INTERAKCIJA IZMEĐU MEZENHIMALNIH MATIČNIH ĆELIJA I MAKROFAGA U INFLAMATORNOJ MIKROSREDINI

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REVIEW ARTICLE

THE INTERACTION BETWEEN MESENCHYMAL STEM CELLS AND MACROPHAGES IN THE INFLAMMATORY MICROENVIRONMENT

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SAŽETAK

Mezenhimalne matične ćelije (MMĆ; engl. *mesenchymal stem cells - MSC*) su ćelije koje imaju veliki terapijski potencijal u regenerativnoj medicini, prevashodno zahvaljujući svojoj sposobnosti samoobnavljanja i diferencijacije u različite tipove ćelija. Imunomodulatorna svojstva ovih ćelija omogućavaju im da regulišu proces inflamacije, u zavisnosti od interakcije sa ćelijama imunskog sistema. Makrofagi, koji su deo urođenog imunskog sistema, mogu da ispoljavaju proinflamatorni M1 ili antiinflamatorni M2 fenotip i utiču na imunski odgovor i homeostazu tkiva. Mezenhimalne matične ćelije utiču na polarizaciju makrofaga, čime modulišu njihove efektorske funkcije. S druge strane, makrofagi mogu da utiču na potencijal za diferencijaciju mezenhimalnih matičnih ćelija i njihovu imunoregulatornu funkciju. Interakcija između mezenhimalnih matičnih ćelija i makrofaga, kao i njihova interakcija sa različitim imunskim i neimunskim ćelijama, ukazuje na složenost procesa unutar inflamatorne mikrosredine. Interakcija između ovih ćelija je od suštinskog značaja za proces reparacije tkiva. U ovom kratkom pregledu nastojaćemo da objasnimo značaj interakcije mezenhimalnih matičnih ćelija i makrofaga u nekim bolestima povezanim sa upalom, sa posebnim naglaskom na ključnu ulogu inflamatorne mikrosredine i terapijski potencijal ovih ćelija.

Ključne reči: MMĆ, makrofagi, inflamacija, imunski sistem

ABSTRACT

Mesenchymal stem cells (MSCs) are cells with significant therapeutic potential in regenerative medicine, primarily due to their capacity for self-renewal and differentiation into various cell types. The immunomodulatory properties of these cells enable them to regulate the inflammatory process, depending on their interaction with immune system cells. Macrophages, which are part of the innate immune system, can exhibit a pro-inflammatory M1 or an anti-inflammatory M2 phenotype, thereby influencing the immune response and tissue homeostasis. Mesenchymal stem cells affect macrophage polarization, thus modulating their effector functions. Conversely, macrophages can influence the differentiation potential of mesenchymal stem cells and their immunoregulatory function. The interaction between mesenchymal stem cells and macrophages, as well as their interaction with various immune and non-immune cells, highlights the complexity of processes within the inflammatory microenvironment. The interaction between these cells is essential for the tissue repair process. This brief review aims to analyze the importance of the interaction between mesenchymal stem cells and macrophages in certain inflammation-associated diseases, with special emphasis on the key role of the inflammatory microenvironment and the therapeutic potential of these cells.

Keywords: MSCs, macrophages, inflammation, immune system

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UVOD

Mezenhimalne matične ćelije (MMĆ; engl. *mesenchymal stem cells – MSC*) su multipotentne matične ćelije koje poseduju sposobnost samoobnavljanja i diferencijacije. Iako se MMĆ mogu izdvojiti iz gotovo svih tkiva u ljudskom telu, glavni izvori su koštana srž i masno tkivo. MMĆ se mogu diferencirati u više ćelijskih linija, uključujući osteoblaste, hondrocite, miocite i adipocite, što omogućava njihovu primenu u regenerativnoj medicini i terapiji bolesti [1]. MMĆ mogu da komuniciraju sa imunskim ćelijama putem sekrecije regulatornih molekula i citokina, kao i putem direktnih međućelijskih kontakata [2]. Zbog svog uticaja na ćelije adaptivnog i urođenog imuniteta, naročito makrofage, primenjuju se u terapiji brojnih imunoloških poremećaja [3].

Poznato je da dolazi do akumulacije mezenhimalnih matičnih ćelija na mestu povrede gde one započinju proces reparacije zahvaljujući svojim izuzetnim imunomodulatornim svojstvima [4]. U zavisnosti od različitih stimulansa, mezenhimalne matične ćelije mogu biti proinflamatorne (*MSC*1) ili antiinflamatorne (*MSC*2). Kada se aktiviraju stimulusima kao što su hipoksija, citokinska mikrosredina i ligandi za receptore slične „*toll*-u", MMĆ proizvode različite imunomodulatore, uključujući azot-monoksid (NO), indolamin 2,3-dioksigenazu (IDO), prostaglandin E2 (PGE2), interleukin (IL)-6 i IL-10 [5]. Poznato je da MMĆ igraju ključnu ulogu kao imunosupresivne ćelije putem produkcije molekula kao što su PGE2 i protein gena 6 stimulisan faktorom nekroze tumora (engl. *tumor necrosis factor-stimulated gene 6 protein - TSG-6*) [6].

