REVIEW ARTICLE

The Crosstalk between Mesenchymal Stem Cells and Damaged Cartilage in Osteoarthritis

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ABSTRACT

Human cartilage contains multipotent stem cells, namely mesenchymal stem cells (MSCs) which are progenitors of connective tissue that play homeostatic and reparative roles. Although the major constituent cells in the cartilage are chondrocytes, they possess a limited regenerative ability, and as a result, spontaneous cartilage repair by chondrocytes leads to the synthesis of fibrocartilage. Similarly, MSCs derived from articular cartilage of osteoarthritis patients have demonstrated inadequacy in cartilage repair. The role of MSCs in the pathophysiology of osteoarthritis (OA) is not entirely understood, whether the inflammatory milieu associated with OA joints affects the reparative properties of MSCs or the inherent defects of OA cartilage-derived MSCs impair the proper execution of the required immunosuppressive and reparative functions. Therefore, the current review explores the biological characteristics and features of MSCs derived from physiological state and OA condition with the aim of identifying how OA affects MSC functions as well as the role of MSCs in the pathophysiology of OA.

Keywords: Cell differentiation, Cartilage, Mesenchymal stem cells, Osteoarthritis

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INTRODUCTION

The familiar form of arthritis is osteoarthritis (OA). It is a disease that results in the degradation of joint tissue, and associated with severe pain and causes disability in adults (1). The OA involves the action of inflammatory mediators at the joint resulting in an irregular remodelling of the joint tissues (2). There are several risk factors associated with OA; however, obesity, age, gender, prior joint injury, and genetic history are among the most important ones (3). Although OA has been identified as a complex condition with a very obscure aetiology, the damage or loss of articular cartilage accompanied by changes in the subchondral bone with synovial inflammation being the consistent element that defines the disease (4). Synovial inflammation can disturb joint homeostasis (5), and it has been linked with pain and the progression of OA disease (6). The main cellular components of cartilage tissue are the chondrocytes which are inert cells with limited regenerative capacity (7). Consequent of the poor replicative capability of chondrocytes, different treatment approaches have been developed over the last decade, most noticeable of which is the autologous chondrocyte transplantation (ACT) (8). The ACT involves isolation of chondrocytes from the cartilage tissue biopsy obtained from the patient. These chondrocytes are then expanded and administered into the patient to fill the cartilage defect (9). Although ACT has recorded impressive clinical results, the surgical technique is being faced with significant setbacks resulting primarily from the phenomenon of chondrocyte de-differentiation where the infused chondrocytes on exposure to inflammatory factors during the expansion phase, lose their phenotype and hence their ability to synthesize extracellular matrix (ECM) molecules such as COL II and aggrecan (8, 10). For this reason, researchers are considering mesenchymal stem cells (MSCs) as a potential alternative cell source for cartilage tissue regeneration (11).

MSCS AND THEIR CHARACTERISTICS IN OA

Resident MSCs populations have been found in the cartilage tissue, synovium and synovial fluid of healthy (non-OA) individuals. As compared to the BM-MSCS, cartilage-derived MSCs are able to differentiate into cartilage, fat, bone and muscle tissues coupled with potent immunomodulatory prowess, injury/inflammation-triggered migration as well as secretion of various soluble factors. Cartilage-derived MSCs reside at the joint area to serve in the maintenance of tissue

homeostasis and exert tissue reparative functions in response to tissue damage resulting from mechanical injury and/or degenerative diseases (12).

However, the ability of MSCs to execute their physiological function can be affected by non-age related factors. Specifically, MSCs isolated from arthritic tissues have exhibited some form of deficiency in biological characteristics such as proliferation rate, differentiation potential as well as immunosuppressive prowess, when compared to those from healthy tissues (13). Global gene profiling and microRNA studies have identified differentially regulated genes involved in bone metabolism (14) as well as the difference in the levels of microRNAs that are related to osteogenesis (15) in OA-MSCs when compared to non-OAMSCs, supporting the opinion that nearly all diseases have genetic aetiology (16). Low proliferative capacity, reduced chondrogenesis and poor immunosuppressive ability have been reported in MSCs derived from OA tissues. Table I highlights the changes observed in some biological characteristics of OA-MSCs concerning healthy MSCs as reported by previous studies.

