+, CD25+, Foxp3+ regulatory T cells and IL-10 secretion [64].

Several studies have been published about the interaction of MSCs with Tregs. It has also been shown that for induction of Tregs, MSCs require the cell to cell contact and secretion of PGE2 and TGF β -1 or human leukocyte antigen-G5 (HLA-G5) by them [45, 46]. The effects of MSCs on colitis-associated colorectal cancer were studied by Tang et al. The results of the study showed that injected cells effectively have activated the differentiation of Tregs through Smad2 signaling and elevated levels of TGF- β [62]. Le Blanc et al. reported interesting findings on the interaction of MSCs with immune system cells. According to the author, MSCs can activate the complement cascade through all three known complement pathways (classical, lectin and alternative). However, as it was suggested, an alternative pathway plays a major role in MSCs' induced complement activation, in which these cells suppressed the inflammatory processes by inducing the generation of Tregs and active macrophages M2 in the inflammation site.

It is well known that macrophages react with antimicrobial immunity in mammals. The past literature has indicated that M1 which is a pro-inflammatory, and M2 which is anti-inflammatory macrophages are responding to this processes. Intriguingly, some studies have shown that MSCs are able to induce a polarization of macrophages (M1 type) toward active anti-inflammatory macrophages M2 [26]. These significant observations showed that MSCs are interacting with immune cells through the cell to cell contact with subsequent release of both pro-inflammatory and anti-inflammatory factors.

The analyzed data results of the interaction of MSCs with immune system cells are presented in a Fig.1.

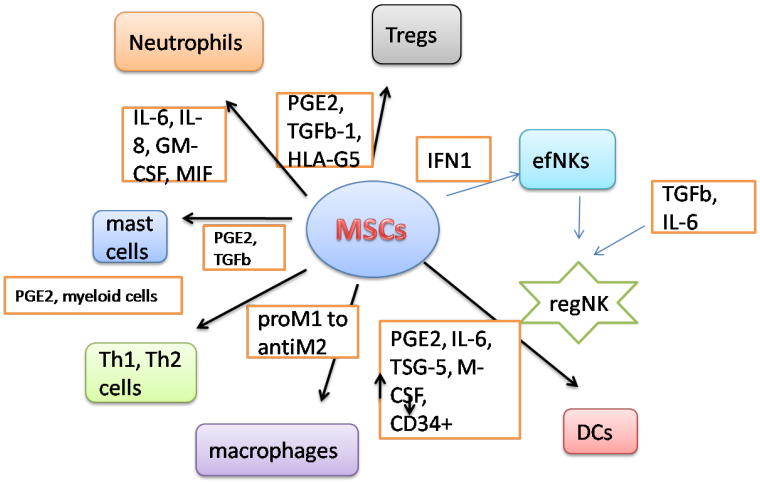

Figure 1 – Mechanism of interaction of MSCs with immune system cells.

MSCs in anticancer immunity

Several recent reports have demonstrated the role of MSCs in anticancer immunity. In the Pubmed database, more than 45 studies on the "immunity of MSCs and cancer" term were found, which indicates that the interest in this field of research began to increase in recent years. The tumor of a neoplastic epithelium, which is probably associated with stromal mutations and other multiple risk factors, has been studied by Houghton et al. They showed that the injection of p53-deficient MSCs (p53MSCs) to mice with Apc Min/+ mutation have promoted neoplastic growth and tumor formation, as well as negative immunity. However, the authors pointed to the unknown mechanism of this evidence. Meanwhile, referring to other reports, they have suggested that secretion of MCP-1, IL-6, MMP-2, MMP-9, and TNF-α by p53MSCs in combination with mutations in epithelial cells and stroma has contributed to avoidance of the immune dysregulation and have promoted growth tumor [28].

Ling W et al. have found that IDO-expressing humanized MSCs (MSCs-IDO) have suppressed the proliferation of T lymphocytes, namely CD8+ T cells and B cells. In addition, the inflammatory microenvironment in mice, transfected with MSCs-IDO, was formed under the influence of high IDO expression and its immunomodulatory effect. Thus, MSCs-IDO in the melanoma model and in *in vivo* lymphoma model has promoted the tumor growth, but this process can be reduced by a 1-methyl-tryptophan inhibitor. The authors suggested that IDO produced by MSCs has to lead to tumor growth without the use of other adaptive immune cells. Ling W and others suggested that MSCs have produced IDO in response to inflammatory cytokines in the tumor microenvironment, and the tumor cells are able to capture these IDO molecules in order to avoid the immune observation of the host organism.