Makrofagi, kao ćelije urođenog imunskog sistema, predstavljaju ključnu komponentu prve linije odbrane protiv patogena i ćelija tumora [7]. To su veoma plastične ćelije koje mogu poprimiti različite fenotipe aktivacije sa specifičnim efektorskim funkcijama kao odgovor na različite stimuluse iz okolne mikrosredine. Iako su makrofagi standardno klasifikovani u dve kategorije – M1 proinflamatorni makrofagi i M2 antiinflamatorni makrofagi sa sposobnostima reparacije tkiva – najnovija dostignuća u tehnologijama sekvenciranja na nivou pojedinačnih ćelija otkrila su mnogo širi spektar stanja aktivacije makrofaga, koji prevazilazi ovu pojednostavljenu podelu [8]. Migracija makrofaga ka mestu inflamacije, gde vrše fagocitozu oštećenih ili mrtvih ćelija, od suštinskog je značaja za homeostazu i regeneraciju tkiva [7]. U početnoj fazi inflamatornog procesa, makrofagi pretežno ispoljavaju proinflamatorne karakteristike, odnosno M1-nalik fenotip, lučeći faktor nekroze tumora-alfa (engl. *tumor necrosis factor-alpha – TNF-α*), IL-1β i IL-12.

Međutim, kako bi se sprečilo oštećenje tkiva u uslovima akutne inflamacije, M2-nalik makrofagi luče velike količine interleukina 10 (IL-10) i faktora rasta tumo-

INTRODUCTION

Mesenchymal stem cells (MSCs) are multipotent stem cells that possess self-renewal and differentiation capacities. Although MSCs can be obtained from almost all tissues within the human body, the main sources are the bone marrow and adipose tissue. MSCs can differentiate into multiple cell lineages, including osteoblasts, chondrocytes, myocytes, and adipocytes, which enables their applicability in regenerative medicine and disease therapy [1]. MSCs can interact with immune cells by secreting regulatory molecules and cytokines or via cell-to-cell contacts [2]. Due to their effect on adaptive and innate immune cells, especially macrophages, they have been applied in many immune disorders [3].

It is known that MSCs accumulate at the injured site and initiate the repair process due to their remarkable immunomodulatory properties [4]. Depending on different stimuli, MSCs can be proinflammatory (MSC1), or anti-inflammatory (MSC2). Once they are activated with stimuli such as hypoxia, the cytokine milieu, and toll-like receptor ligands, MSCs produce various immunomodulators, including nitric oxide (NO), indoleamine 2,3-dioxygenase (IDO), prostaglandin E2 (PGE2), interleukin (IL)-6, and IL-10 [5]. MSCs are known to play a crucial role as immunosuppressive cells by producing molecules like PGE2 and tumor necrosis factor-stimulated gene 6 protein (TSG-6) [6].

Macrophages, as cells of the innate immune system, are an essential component of the first line of defense against pathogens and tumor cells [7]. These are highly plastic cells that can adopt different activation phenotypes with distinct effector functions as a result of diverse stimuli from the surrounding microenvironment. Although macrophages have traditionally been classified into two categories, M1 proinflammatory macrophages and M2 anti-inflammatory macrophages with tissue repair capabilities, recent advancements in single-cell technologies have revealed a wider range of macrophage activation states that extend beyond this simplified classification [8]. Their migration to the inflammatory site, where they perform phagocytosis of damaged or dead cells, is crucial for tissue homeostasis and regeneration [7]. In the initial phase of an inflammatory process, macrophages primarily exhibit pro-inflammatory characteristics, the M1-like phenotype, by secreting tumor necrosis factor α (TNF-α), IL-1β, and IL-12.

However, to prevent tissue damage in acute inflammatory conditions, M2-like macrophages secrete copious amounts of IL-10 and tumor growth factor β (TGF-β), thus contributing to the resolution of inflammation and tissue regeneration, stimulating angiogenesis, and maintaining tissue homeostasis [9]. In

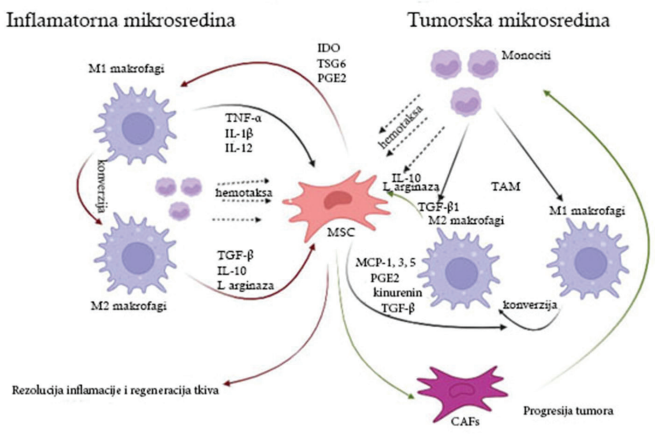
ra-beta (engl. *tumor growth factor-beta – TGF-β*), čime doprinose razrešenju inflamacije i regeneraciji tkiva, stimulišu angiogenezu i održavaju homeostazu tkiva [9]. Takođe, makrofagi imaju i ključnu ulogu u imunomodulaciji i prezentaciji antigena [10]. Oni aktiviraju druge imunske ćelije putem lučenja proinflamatornih citokina kao što su IL-1β, *TNF*-α, IL-6, kao i drugih rastvorljivih faktora [7].