Table I: Biological characteristics of MSCs from OA and non-OA from different sources

No	Biological characteristic	Tissue source (OA-MSCs)	Tissue source (non-OA MSCs)	Outcome in OA-MSCs
1	Cell number (yield)	Synovial fluid	Synovial fluid & Synovium	Increased in cell number noted with the severity of OA (14)
		Cartilage	Cartilage	Reduced percentage of cell fraction (15)
2	Morphology	Synovial fluid	Bone marrow	Minute variation in cell morphology. Slightly deviating the typical spindle shape (14)
3	Chondrogenic differentiation	Bone marrow	Bone marrow	Reduced chondrogenic ability (17)
4	Osteogenic differentiation	Cartilage	Cartilage	Enhanced osteogeneic differentiation (15)
5	Adipogenic differentiation	Bone marrow	Bone marrow	Reduced adipogenic differentiation (17)
		Cartilage	Cartilage	Weaker adipogeneic differentiation (15)
6	Proliferative capacity	Bone marrow	Bone marrow	Lower proliferative capability (17, 18)
		Cartilage	Cartilage	Reduced proliferative ability (15)
7	Immunosuppression	Adipose tissue	Adipose tissue	Reduced T-cell immunosuppression (19)
8	MicroRNA expression	Cartilage	Cartilage	Downregulation of mir-31-5p & mir-424-5p (related to osteogenesis) (15)
9	Gene profile	Cartilage	Cartilage	Upregulation of osteogenic key transcription factor RUNX2 (15)
		Synovial fluid	Bone marrow	Upregulation of bone metabolism genes (with SMOC2, GPR133 & SFRP4 confirmed by RT PCR) (14)

CARTILAGE-DERIVED MESENCHYMAL STEM CELLS

The first isolation of multipotent MSCs from joint tissue was conducted in 2001 (20). The MSCs were isolated from the synovial membrane of a healthy adult human by enzymatic digestion technique. These cells showed the capacity for osteogenesis, chondrogenesis and adipogenesis when subjected to the conducive stimulants (20). Clonal heterogeneity has been reported in MSCs derived from the synovium obtained from healthy adult humans as well as from those with a history of OA. Their adherent cells show a distinct proliferative and differentiation capacity (21). Also, MSCs derived from the synovium appeared to show to a higher chondrogenic potential when compared with cells derived from the bone marrow (BM) or Hoffa's fat pad (22). Interestingly, the synovial fluid of non-OA and OA patients are not abundant but potential sources of MSCs with the cells showing greater clonogenicity and chondrogenic differentiation capacity relative to BM-MSCs (23).

Many research groups have successfully isolated MSCs from cartilage tissue and have recorded similar patterns of the proliferation rate, multipotential differentiation, clonogenicity and expression of cell surface markers that similar to the other sources of MSCs. Su et al. reported that the morphology, phenotype and differentiation capacity of cartilage-derived stromal cells adheres to the standard minimal definition for MSCs (24, 25). In one of the elegant studies, Peng et al. had delineated that MSCs generated from the cartilage tissue exhibited a superior ability of chondrogenesis through cartilage matrix formation when compared to the BM-MSCs and adipose tissue-derived MSCs (26). Table II highlights differences in the chondrogenic differentiation abilities of MSCs derived from various sources as reported by previous studies.

Generally bone marrow MSCs showed superior chondrogenic potential relative to MSCs derived from adipose tissues, muscle and synovium (Table II). On the other hand, Shirasawa S. et al., 2016, showed that MSCs derived from synovium exhibited a greater chondrogenic potential as compared to the bone marrow origin which could be attributed to the other confounding factor such as age, inflammation and the cellular fraction of the tissue origin (22). However, cartilage derived MSCs displayed a higher chondrogenic competitive advantage over the bone marrow-derived cells. Additionally, Somoza et al. identified what they referred to as "molecular phenotype of superior quality"

Table II: Comparison of chondrogenic differentiation of MSCs from different sources

No	Sources of MSCs compared	Source with superior chondrogenic ability	Competitive advantage
1	Bone marrow & Adipose tissue	Bone marrow	More extensive staining in aggregates formed Higher proteoglycan deposition (27)
2	Bone marrow, Synovium, Adipose tissue & Muscle	Bone marrow	Produced more cartilage matrix (28)
3	Bone marrow & Synovium	Synovium	Formed larger and heavier cartilage pellets (22).
4	Bone marrow & Cartilage	Cartilage	Median chondrogenic capacity above bone marrow by 2-5 fold (29)
5	Bone marrow, Cartilage & Adipose tissue	Cartilage	Formed more cartilage pellets in both induced and non-induced group Shorter time to reach maximum mRNA expression levels of chondrogenic markers COL II & Aggrecan (26).

in cartilage synthesised from human neonatal articular cartilage derived MSCs (hNAC-MSCs) compared to those synthesized from BM-MSCs (30), suggesting that human cartilage-derived MSCs (C-MSC) could be the ideal source for cartilage tissue engineering.