Melzer et al. reported on the interaction of MSCs with tumor cells, indicating that the local microenvironment of tumors is critical in the network of cytokines, chemokines, growth factors and various metabolites in the body. According to the literature data, under normal conditions, MSCs can migrate to the area of damage and mediate immunomodulation and recovery processes. Meanwhile, it was found that with the development of the tumor, MSCs showed similar functions to the formation of the inflammatory site. However, the ability of MSCs to secrete paracrine factors can also contribute to pro- and/or antitumor intercellular communication [30]. Several signaling mechanisms have been implicated in MSCs-mediated stimulation of cancer cell growth, including Notch signaling, nanotube formation, intercellular communication, and/or exchange of cytokines/chemokines, extracellular vesicles and exosomes [31-32]. The MSCs-mediated release of factors as cellular modulator was shown in association with CCL5 secreted by MSCs with cytokines: CCR1, CCR3 or CCR5 [33]. Previous results showed that PGE2 and IDO, secreted by MSCs, have released their stimulation effect on the tumor microenvironment (TME) [34, 35]. In addition, some data suggested that exosomes and microvesicles of MSCs which contain a large group of proteins, functional mRNAs and regulatory miRNAs (miRs), can activate tumor cells by inducing matrix metalloproteinase or

inhibiting the cell-cycle arrest, as described in the study on urinary bladder tumor [37]. It was found that the direct interaction of MSCs with tumor cells can be mediated by trogocytosis and through the process of the formation of hybrid MSCs cells and tumor cells [30]. Moreover, in some studies it has been found that the interaction of MSCs with tumor cells was associated with such molecular mechanisms as increasing regulation of mitotic binding factors (MZT2A) and epithelial mitogens (EPGN) in ovarian cancer cells; lowering regulation of factor TAL1, transcripts of the main family of spiral-helical FOS and FOSB, HES1 and HES5 [32]; excessive expression of bone morphogenetic protein signals in adenocarcinoma; activation of genes of the KRT family [38]; epithelial-mesenchymal transition (EMT) in cancer cells [31].

Lee et al. demonstrated the positive effect of exosomes produced by MSCs in the suppression of angiogenesis in breast cancer cells. They found that the molecular mechanism of this inhibition process is the transfer of mRNA and miRNAs containing exosomes of MSCs to tumor cells. In this regard, miR-16 has reduced the expression of VEGF. Consequently, mRNA and miRNAs obtained from the exosomes of MSCs had the ability to perform epigenetic reprogramming processes [39].

Previous reports suggested that MSCs are precursors of cancer-related fibroblasts (CAF), and these cells are capable to express similar markers of the cell surface [41]. O'Malley G. et al. investigated the role of MSCs in the antitumor immune response of colorectal cancer. O'Malley G. and others have found that the administration of MSCs have activated the tumor growth and demonstrated the expression of CAF-determining markers by TGF-β/SMAD signaling. However, in some studies, it has been established that TGF-β plays an important role in the activation of NF-κB, PI3K, and STAT-1 pathways [37, 42]. Moreover, the molecules of CXCR4, MCP-1, and VCAM-1 facilitated the involvement of MSCs in TME through the NF-κB signaling pathway.

Application of MSCs in therapy. Discussion of the current preclinical studies considered interest to examine the existing clinical trials of MSCs. To date, more than 820 clinical trials using MSCs-based treatments of various diseases have been reported at the National Institutes of Health of the United States (NIH). Among them, about 11 studies were reported as "recruiting," "completed," "intervention," and either clinically tested in phase I or phase II [27]. In addition, Gao et al. [5] reported about 34 studies of the clinical trials using MSCs, which are currently conducting by research groups around the world. It is important to note that among them only 15 passed either phase I or II of testing procedures. On average, there is definite evidence that most of them were aimed for the treatment of autoimmune, inflammatory diseases and conditions of transplantation. As a rule, preclinical and clinical application of MSCs requires an accurate testing for identity, purity, safety, sterility, toxicity, pyrogenicity, viability, potency, dosage, stability properties by reliable assays. Noting this, for many studies on MSCs therapy this is the main problem, and some difficulties in this aspect are necessary to overcome. It is well known that autoimmune diseases are more common immune disorder in the world among people. In this regard, MSCs derived from BM-MSCs and other tissues have been widely used in the treatment of various conditions of those immune disorders.