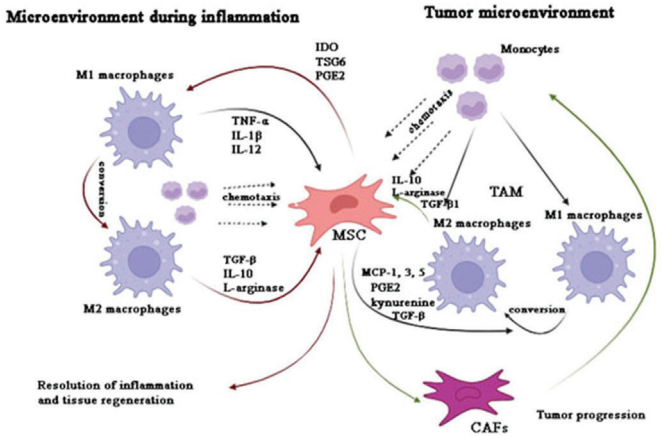
Interakcija između mezenhimalnih matičnih ćelija i makrofaga važna je u mnogim aspektima, uključujući reparaciju tkiva, imunsku modulaciju i terapijske intervencije. Konkretno, MMĆ dovode do promene u polarizaciji makrofaga sa M1 proinflamatornog na M2 antiinflamatorni fenotip (Slika 1), što je pokazano na *in vitro* modelu koji su sproveli Kim i saradnici [11]. Utvrđeno je da MMĆ mogu da prouzrokuju polarizaciju makrofaga i njihovu transformaciju od inflamatornog M1 u antiinflamatorni M2 fenotip pomoću ciklooksigenaza-2-prostaglandin E2 (engl. *cyclooxygenase-2-prostaglandin E2 – COX2-PGE2*) puta, kao i putem proizvoda indoleamin 2,3-dioksigenaze (IDO) i *TSG-6* [12]. MMĆ mogu biti fagocitovane od strane makrofaga i mogu pasivno da utiču na njihov profil, suzbijajući proizvodnju *TNF*-α, IL-1β, IL-6 i inducibilne azot oksid sintaze (iNOS), istovremeno podstičući proizvodnju IL-10 [13]. Takođe, MMĆ mogu da pojačaju fagocitozu makrofaga putem transfera mitohondrija u određenim bolestima, kao što su akutni respiratorni distres sindrom i sepsa [14]. Pored toga, u inflamatornoj mikrosredini MMĆ proizvode citokine kao što je monocitni hemoatraktantni protein-1 (engl. *monocyte chemoattractant protein-1 – MCP-1*), makrofagni inflamatorni protein-1 alfa (engl. *macrophage inflammatory protein-1 alpha – MIP-1α*) i hemokin (C-C motiv) ligand 12 (engl. *C-C motif chemokine ligand 12 – CCL12*), čime pospešuju hemotaksiju monocita i makrofaga koji imaju ulogu u zarastanju rana [15].

addition, macrophages also have a critical role in immunomodulation and antigen presentation [10]. They activate other immune cells via the secretion of proinflammatory cytokines such as IL-1β, TNF-α, IL-6, as well as other soluble factors [7].

The interaction between mesenchymal stem cells and macrophages is important in many respects, including tissue repair, immune modulation, and therapeutic intervention. Specifically, MSCs lead to changes in macrophage polarization from the M1 pro-inflammatory to the M2 anti-inflammatory phenotype (Figure 1), as Kim et al. demonstrated in an in vitro model [11]. It has been shown that MSCs can trigger macrophage polarization and transform them from an inflammatory M1 to an anti-inflammatory M2 phenotype via the cyclooxygenase-2-prostaglandin E2 (COX2-PGE2) pathway, the products of IDO, and TSG-6 [12]. MSCs can be phagocytosed by macrophages and can passively affect the profile of macrophages, suppressing the production of TNF-α, IL-1β, IL-6, and inducible nitric oxide synthase (iNOS) and promoting the production of IL-10 [13]. MSCs can also enhance macrophage phagocytosis via mitochondrial transfer in some diseases, such as acute respiratory distress syndrome and sepsis [14]. Furthermore, in the inflammatory microenvironment, MSCs produce cytokines, such as monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-1 alpha (MIP-1 α), and C-C motif chemokine ligand 12 (CCL12), thus leading to the chemoattraction of monocytes and macrophages that play a role in wound healing [15].