Exploring the structural biology of the cartilage tissue holds the key to identifying the availability, characteristics and function of C-MSCs as there is a paradigm shift in the understanding of the origin of articular cartilage tissue-resident MSCs. The initial thought that the articular cartilage is formed from epiphyseal cartilage that survived endochondral ossification and hence, they contain MSCs is no longer applicable (31). Similarly, the idea that cartilage tissue regeneration occurs from the deep zone outward has become obsolete (32). Recent studies have now shown that chondrocyte turnover in the articular cartilage is appositional and not interstitial, i.e. it occurs from the superficial zone rather than the deep zone (33), and this explains the presence of MSC-like resident population in the superficial zone (34). Also, the damage of the articular cartilage in early chondrogenic OA occurs at the superficial zone (33); thus, the MSC population may be located therein to function as a source of chondrocyte replenishment. Figure 1 illustrates the appositional direction of chondrocyte differentiation lineage that leads to the formation and regeneration of the articular cartilage.

Although techniques have been developed and optimized to maximize the yield of MSCs isolated from OA cartilage tissue (35) the unavailability of specific markers for C-MSCs has hindered detailed understanding of their putative roles cartilage tissue homeostasis. Additionally, OA and non-OA C-MSCs have shown remarkable ability to undergo long-range migration (culture-expanded cells derived from the cartilage of patients with OA (>1 mm) in vitro (36) suggesting that this superficial zone cartilage-resident cells may have originated from the joint cavity.

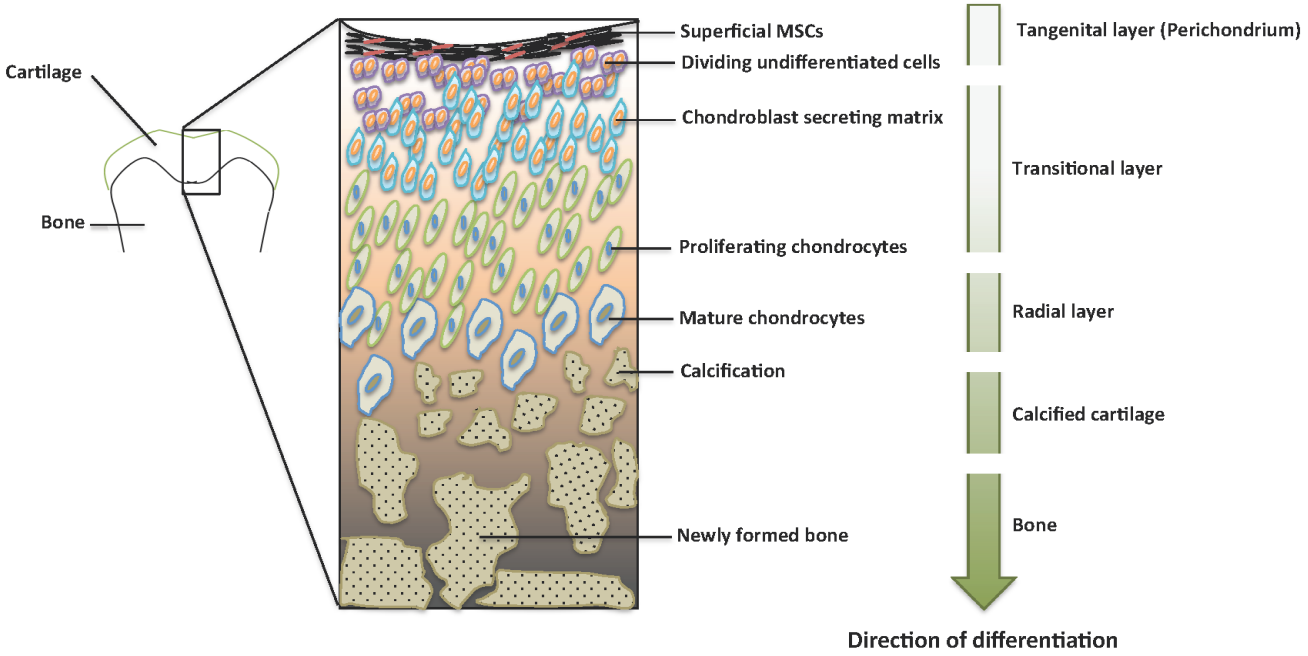

Figure 1: The appositional direction of articular cartilage growth. The growth of articular cartilage is achieved by apposition from the articular surface where undifferentiated progenitor/ stem cells reside and begin to divide. These committed cells differentiate into chondroblasts that secrete cartilage matrix materials. Due to matrix formation, the chondroblasts move apart and develop into chondrocytes which proliferate, secrete more matrix and form new cartilage. Thus, new cartilage results from the addition of matrix secreting chondroblasts to the surface by from the inner layer of the perichondrium. The chondrocytes mature at the radial zone, leading to calcification and formation of bone tissues. Compiled using information sourced from (33, 34).