In recent years cell technologies have developed progressively resulting to investigation and implementation of MSCs-based medical products. In this regard, Gao et al. in the review about the current state of MSCs and their immunomodulation have noted that *Cartistem,* an MSCs- based product were developed and approved for the treatment of arthritis. This means that nowadays various attempts to find a therapeutic product from MSCs by researchers in this field are gradually increasing, and in fact, they have achieved definite and significant results. Moreover, about 27 preclinical studies of MSCs were found by name of "immunomodulation". The mediating mechanism of the MSCs' effects was demonstrated in 13 of them [5]. One of them was the treatment of asthma condition with the use of mouse BM-MSCs, which was explained by three different mechanisms: through IFN-dependent, by TGF-β [14, 15] and by induction of Tregs [16] in 3 studies. With regard to this coincidence, an interesting issue for further research will be the consideration of all three mechanisms in one study of asthma. In another study, the effect of murine BM-MSCs was mediated by IFN-γ-cytokine in experimental autoimmune encephalomyelitis [17]. In addition, the aforementioned BM-MSCs have been used in other states, such as radiation proctitis, whose

mechanism was indicated by activation of the glucocorticoid [18] and in experimental autoimmune encephalomyelitis, which mechanism was designated by TGF-β, IL-6 mediation [19].

At the same time, other scientists have used the MSCs from human adipose tissue for the treatment of autoimmune hearing disorder, which mechanism was determined by IL-10 activation [22]; for the treatment of immune thrombocytopenia, whose mechanism was mediated by T-helper cells [23]; and for the treatment of rheumatoid arthritis whose mechanism was mediated through Tregs [24]. In addition, the rare type of MSCs, namely gingival-MSCs were examined in experimental colitis, in which the suppression effect was demonstrated by interaction with IL-10, IDO factors [10] and in contact dermatitis disease in which the suppression effect was mediated by the secretion of the PGE2 factor [9].

In recent studies of MSCs-based therapies, scientists and clinicians developed medical products such as *Cupistem* and *Prochymal* for the treatment of acute GVHD. Pre-clinical study of GVHD has used human UCB-MSCs and mechanism of the treatment was associated with IDO, TGF-β factors [20] and in rheumatoid arthritis with the mediation of IL-10, IDO, and TGF-β [21]. In detail, phase I studies have used autologous BM-MSCs to treat multiple sclerosis, kidney transplantation, and Crohn's disease. In addition, these phase studies using MSCs from placenta have been conducted for the treatment of multiple sclerosis, type II diabetes, and Crohn's disease. Therefore, BM-MSCs were used in Phase I/II study for the treatment of acute and chronic GVHD, multiple sclerosis, amyotrophic lateral sclerosis, and kidney transplantation conditions. Among them, as it was reported, only several studies have proceeded to phase II (A) of clinical trials. Referring to them, autologous BM-MSCs were used for the treatment of GVHD, multiple sclerosis, and Crohn's disease.

The role of stem cells in the transplantation of kidney organs have been actively studied by Momunaliev et al., who described the use of the technology based on "bioengineered immobilized cell elements" in order to enrich the transplanted graft with hematopoietic stem cells and tolerogenic cells in combination with non-myeloablative conditioning [47]. Moreover, authors indicated that two types of tolerances: central and peripheral are developing in the recipient-organism. The studies on the central tolerance have shown that manipulation with mobilized stem cells and non-myeloablative conditioning represented a safe, practical and reproducible approach to create a sustained chimerism ("simultaneous presence of living cells of different genetic nature (donor and recipient) in one organism") and donor-specific tolerance. According to literature, peripheral tolerance is an activation-induced cell death (AICD), which directed on restraining of the unlimited expansion of T cells, due to antigenic stimulation during a physiological immune response. Momynaliev et al. reported that the problem of the rejection of transplanted organ can be solved by administration of donor mononuclear cells of peripheral blood or MSCs prior to transplantation. Moreover, as some studies have shown, MSCs capacity to modulate the activity of T cells and DCs has contributed to decreasing the graft rejection or tolerance conditions. In particular, infusion of MSCs has induced the tolerance of half-alveolar heart transplant in mice via the generation of Tregs [54]. Thus, many data support the evidence that MSCs is a promising tool to reduce the levels of graft rejections in organ transplantation studies [55].

Conclusion. Taken together, MSCs can mediate their immunomodulatory abilities by the cell to a cell contact with immune cells and by secretion of the factors: TGF-β1, PGE2, HGF, IDO, NO, IL-10. In support of this, the immunosuppression effect of MSCs exists in direct relation to the type of immune cells and condition of the microenvironment at the site of inflammation or damaged cells and tissues. However, in the study of cancer with connection to MSCs studies, it has been shown that interaction of growth factors and cytokines, produced by MSCs with TME can contribute to the activation or inhibition of tumor formation, which depended on the molecular mechanisms of cells. It should be noted, that the majority of preclinical and clinical applications of MSCs were directed for the treatment of autoimmune, inflammatory diseases and conditions of transplantation of tissues and organs. In addition, reliable results of the therapeutic effects of MSCs have been demonstrated in several I/II phase clinical trials. In summary, our findings on the mechanisms and approaches that influenced on the regulation of immune responses by MSCs present a valuable source to improve the understanding of immunomodulation and immunosuppression by MSCs and could be applied for further investigation of therapeutic effect in *in vivo* and in *in vitro* studies.