In the inflammatory microenvironment, through cytokine production, MSCs influence monocyte chemotaxis, favoring M2 phenotypes, which consequently leads to immunosuppression and resolution of inflammation. In the tumor microenvironment, MSCs influ-





Slika 1. Interakcija između mezenhimalnih matičnih ćelija i makrofaga u inflamatornoj i tumorskoj mikrosredini

Figure 1. Interaction between mesenchymal stem cells and macrophages in inflammation and tumor microenvironments

U inflamatornoj mikrosredini, putem produkcije citokina, mezenhimalne matične ćelije utiču na hemotaksu monocita, favorizujući M2 fenotipove, što za posledicu ima imunosupresiju i razrešavanje inflamacije. U tumorskoj mikrosredini, MMĆ utiču na formiranje makrofaga povezanih sa tumorom (engl. *tumor-associated macrophages – TAM*), koji su pretežno M2 fenotipovi, a pod njihovim uticajem MMĆ mogu da se diferenciraju u fibroblaste povezane sa karcinomom (engl. *carcinoma-associated fibroblasts – CAF*), dodatno pospešujući progresiju tumora.

Interakcija između mezenhimalnih matičnih ćelija i makrofaga u inflamatornim stanjima – dijabetes melitus i psorijaza kao modeli bolesti

U hroničnim zapaljenskim stanjima koja dovode do hroničnih bolesti, kao što su dijabetes melitus (hronični metabolički poremećaj karakterisan niskogradusnom inflamacijom) i psorijaza (inflamatorno imunološko oboljenje kože), dolazi do narušavanja ravnoteže između M1-nalik i M2-nalik tipova makrofaga, što može imati za posledicu trajno oštećenje tkiva [16, 17]. Pokazano je da je insulinska rezistencija, koja se često javlja pre pojave dijabetesa tipa 2 (*diabetes mellitus* tip II – DMT2), u osnovi pokrenuta hroničnim, niskogradusnim inflamatornim stanjem [18]. Konkretno, *TNF*-α i IL-1β koje produkuju makrofagi u masnom tkivu, a koji ispoljavaju karakteristike M1 tipa makrofaga, identifikovani su kao ključni faktori u razvoju insulinske rezistencije [19]. Kod pacijenata sa dijabetesom tipa 1, izazvanim imunskim odgovorom, studije su pokazale povećan broj M1-nalik makrofaga. Istovremeno, dokazano je da miševi sa dijabetesom imaju povećan broj CD169+ ćelija sa sposobnošću zadržavanja matičnih ćelija. Takođe je pokazano da dijabetes utiče na oslobađanje matičnih ćelija putem faktora izvedenog iz stromalnih ćelija-1 (engl. *stromal cell-derived factor-1 – SDF-1*), koji luče M1-nalik makrofagi, što sprečava oslobađanje mezenhimalnih matičnih ćelija iz koštane srži, stvarajući tako začarani krug. Zbog ovog procesa, potencijal mezenhimalnih matičnih ćelija za regeneraciju krvnih sudova i drugih organa dodatno je oslabljen [20]. Stoga je hitno i važno iskoristiti potencijal ciljane terapije u kontrolisanju ravnoteže između makrofaga i mezenhimalnih matičnih ćelija i smanjenju komorbiditeta izazvanih osnovnom bolešću.

Novije studije su pokazale da mezenhimalne matične ćelije kod pacijenata sa psorijazom ispoljavaju određene abnormalnosti. Ove ćelije imaju smanjenu sposobnost regulacije inflamacije i regeneracije. Orciani i saradnici su pokazali da mezenhimalne matične ćelije izolovane iz psorijatičnih kožnih lezija ispoljavaju povećanu ekspresiju vaskularnog endotelnog faktora rasta (engl. *vascular endothelial growth factor – VEGF*) i

ence the formation of tumor-associated macrophages (TAMs), which are predominantly M2 phenotypes, and under their influence, MSCs may differentiate into carcinoma-associated fibroblasts (CAFs), further supporting tumor progression.

Interaction between mesenchymal stem cells and macrophages in inflammatory conditions – diabetes mellitus and psoriasis as disease model systems

In chronic inflammatory conditions that lead to chronic diseases, such as diabetes mellitus (a chronic metabolic disorder characterized by low-grade inflammation) and psoriasis (an inflammatory immune skin disease), there is a disrupted balance between M1-like and M2-like macrophage types, which can result in permanent tissue damage [16,17]. It has been shown that insulin resistance, which frequently occurs before the onset of type 2 diabetes (diabetes mellitus type II – DMT2), is fundamentally driven by a chronic, low-grade inflammatory state [18]. Specifically, TNF-α and IL-1β produced by adipose tissue macrophages, which exhibit characteristics of the M1 macrophage type, have been identified as key factors in the development of insulin resistance [19]. In patients with type 1 diabetes caused by an immune response, studies have shown increased M1-like macrophages. At the same time, it has been demonstrated that diabetic mice have increased CD169+ cells with stem cell retaining activity. It has also been shown that diabetes affects the release of stem cells via the stromal cell-derived factor-1 (SDF-1) secreted by M1-like macrophages, which prevents the release of MSCs from the bone marrow, resulting in a vicious cycle. Due to this process, the potential of MSCs to regenerate blood vessels and other organs is further impaired [20]. Therefore, it is urgent and important to utilize the potential of targeted therapies in controlling the balance between macrophages and MSCs and reducing comorbidities caused by the underlying disease.