MECHANISM OF MSC-MEDIATED TISSUE REGENERATION

In recent years, research in translational medicine has focused on the application of MSCs in the development of therapeutic interventions for the treatment of various diseases (37). Although some controversies regarding the primary effect of the cells on an injured environment still exist, many data suggested that therapeutic potential of these cells can be ascribed to paracrine and immunomodulatory influence resulting to the production of factors that support host cell survival by modulating the immune response. These factors also stimulate endogenous tissue precursor cells which reside in the site of injury to undergo mitosis while simultaneously trigger an angiogenic response and prevent abnormal fibrotic response (38).

Inflammation is a putative mediator of tissue injuries, and chronic inflammation contributes significantly to the many degenerative diseases such as OA and cancers. Naturally, MSCs do not provoke the activation of T-cells, as they do not express major histocompatibility complex class II (MHC II), molecules that present antigen to the T helper cells (39). However, injured tissues such as inflamed joints in OA, always result in the stimulation of immune cells namely, B cells, CD8+ T cells, CD4+ T cells, neutrophils and macrophages (40). On the other hand, injured cells can spill their intracellular contents, thereby triggering phagocytes to produce inflammatory mediators like free radicals, IL-1β, TNF-α and other chemokines (41). The localization of immune cells, coupled with the accumulation of the inflammatory mediators, creates an inflammatory microenvironment that induces the migration of MSCs to the site of injury (42). Cartilage tissue injuries are mostly inflammatory mediated, and such an inflammatory milieu serve as an ideal trigger of MSCs' immunosuppressive and regenerative functions (43). This is evident from the discovery that therapeutically infused MSCs migrate to the site of inflammation, and such migration is probably as a result of the upregulation of chemokine receptors on MSCs by the inflammatory factors and chemokines produced by the injured chondrocytes (44). Figure 2 schematically shows the mechanism of MSC-mediated chondrocyte replenishment.

MESENCHYMAL STEM CELLS, INFLAMMATORY CYTOKINES AND PARACRINE FACTORS

During the migration, MSCs enter the tissue-specific microenvironment of injured cartilage tissue, exert paracrine interaction by releasing many soluble factors that include growth factors, cytokines and other proteins. Growth factors such as angiopoietin-1 (Ang-1), transforming growth factor-b (TGF-b), epidermal growth factor (EGF), platelet-derived growth factor (PDGF), hepatocyte growth factor (HGF), fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), insulin growth factor-1 (IGF-1), keratinocyte growth factor (KGF) and stromal cell-derived factor-1 (SDF-1) released by MSCs are crucial elements in mediating tissue repair and regeneration (31, 45). Although cartilage contains a small pool of tissue-resident stem cells that resemble MSCs, extensive tissue damage and non-conducive microenvironment in the inflamed synovium hinder the execution of tissue-resident stem cells. However, it could be possible that the locally injected MSCs or MSCs migrated from bone marrow during the inflammation enhance the repair and regeneration of cartilage by secreting an array of aforementioned growth factors. The growth factors induce tissue regeneration and repair