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Иммундық жауаптарды реттеудегі мезенхималды діңгек жасушаларының рөлі

Аннотация: Көптеген аутоиммундық ауруларды емдеуде иммунорегуляциялық қасиеттеріне ие болған мезенхималды діңгек жасушалар (МДЖ-лар) қолданылады. Қазіргі кезде МБЖ-ларының терапевтикалық әсерінің механизмдері белсенді зерттеліп жатыр және оларды дұрыс қолдану үшін МБЖ-лар мен иммундық жасушалармен өзара әрекеттесуін анық түсіну қажет.

Бұл шолу мақаласы *in vivo* жануарлар үлгілерінде мен клиникалық сынақтардадағы МДЖ-лар мен иммундық жасушалардың өзара әрекеттесу механизмдерін және де иммундық жауапты қалай байланыстырғаны туралы ағымдық басылымдарды зерттеу үшін бағытталған.

Түйін сөздер: Мезенхималды бағаналы жасушалар, иммуномодуляция, иммуносупрессия, доклиникалық зерттеулер, клиникалық зерттеулер.

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Роль мезенхимальных стволовых клеток в регуляции иммунного ответа

Аннотация: Мезенхимальные стволовые клетки (МСК), обладающие иммунорегуляторными свойствами, используются при лечении многих иммунных заболеваний. В настоящее время механизмы их терапевтического эффекта активно изучаются, и для их надлежащего применения необходимо очевидное понимание взаимодействия МСК с иммунными клетками.

Этот обзор предназначен для изучения текущих работ по механизмам взаимодействия МСК с иммунными клетками и как они соотносятся с иммунным ответом как в моделях животных *in vivo*, так и в клинических испытаниях.

Ключевые слова: Мезенхимальные стволовые клетки, иммуномодуляция, иммуносупрессия, доклинические исследования, клинические испытания.

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1. Журнал мақсаты. Биохимия, молекулалық биология, биотехнология, биоинформатика, вирусология, биофизика, биоинженерия, физиология, ботаника, зоология, эволюциялық биология, генетика, микробиология, биомедицина салалары бойынша мұқият тексеруден өткен ғылыми құндылығы бар мақалалар жариялау.

2. Журналда мақала жариялаушы автор мақаланың қол қойылған бір дана қағаз нұсқасын Ғылыми басылымдар бөліміне (редакцияға, мекенжайы: 010008, Қазақстан Республикасы, Астана қаласы, Қ. Сәтпаев көшесі, 2, Л.Н. Гумилев атындағы Еуразия ұлттық университеті, Бас ғимарат, 408 кабинет) және *eurjourbio@enu.kz* электрондық поштасына PDF, Tex форматтарындағы нұсқаларын жіберу қажет. Мақаланұң мәтінінің қағаз нұсқасы мен электронды нұсқалары бірдей болулары қажет. Мақалалар қазақ, орыс, ағылшын тілдерінде қабылданады. Мақаланың тех фарматындағы үлгісі bulbio.enu.kz журнал сайытында берілген.

3. Автордың қолжазбаны редакцияға жіберуі мақаланың Л.Н. Гумилев атындағы Еуразия ұлттық университетінің хабаршысында басуға келісімін, шетел тіліне аударылып қайта басылуына келісімін білдіреді. Автор мақаланы редакцияға жіберу арқылы автор туралы мәліметтің дұрыстығына, мақала көшірілмегендігіне (плагиаттың жоқтығына) және басқа да заңсыз көшірмелердің жоқтығына кепілдеме береді.

4. Мақаланың көлемі 18 беттен аспауға тиіс (6 беттен бастап).