Recent studies have shown that, in patients with psoriasis, MSCs exhibit abnormalities. These cells have a reduced ability to regulate inflammation and regeneration. Orciani et al. demonstrated that MSCs isolated from psoriatic skin lesions exhibit increased expression of vascular endothelial growth factor (VEGF) and inducible nitric oxide synthase (iNOS) [21]. Jiao et al. demonstrated that MSCs from skin lesions of psoriasis patients decreased the levels of TGF-β and its receptors, thus increasing the Th17/Treg ratio, which resulted in an immune imbalance in these patients [22]. MSCs isolated from the bone marrow of psoriasis patients also exhibited abnormalities. This aligns with

inducibilne azot oksid sintaze (*iNOS*) [21]. Žao i saradnici su pokazali da MMĆ iz kožnih lezija pacijenata sa psorijazom smanjuju nivoe TGF-β i njegovih receptora, čime se povećava odnos *Th17/Treg* ćelija, što ima za posledicu imunsku neravnotežu kod ovih pacijenata [22]. MMĆ izolovane iz koštane srži pacijenata sa psorijazom takođe su pokazale abnormalnosti. Ovo je u skladu sa istraživanjima koja ukazuju na to da je psorijaza povezana sa poremećenom hematopoezom [23].

Takođe je primećeno da je hronični psihološki stres jedan od glavnih faktora u razvoju psorijaze i da istovremeno dovodi do razvoja stresne eritropoeze, uz sledstvene promene unutar mikrosredine koštane srži [24,25,26]. Mezenhimalne matične ćelije i njihove interakcije sa ćelijama imunskog sistema mogu biti ključni učesnici u patogenezi ove bolesti.

Sa druge strane, psorijatične lezije pretežno sadrže M1-nalik makrofage za koje je pokazano da luče *TNF*-α i IL-23 [16]. Međutim, u mišjem modelu psorijaze dokazano je da M2 fenotip ima regulatornu ulogu [26]. Neke studije sugerišu da deplecija makrofaga smanjuje inflamaciju [27]. Nasuprot tome, druge studije na miševima pokazale su da stimulacija glukokortikoidnih receptora u makrofagima dovodi do polarizacije ka M1-nalik fenotipu putem fosforilacije prenosioca signala i aktivatora transkripcije 1 (engl. *signal transducer and activator of transcription 1 – STAT1*), dok blokiranje ovog signalnog puta smanjuje inflamaciju, što dodatno ističe značaj stresa u razvoju psorijaze [28]. Postoji ograničen broj istraživanja koja naglašavaju značaj interakcije između MMĆ i makrofaga u patogenezi psorijaze. Ipak, studije ukazuju na terapijski potencijal MMĆ zasnovan na njihovoj sposobnosti da modulišu imunski odgovor regulacijom polarizacije makrofaga.

Interakcija između mezenhimalnih matičnih ćelija i makrofaga u tumorskoj mikrosredini

Neke hipoteze zastupaju stanovište da se karcinogeneza i rast tumora zasnivaju na hroničnoj inflamaciji, koja narušava ravnotežu između proinflamatornih i antiinflamatornih odgovora. Takva neravnoteža narušava adekvatan imunski odgovor u eliminaciji tumorskih ćelija, stvarajući time povoljne uslove za rast tumora [29]. Brojne savremene studije ističu značajnu ulogu mezenhimalnih matičnih ćelija, makrofaga i njihovih interakcija u razvoju tumora, što proizilazi iz njihovih imunomodulatornih sposobnosti. Pored interakcije sa T i B limfocitima tokom karcinogeneze, MMĆ takođe ostvaruju interakcije sa makrofagima, modulišući njihovu aktivnost. Za razliku od procesa inflamacije, gde prelazak sa M1-nalik na M2-nalik makrofage vodi ka razrešavanju inflamacije, u tumorskoj mikrosredini M2-nalik makrofagi doprinose progresiji raka (Slika 1).

research suggesting that psoriasis is associated with aberrant hematopoiesis [23].

It has also been noted that chronic psychological stress is one of the main factors in the development of psoriasis and that it simultaneously leads to the development of stress erythropoiesis with subsequent changes within the bone marrow microenvironment [24,25,26]. MSCs and their interactions with immune system cells may be the key players in the pathogenesis of this disease.

On the other hand, psoriatic lesions predominantly feature M1-like macrophages, which have been shown to secrete TNF-α and IL-23 [16]. However, in a mouse model of psoriasis, it has been demonstrated that the M2 phenotype plays a regulatory role [26]. Some studies suggest that macrophage depletion reduces inflammation [27]. In contrast, other studies on mice have demonstrated that the stimulation of glucocorticoid receptors in macrophages leads to M1-like macrophage polarization via phosphorylation of signal transducer and activator of transcription 1 (STAT1), whereas blocking this signaling pathway reduces inflammation, further highlighting the importance of stress in the development of psoriasis [28]. There is a limited body of research emphasizing the significance of MSC-macrophage interactions in the pathogenesis of psoriasis. Nonetheless, studies suggest a therapeutic potential of MSCs based on their ability to modulate the immune response by regulating macrophage polarization.

Interaction between mesenchymal stem cells and macrophages in the tumor microenvironment

Some hypotheses state that carcinogenesis and tumor growth are based on chronic inflammation, which disrupts the balance between proinflammatory and anti-inflammatory responses. Such an imbalance impairs an adequate immune response in eliminating tumor cells, thereby creating favorable conditions for tumor growth [29]. Many recent studies have highlighted the significant role of MSCs, macrophages, and their interactions in tumor development, due to their immunomodulatory capabilities. In addition to interacting with T and B lymphocytes during carcinogenesis, MSCs also establish interactions with macrophages, modulating their activity. Unlike the inflammation process, where the transition from M1-like to M2-like macrophage types leads to the resolution of the inflammatory process in the tumor microenvironment, M2-like macrophages contribute to cancer progression (Figure 1).

A special type of macrophage is present within the tumor microenvironment – tumor-associated macro-

Poseban tip makrofaga prisutan je u tumorskoj mikrosredini – makrofagi povezani sa tumorom (*TAM*). Ovi makrofagi mogu da ispoljavaju fenotipske karakteristike i M1-nalik i M2-nalik makrofaga i predstavljaju značajnu komponentu imunskog sistema i same tumorske mikrosredine [30]. Istraživanja su pokazala da M1-nalik makrofagi mogu da eliminišu tumorske ćelije putem fagocitoze ili aktivacijom T-ćelijskog odgovora [31].

Nasuprot tome, M2-nalik makrofagi imaju ključnu ulogu u progresiji tumora jer luče matriksne metaloproteinaze, čime omogućavaju migraciju tumorskih ćelija i stromalnih ćelija tumora. Takođe podstiču angiogenezu oslobađanjem angiogenih molekula i ekspresijom niza enzima uključenih u regulaciju angiogeneze [30]. M2-nalik makrofage karakteriše povećana ekspresija L-arginaze, IL-10 i liganda proteina programirane ćelijske smrti 1 (engl. *programmed cell death ligand 1 – PD-L1*), što dovodi do imunosupresije i potiskivanja funkcije T-ćelija i kao krajnji rezultat podstiče rast tumora [32]. Makrofagi utiču na mezenhimalne matične ćelije da poprime fenotip fibroblasta povezanih sa karcinomom (*CAF*), čime dodatno pospešuju progresiju karcinoma.

Mezenhimalne matične ćelije, u kombinaciji sa izmenjenim uslovima unutar tumorske mikrosredine, doprinose formiranju makrofaga povezanih sa tumorom (*TAM*). MMĆ putem prostaglandina E2 (PGE2) i kinurenina, zajedno sa MIP-1α i MIP-2α, koje produkuju inflamatorni makrofagi, doprinose transformaciji inflamatornih M1-nalik makrofaga u alternativno aktivisane, imunosupresivne M2-nalik makrofage [34]. Na taj način, MMĆ i izmenjeni uslovi unutar tumorske mikrosredine modulišu aktivnost makrofaga.

Studije na modelima melanoma B16 F0 i limfoma EL4 pokazale su da egzozomi poreklom iz tumorskih ćelija utiču na mezenhimalne matične ćelije tako da pojačavaju infiltraciju makrofaga [35]. Nakon infiltracije makrofaga u tumorsku mikrosredinu, oni se pod uticajem *MCP-1*, *MCP-3* i *MCP-5* – produkata MMĆ – polarizuju u M2 tumorske fenotipove [36]. S druge strane, kod karcinoma dojke, produkti MMĆ – TGF-β, C1q i semaforini – doprinose M2 polarizaciji makrofaga [32]. Kao što je pokazano, hronični stres je jedan od faktora koji doprinosi razvoju karcinoma [37].

Jang i saradnici su pokazali da stres utiče na polarizaciju makrofaga, čime ima uticaj na razvoj karcinoma [38]. S druge strane, *in vivo* studije su pokazale da medijatori stresa utiču na međućelijsku interakciju između mezenhimalnih matičnih ćelija i makrofaga [39].

TERAPIJSKI POTENCIJAL

Tokom poslednjih godina značajna pažnja se posvećuje terapijskom potencijalu mezenhimalnih matičnih ćelija. Zbog svojih snažnih imunomodulatornih efekaphages (TAMs). These macrophages may exhibit phenotypic characteristics of both M1-like and M2-like macrophages and are a significant component of the immune system and the tumor microenvironment [30]. Research has shown that M1-like macrophages can eliminate tumor cells through phagocytosis or by activating the T-cell response [31].

In contrast, M2-like macrophages play a crucial role in tumor progression by secreting matrix metalloproteinases, facilitating the migration of tumor cells and tumor stromal cells. They also promote angiogenesis by releasing angiogenic molecules and expressing a range of enzymes involved in regulating angiogenesis [30]. M2-like macrophages are characterized by an increased expression of L-arginase, IL-10, and programmed cell death ligand 1 (PD-L1), which leads to immunosuppression and suppression of T-cell functions, ultimately promoting tumor growth [32]. Macrophages influence mesenchymal stem cells (MSCs) to acquire the carcinoma-associated fibroblast (CAF)-like phenotype, thereby promoting cancer progression.