5. Мақаланың құрылымы

ҒТАМРК http://grnti.ru/

Автор(лар)дың аты-жөні

Мекеменің толық атауы, қаласы, мемлекеті (егер авторлар әртүрлі мекемеде жұмыс жасайтын болса, онда әр автор мен оның жұмыс мекемесі қасында бірдей белгі қойылу керек)

Автор(лар)дың E-mail-ы

Мақала атауы

Аннотация (100-200 сөз; формуласыз, мақаланың атауын мейлінше қайталамауы қажет; әдебиеттерге сілтемелер болмауы қажет; мақаланың құрылысын (кіріспе /мақаланың мақсаты/ міндеттері /қарастырылып отырған сұрақтың тарихы, зерттеу әдістері, нәтижелер/талқылау, қорытынды) сақтай отырып, мақаланың қысқаша мазмұны берілуі қажет).

Түйін сөздер (6-8 сөз не сөз тіркесі. Түйін сөздер мақала мазмұнын көрсетіп, мейлінше мақала атауы мен аннотациядағы сөздерді қайталамай, мақала мазмұнындағы сөздерді қолдану қажет. Сонымен қатар, ақпараттық-іздестіру жүйелерінде мақаланы жеңіл табуға мүмкіндік беретін ғылым салаларының терминдерін қолдану қажет).

Негізгі мәтін мақаланың мақсаты/ міндеттері/ қарастырылып отырған сұрақтың тарихы, зерттеу әдістері,нәтижелер/талқылау, қорытынды бөлімдерін қамтуы қажет.

Таблица, суреттер – аталғаннан кейін орналастырылады. Әр таблица, сурет қасында оның аталуы болуы қажет. Сурет айқын, сканерден өтпеген болуы керек.

Мақаладағы ***формулалар*** тек мәтінде оларға сілтеме берілсе ғана нөмірленеді.

Жалпы қолданыста бар ***аббревиатуралар*** мен ***қысқартулардан*** басқалары міндетті түрде алғаш қолданғанда түсіндірілуі берілуі қажет. ***Қаржылай көмек туралы*** ақпарат бірінші бетте көрсетіледі.

Әдебиеттер тізімі

Мәтінде әдібиеттерге сілтемелер тікжақшаға алынады. Мәтіндегі әдебиеттер тізіміне сілтемелердің нөмерленуі мәтінде қолданылуына қатысты жүргізіледі: мәтінде кездескен әдебиетке алғашқы сілтеме [1] арқылы, екінші сілтеме [2] арқылы т.с.с. жүргізіледі. Кітапқа жасалатын сілтемелерде қолданылған беттер де көрсетілуі керек (мысалы, [1, 45 бет]). Жарияланбаған еңбектерге сілтемелер жасалмайды. Сонымен қатар, рецензиядан өтпейтін басылымдарға да сілтемелер жасалмайды (әдебиеттер тізімінін әзірлеу үлгілерін төмендегі мақаланы рәсімдеу үлгісінен қараңыз).

Мақала соңындағы әдебиеттер тізімінен кейін ***библиографиялық мәліметтер*** орыс және ағылшын тілінде (егер мақала қазақ тілінде жазылса), қазақ және ағылшын тілінде (егер мақала орыс тілінде жазылса), орыс және қазақ тілінде (егер мақала ағылшын тілінде жазылған болса) беріледі.

Авторлар туралы мәлімет: автордың аты-жөні, ғылыми атағы, қызметі, жұмыс орны, жұмыс орнының мекенжайы, телефон, e-mail – қазақ, орыс және ағылшын тілдерінде толтырылады.

6. Қолжазба мұқият тексерілген болуы қажет. Техникалық талаптарға сай келмеген қолжазбалар қайта өңдеуге қайтарылады. Қолжазбаның қайтарылуы оның журналда басылуына жіберілуін білдірмейді.

7. Редакцияға түскен мақала жабық (анонимді) тексеруге жіберіледі. Барлық рецензиялар авторларға жіберіледі. Автор (рецензент мақаланы түзетуге ұсыныс берген жағдайда) үш күн аралығында қайта қарап, қолжазбаның түзетілген нұсқасын редакцияға қайта жіберуі керек. Рецензент жарамсыз деп таныған мақала қайтара қарастырылмайды. Мақаланың түзетілген нұсқасы мен автордың рецензентке жауабы редакцияға жіберіледі.

8. Төлемақы. Басылымға рұқсат етілген мақала авторларына төлем жасау туралы ескертіледі. Төлем көлемі 2018 жылы 4500 тенге – ЕҰУ қызметкерлері үшін және 5500 тенге басқа ұйым қызметкерлеріне.

Provision on articles submitted to the journal "Bulletin of L.N. Gumilyov Eurasian National University. BIOSCIENCE Series"

1.Purpose of the journal. Publication of carefully selected original scientific works in the fields of Biochemistry, Molecular Biology, Biotechnology, Bioinformatics, Virology, Biophysics, Bioengineering, Physiology, Botany, Zoology, Evolutionary Biology, Genetics, Microbiology, Biomedicine.