MSCs, in combination with altered conditions within the tumor microenvironment, contribute to the formation of TAMs. MSCs, via PGE2 and kynurenine, with MIP-1α and MIP-2α produced by inflammatory macrophages, contribute to the conversion of inflammatory M1-like macrophages into alternatively activated, immunosuppressive M2-like macrophages [34]. In this way, MSCs and altered conditions within the tumor microenvironment modulate macrophage activity.

Studies on B16 F0 melanoma and EL4 lymphoma models have demonstrated that exosomes derived from tumor cells influence MSCs to enhance macrophage infiltration [35]. After macrophage infiltration within the tumor microenvironment, they polarize into the M2 tumor phenotypes under the influence of MCP-1, MCP-3, and MCP-5, which are products of MSCs [36]. On the other hand, in breast cancer, MSC products – TGF-β, C1q, and semaphorins, contribute to the M2 polarization of macrophages [32]. As has been shown, chronic stress is one of the factors contributing to cancer development [37].

Yang et al. demonstrated that stress influences macrophage polarization, impacting cancer development [38]. On the other hand, *in vivo* studies have shown that stress mediators affect the intercellular interaction between MSCs and macrophages [39].

THERAPEUTIC POTENTIAL

In recent years, there has been a significant focus on the therapeutic potential of MSCs. Due to their strong immunomodulatory effects, MSCs and their derivatives show great potential in treating various inflammato-

ta, MMĆ i njihovi derivati pokazuju veliki potencijal u lečenju različitih inflamatornih bolesti. Nakon primene, MMĆ migriraju ka mestima inflamacije, što dodatno ističe njihov potencijal u tretiranju takvih stanja [40]. Međutim, MMĆ dobijene iz različitih tkiva ispoljavaju različite citokine koji utiču na njihov imunomodulatorni potencijal [41].

Pored samih MMĆ, brojna istraživanja sprovedena su i o terapijskom potencijalu egzozoma mezenhimalnih matičnih ćelija. Egzozomi MMĆ se smatraju potencijalnim nosačima različitih citokina, imunomodulatora, pa čak i genske terapije. Studije su pokazale terapijski potencijal MMĆ u određenim inflamatornim oboljenjima kroz regulaciju aktivnosti makrofaga. Pokazano je da PGE2, koji proizvode mezenhimalne matične ćelije, utiče na makrofage tako što stimuliše produkciju IL-10 i inhibira diferencijaciju monocita u dendritske ćelije [42]. Produkcija PGE2 od strane MMĆ zavisi od signalizacije *TNF-α* i iNOS iz monocita/makrofaga, što ukazuje na složenost njihovog međusobnog odnosa [43].

In vivo i *in vitro* studije koje su ispitivale terapijsku efikasnost mezenhimalnih matičnih ćelija u zarastanju rana pokazale su da MMĆ ispoljavaju svoje imunomodulatorne efekte pretežno stimulacijom polarizacije makrofaga ka M2 fenotipu [44]. Brojne studije takođe potvrđuju terapijski potencijal MMĆ u lečenju psorijaze. Primena MMĆ ili egzozoma mezenhimalnih matičnih ćelija, intravenski ili subkutano, u mišjim modelima psorijaze dovela je do značajne imunomodulacije i antiinflamatornih efekata [45]. To se manifestovalo smanjenjem simptoma psorijaze, normalizacijom diferencijacije epidermisa, redukcijom angiogeneze i hiperproliferacije, kao i smanjenjem infiltracije imunskih ćelija u koži [42]. Pokazano je da MMĆ sprečavaju proliferaciju keratinocita inhibicijom produkcije *TNF*-α od strane monocita i makrofaga [46].

Sie i saradnici su pokazali da mezenhimalne matične ćelije izolovane iz pupčane vrpce smanjuju insulinsku rezistenciju reprogramiranjem makrofaga sa M1-nalik na M2-nalik tip kod pacova sa dijabetesom tip 2 [47]. Konkretno, MMĆ stimulišu M1-nalik makrofage da povećaju ekspresiju IL-6, što zatim dovodi do povećanja ekspresije IL-4 receptora, rezultujući fosforilacijom prenosioca signala i aktivatora transkripcije 6 (*STAT6*) u makrofagima i sledstvenom transformacijom makrofaga u M2-nalik fenotipove [47]. Sa druge strane, pokazano je da terapija mezenhimalnim matičnim ćelijama smanjuje infiltraciju makrofaga smanjenjem ekspresije *MCP-1* [48]. U dijabetesnoj nefropatiji, koštano-ćelijske MMĆ, MMĆ iz pupčane vrpce, kao i njihovi izvedeni egzozomi i mikroRNK, pokazali su sposobnost da pojačaju M2 polarizaciju makrofaga, što dovodi do proinflamatornog odgovora i smanjuje oštećenje

ry diseases. After application, MSCs migrate to sites of inflammation, which highlights their potential for treating such conditions [40]. However, MSCs obtained from different tissues express different cytokines that affect their immunomodulatory potential [41].