2. An author who wishes to publish an article in a journal must submit the article in hard copy (printed version) in one copy, signed by the author to the scientific publication office (at the address: 010008, Republic of Kazakhstan, Astana, Satpayev St., 2. L.N. Gumilyov Eurasian National University, Main Building, room 408) and by e-mail *eurjourbio@enu.kz* in Word, PDF and Tex format. At the same time, the correspondence between Tex-version, PDF-version and the hard copy must be strictly maintained. Article template in tex-format you can find on the journal web-site bulbio.enu.kz

Language of publications: Kazakh, Russian, English.

3. Submission of articles to the scientific publication office means the authors' consent to the right of the Publisher, L.N. Gumilyov Eurasian National University, to publish articles in the journal and the re-publication of it in any foreign language. Submitting the text of the work for publication in the journal, the author guarantees the correctness of all information about himself, the lack of plagiarism and other forms of improper borrowing in the article, the proper formulation of all borrowings of text, tables, diagrams, illustrations.

4. The volume of the article should not exceed 18 pages (from 6 pages).

5. Structure of the article

GRNTI http://grnti.ru/

Initials and Surname of the author (s)

Full name of the organization, city, country (if the authors work in different organizations, you need to put the same icon next to the name of the author and the corresponding organization)

Author's e-mail (s)

Article title

Abstract (100-200 words, it should not contain a formula, the article title should not repeat in the content, it should not contain bibliographic references, it should reflect the summary of the article, preserving the structure of the article - introduction/ problem statement /goals/ history, research methods, results /discussion, conclusion).

Keywords (6-8 words/word combination. Keywords should reflect the main content of the article, use terms from the article, as well as terms that define the subject area and include other important concepts that make it easier and more convenient to find the article using the information retrieval system).

The main text of the article should contain an introduction/ problem statement/ goals/ history, research methods, results / discussion, conclusion. Tables, figures should be placed after the mention. Each illustration should be followed by an inscription. Figures should be clear, clean, not scanned.

In the article, only those ***formulas*** are numbered, to which the text has references.

All ***abbreviations***, with the exception of those known to be generally known, must be deciphered when first used in the text.

Information on ***the financial support*** of the article is indicated on the first page in the form of a footnote.

References

In the text references are indicated in square brackets. References should be numbered strictly in the order of the mention in the text. The first reference in the text to the literature should have the number [1], the second - [2], etc. The reference to the book in the main text of the article should be accompanied by an indication of the pages used (for example, [1, 45 p.]). References to unpublished works are not allowed. Unreasonable references to unreviewed publications (examples of the description of the list of literature, descriptions of the list of literature in English, see below in the sample of article design).

At the end of the article, after the list of references, it is necessary to indicate bibliographic data in Russian and English (if the article is in Kazakh), in Kazakh and English (if the article is in Russian) and in Russian and Kazakh languages (if the article is English language).

Information about authors: surname, name, patronymic, scientific degree, position, place of work, full work address, telephone, e-mail - in Kazakh, Russian and English.

6. The article must be **carefully verified**. Articles that do not meet technical requirements will be returned for revision. Returning for revision does not mean that the article has been accepted for publication.

7. Work with electronic proofreading. Articles received by the Department of Scientific Publications (editorial office) are sent to anonymous review. All reviews of the article are sent to the author. The authors must send the proof of the article within three days. Articles that receive a negative review for a second review are not accepted. Corrected versions of articles and the author's response to the reviewer are sent to the editorial office. Articles that have positive reviews are submitted to the editorial boards of the journal for discussion and approval for publication.

Periodicity of the journal: 4 times a year.

8. Payment. Authors who have received a positive conclusion for publication should make payment on the following requisites (for ENU employees - 4,500 tenge, for outside organizations - 5,500 tenge):

Положение о рукописях, представляемых в журнал «Вестник Евразийского национального университета имени Л.Н.Гумилева. Серия Биологические науки»

1. Цель журнала. Публикация тщательно отобранных оригинальных научных работ по направлениям биохимия, молекулярная биология, биотехнология, биоинформатика, вирусология, биофизика, биоинженерия, физиология, ботаника, зоология, эволюционная биология, генетика, микробиология, биомедицина.

2. Автору, желающему опубликовать статью в журнале необходимо представить рукопись в твердой копии (распечатанном варианте) в одном экземпляре, подписанном автором в Отдел научных изданий (по адресу: 010008, Казахстан, г.Астана, ул. Сатпаева, 2, Евразийский национальный университет им. Л.Н.Гумилева, Учебно-административный корпус, каб. 408) и по e-mail *eurjourbio@enu.kz* в формате Tex и PDF . При этом должно быть строго выдержано соответствие между Tex-файлом, PDF-файлом и твердой копией. Шаблон статьи в формате tex приведен на сайте журнала bulbio.enu.kz.

Язык публикаций: Казахский, русский, английский.

3. Отправление статей в редакцию означает согласие авторов на право Издателя, Евразийского национального университета имени Л.Н. Гумилева, издания статей в журнале и переиздания их на любом иностранном языке. Представляя текст работы для публикации в журнале, автор гарантирует правильность всех сведений о себе, отсутствие плагиата и других форм неправомерного заимствования в рукописи, надлежащее оформление всех заимствований текста, таблиц, схем, иллюстраций.

4. Объем статьи не должен превышать 18 страниц (от 6 страниц).

5. Схема построения статьи

ГРНТИ http://grnti.ru/

Инициалы и Фамилию автора(ов)

Полное наименование организации, город, страна (если авторы работают в разных организациях, необходимо поставить одинаковый значок около фамилии автора и соответствующей организации)

E-mail автора(ов)

Название статьи

Аннотация (100-200 слов; не должна содержать формулы, по содержанию повторять название статьи; не должна содержать библиографические ссылки; должна отражать краткое содержание статьи, сохраняя структуру статьи – введение/ постановка задачи/ цели/ история, методы исследования, результаты/обсуждения, заключение/выводы).

Ключевые слова (6-8 слов/словосочетаний. Ключевые слова должны отражать основное содержание статьи, использовать термины из текста статьи, а также термины, определяющие предметную область и включающие другие важные понятия, позволяющие облегчить и расширить возможности нахождения статьи средствами информационно-поисковой системы).

Основной текст статьи должен содержать введение/ постановку задачи/ цели/ историю, методы исследования, результаты/обсуждение, заключение/выводы.

Таблицы, рисунки необходимо располагать после упоминания. С каждой иллюстрацией должна следовать надпись. Рисунки должны быть четкими, чистыми, несканированными.

В статье нумеруются лишь те ***формулы***, на которые по тексту есть ссылки.

Все ***аббревиатуры и сокращения***, за исключением заведомо общеизвестных, должны быть расшифрованы при первом употреблении в тексте.

Сведения о ***финансовой поддержке*** работы указываются на первой странице в виде сноски.

Список литературы

В тексте ссылки обозначаются в квадратных скобках. Ссылки должны быть пронумерованы строго по порядку упоминания в тексте. Первая ссылка в тексте на литературу должна иметь номер [1], вторая - [2] и т.д. Ссылка на книгу в основном тексте статьи должна сопровождаться указанием использованных страниц (например, [1, 45 стр.]). Ссылки на неопубликованные работы не допускаются. Нежелательны ссылки на нерецензируемые издания (примеры описания списка литературы, описания списка литературы см. ниже в образце оформления статьи).

В конце статьи, после списка литературы, необходимо указать ***библиографические данные*** на русском и английском языках (если статья оформлена на казахском языке), на казахском и английском языках (если статья оформлена на русском языке) и на русском и казахском языках (если статья оформлена на английском языке).

Сведения об авторах: фамилия, имя, отчество, научная степен, должность, место работы, полный служебный адрес, телефон, e-mail – на казахском, русском и английском языках.

6. Рукопись должна быть **тщательно выверена**. Рукописи, не соответствующие техническим требованиям, будут возвращены на доработку. Возвращение на доработку не означает, что рукопись принята к опубликованию.

7. Работа с электронной корректурой. Статьи, поступившие в Отдел научных изданий (редакция), отправляются на анонимное рецензирование. Все рецензии по статье отправляются автору. Авторам в течение трех дней необходимо отправить корректуру статьи. Статьи, получившие отрицательную рецензию к повторному рассмотрению не принимаются. Исправленные варианты статей и ответ автора рецензенту присылаются в редакцию. Статьи, имеющие положительные рецензии, представляются редколлегии журнала для обсуждения и утверждения для публикации.

Периодичность журнала: 4 раза в год.