In addition to MSCs, numerous studies have been conducted on the therapeutic potential of MSC exosomes. MSC exosomes are considered to be potential carriers of various cytokines, immunomodulators, or even gene therapy. Studies have shown the therapeutic potential of MSCs in certain inflammatory diseases by regulating macrophage activity. It has been shown that PGE2, produced by MSCs influences macrophages by stimulating IL-10 production and inhibiting monocyte differentiation into dendritic cells [42]. The generation of PGE2 by MSCs is dependent upon TNF-α and iNOS signaling from monocytes/macrophages, indicating the complexity of their relationship [43].

In vivo and *in vitro* studies investigating the therapeutic efficacy of MSCs in wound healing have demonstrated that MSCs exert their immunomodulatory effects primarily through the stimulation of M2 macrophage polarization [44]. Many studies have also substantiated the therapeutic potential of MSCs in treating psoriasis. The administration of MSCs or MSC exosomes, intravenously or subcutaneously in psoriasis mouse models has resulted in significant immunomodulation and anti-inflammatory effects [45]. This manifested in the reduction of psoriasis symptoms, the normalization of epidermal differentiation, a reduction in angiogenesis and hyperproliferation, and a decrease in immune cell infiltration within the skin [42]. It has been shown that MSCs prevent keratinocyte proliferation by inhibiting TNF-α production by monocytes and macrophages [46].

Xie et al. have demonstrated that MSCs isolated from the umbilical cord reduce insulin resistance by reprogramming macrophages from the M1-like to the M2-like types in rats with type 2 diabetes mellitus [47]. Specifically, MSCs stimulate the M1-like macrophage phenotypes to increase IL-6 expression, which then leads to an increase in IL-4 receptor expression, resulting in the phosphorylation of signal transducer and activator of transcription 6 (STAT6) in macrophages and the subsequent transformation of macrophages into the M2-like phenotypes [47]. On the other hand, it has been shown that MSC treatment reduces macrophage infiltration by decreasing MCP-1 expression [48]. In diabetic nephropathy, bone marrow MSCs, umbilical cord MSCs, and their derived exosomes and microRNAs have been shown to enhance macrophage M2 polarization, leading to a pro-inflammatory response and reducing kidney damage caused by diabetes [49].

bubrega izazvano dijabetesom [49]. Terapija mezenhimalnim matičnim ćelijama se takođe pokazala korisnom u regulaciji mitohondrijske disfunkcije stimulacijom arginaze 1 – markera M2-nalik makrofaga [49].

Manipulacija makrofagima, u smislu njihove aktivacije i deplecije, pokazala je potencijalne terapijske efekte u inflamaciji i karcinomu. Adaptivna terapija makrofagima pokazala se efikasnom u lečenju limfoma i karcinoma dojke. Ren i saradnici su pokazali da mezenhimalne matične ćelije povezane sa tumorom, koje obično podstiču rast tumora, gube svoju funkciju nakon specifične eliminacije makrofaga, te da je kod miševa koji imaju nedostatak C-C hemokinskog receptora tipa 2 (engl. *C-C chemokine receptor type 2 – CCR2*), antitumorni efekat tumorskih mezenhimalnih matičnih ćelija bio smanjen [36]. Takođe je pokazano da dolazi do povećane proizvodnje *MCP*-1 nakon radioterapije, što rezultira pojačanom sposobnošću tumora da privlače mezenhimalne matične ćelije [50].

ZAKLJUČAK

Nesumnjivo je da su interakcije između makrofaga i mezenhimalnih matičnih ćelija ključne za regulaciju inflamatorne mikrosredine, sa značajnim uticajem na nastanak i progresiju bolesti, kao i na reparaciju i remodelovanje tkiva. Međutim, njihov međusobni odnos može da varira u zavisnosti od uslova mikrosredine. Studije ukazuju na to da modulacija ovih interakcija ima terapijski potencijal, a pristup koji je usmeren i prilagođen specifičnim uslovima mikrosredine mogao bi da donese delotvornije rezultate.

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MSCs therapy has also proven beneficial in regulating mitochondrial dysfunction by stimulating arginase 1, a marker of M2-like macrophages [49].

Macrophage manipulation, in terms of activation and depletion, has shown potential therapeutic effects in inflammation and cancer. Adaptive macrophage therapy has proven effective in treating lymphoma and breast cancer. Ren et al. (2012) demonstrated that cancer-associated MSCs, which typically promote tumor growth, lose their function after specific eradication of macrophages and that in C-C chemokine receptor type 2 (CCR2)-deficient mice, the antitumorigenic effect of tumor-associated MSCs was reduced [36]. It has been shown that there is an increased production of MCP-1 after radiation therapy, which results in enhanced ability of tumors to attract MSCs [50].

CONCLUSION

Undoubtedly, the interactions between macrophages and MSCs are crucial in regulating the inflammatory microenvironment, significantly influencing disease onset and progression, as well as tissue repair and remodeling. However, their relationship can vary depending on the microenvironment. Studies suggest that modulating these interactions holds therapeutic potential, and a targeted approach tailored to specific microenvironment conditions could yield more effective results.

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