8.Оплата. Авторам, получившим положительное заключение к опубликованию необходимо произвести оплату по следующим реквизитам (для сотрудников ЕНУ – 4500 тенге, для сторонних организаций – 5500 тенге):

Мақаланы рәсімдеу үлгісі

МРНТИ 27.25.19

А.Ж. Жубанышева [1] , Н. Темиргалиев [2] , А.Б. Утесов [3]

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[2] *Актюбинский региональный государственный университет имени К. Жубанова, Актобе, Казахстан*

(Email: [1] axaulezh@mail.ru, [2] ntmath10@mail.ru, [3] adilzhan_ 71@mail.ru)

Численное дифференцирование функций в контексте Компьютерного (вычислительного) поперечника

Аннотация: В рамках компьютерного (вычислительного) поперечника полностью решена задача приближенного дифференцирования функций, принадлежащих классам Соболева по неточной информации, полученной от произвольного конечного множества тригонометрических коэффициентов Фурье-Лебега дифференцируемой функции... [100-200 слов]

Ключевые слова: приближенное дифференцирование, восстановление по неточной информации, предельная погрешность, компьютерный (вычислительный) поперечник. [6-8 слов/словосочетаний]

Введение

Текст введения...

Авторам не следует использовать нестандартные пакеты LaTeX (используйте их лишь в случае крайней необходимости)

Заголовок секции

1.1 Заголовок подсекции

Окружения.

Теорема 1. ...

Лемма 1. ...

Предложение 1. ...

Определение 1. ...

Следствие 1. ...

Замечание 1. ...

Теорема 2 (Темиргалиев Н. [2])**.** *Текст теоремы.*

Д о к а з а т е л ь с т в о. Текст доказательства.

2. Формулы, таблицы, рисунки

$$\delta_N(\varepsilon_N; D_N)_Y \equiv \delta_N(\varepsilon_N; T; F; D_N)_Y \equiv \inf_{\left(l^{(N)},\varphi_N\right)\in D_N} \delta_N\left(\varepsilon_N; \left(l^{(N)},\varphi_N\right)\right)_Y, \tag{1}$$

где

$$\delta_N\left(\varepsilon_N; \left(l^{(N)},\varphi_N\right)\right)_Y \equiv \delta_N(\varepsilon_N; T; F; \left(l^{(N)},\varphi_N\right))_Y \equiv$$

$$\equiv \sup_{\substack{f\in F \\ \left|\gamma_N^{(\tau)}\right|\le 1(\tau=1,\ldots,N)}} \left\| Tf(\cdot) - \varphi_N\left(l_N^{(1)}(f)+\gamma_N^{(1)}\varepsilon_N^{(1)}, \ldots, l_N^{(N)}(f)+\gamma_N^{(N)}\varepsilon_N^{(N)}; \cdot\right)\right\|_Y.$$

Таблицы, рисунки необходимо располагать после упоминания. С каждой иллюстрацией должна следовать надпись.

3. Ссылки и библиография

Таблица 3 – Название таблицы

Простые	Не простые
2, 3, 5, 7, 11, 13, 17, 19, 23, 29	4, 6, 8, 9, 10, 12, 14

Рисунок 1 – Название рисунка

Для ссылок на утверждения, формулы и т. п. можно использовать метки. Например, теорема 2, Формула (1)

Для руководства по LaTeX и в качестве примера оформления ссылок, см., например, *Львовский С.М.* Набор и верстка в пакете LaTeX. Москва: Космосинформ, 1994.

Список литературы оформляется следующим образом.

Список литературы

1 Локуциевский О.М., Гавриков М.Б. Начала численного анализа. –М.: ТОО "Янус", 1995. –581 с. **- книга**

2 Темиргалиев Н. Компьютерный (вычислительный) поперечник как синтез известного и нового в численном анализе // Вестник Евразийского национального университета имени Л.Н. Гумилева –2014. –Т.4. №101. –С. 16-33. doi: . . . (при наличии) **- статья**

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Компьютерлік (есептеуіш) диаметр мәнмәтінінде функцияларды сандық дифференциалдау

Аннотация: Компьютерлік (есептеуіш) диаметр мәнмәтінінде Соболев класында жататын функцияларды олардың тригонометриялық Фурье-Лебег коэффициенттерінің ақырлы жиынынан алынған дәл емес ақпарат бойынша жуықтау есебі толығымен шешілді [100-200 сөз]

Түйін сөздер: жуықтап дифференциалдау, дәл емес ақпарат бойынша жуықтау, шектік қателік, Компьютерлік (есептеуіш) диаметр [6-8 сөз/сөз тіркестері].

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Numerical differentiation of functions in the context of Computational (numerical) diameter

Abstract: The computational (numerical) diameter is used to completely solve the problem of approximate differentiation of a function given inexact information in the form of an arbitrary finite set of trigonometric Fourier coefficients. [100-200 words]

Keywords: approximate differentiation, recovery from inexact information, limiting error, computational (numerical) diameter, massive limiting error. [6-8 words/word combinations]

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