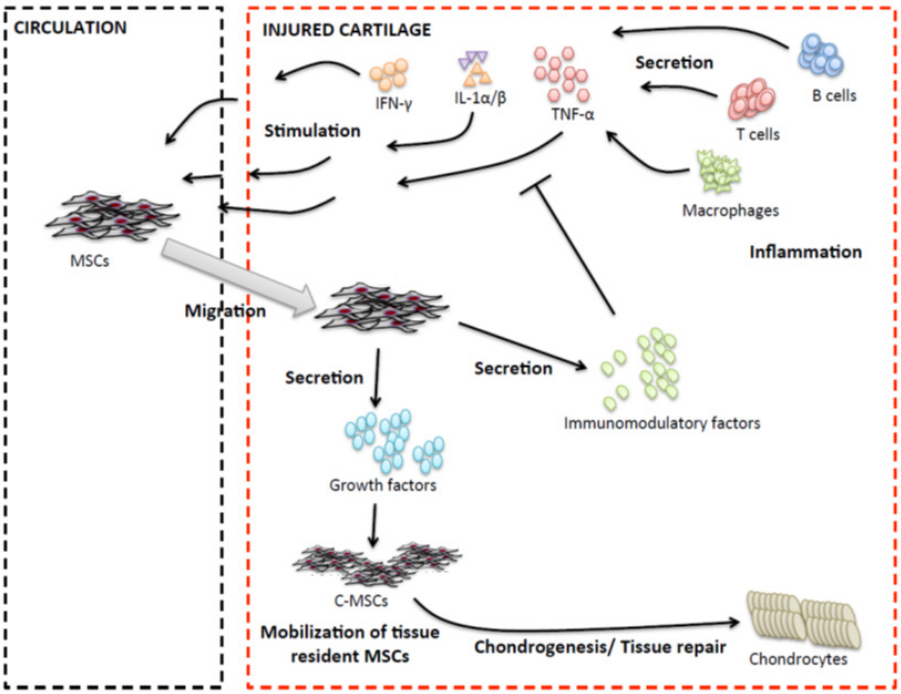

Figure 2: Mechanism of MSC-mediated chondrocyte replenishment. The MSCs in circulation are stimulated to migrate to the injured cartilage by the inflammatory cytokines (TNF-α, Tumour Necrotic Factor-alpha; IL-1α/β, Interleukin-1alpha/ beta and IFN-γ, Interferon-gamma) secreted by immune cells (T cells, B cells and macrophages) at the site of injury. The migrated MSCs secretes immunomodulatory factors that attenuate the inflammation as well as growth factors that stimulate the mobilization of tissue-resident MSCs and promote chondrogenesis and hence chondrocyte replenishment. Compiled using information sourced from Clark KC. et al, 2016 and Atta H. et al., 2016 (42, 48).

act by promoting the development of cartilage tissue precursor, fibroblasts and endothelial cells (31, 42).

The release of growth factors alone is not sufficient to induce tissue repair and regeneration, rather a conducive inflammation-free microenvironment is required; this may, however, be jeopardised by the pro-inflammatory milieu hallmarked in injured cartilage (46). Thus, the need to attenuate the "toxic" microenvironment is equally essential as to induce tissue repair and regeneration. It has been shown that MSCs as well secrete anti-inflammatory/ immunosuppressive agents such as Interleukin-10 (IL-10), Interleukin-1 receptor antagonist (IL-Ra), inducible nitric oxide synthase (iNOS), chemokine ligand 2 (CCL2), indoleamine 2,3-dioxygenase (IDO), Semaphorin-3A, V-set domain-containing T-cell activation inhibitor 1 (VTCNT1), human leukocyte antigen G (HLA-G), leukemia inhibitory factor (LIF), Galectin(s), heme oxygenase-1 (HO-1), Interleukin-6 (IL-6), prostaglandin E2 (PGE2), programmed cell death 1 ligand1/2 (PD-L1/2), TNF-α stimulated gene/protein (TSG) and Fas ligand (FasL) (43, 47). It is important to note, however, that the afore-mentioned anti-inflammatory cytokines and proteins produced by the MSCs are not exclusive to the MSCs and the different type of cytokines produced might vary upon the source and passage of external MSCs. The anti-inflammatory/immunosuppressive factors act mainly by modulating the inflammatory response, inhibiting apoptosis, activating endogenous stem cell proliferation, differentiation and improvement of blood flow in joints (48). Therefore, the interplay between MSCs and the inflammatory immune factors is essential for tissue repair and cartilage regeneration (Figure 3).

CONCLUSION

Understanding the crosstalk between tissue-resident stem cells and damaged cartilages due to OA is important in ensuring timely and effective repair of the injured cartilage. At the initial step of OA pathophysiology, extensive injuries coupled with unbearable immunological/ inflammatory insults supersedes the reparative capability of tissue-resident stem cells. Thus, this review highlights the effect of local inflammation on the MSC function and suggest that treatment of the OA should be focused on correcting the proinflammatory status of damaged cartilage whilst elevating the regenerative ability of the cartilage through infusing of MSCs. Although MSCs are progenitors of the cartilage tissue, the hypothesis that third party MSCs' differentiation is responsible for chondrocytes production is not fully supported in the clinical studies. Thus, it could be assumed that externally delivered MSCs enhance the regenerative potential of the tissue-resident stem cells and attenuates the inflammatory scenario of the affected joint to nurture the repair and regeneration processes.

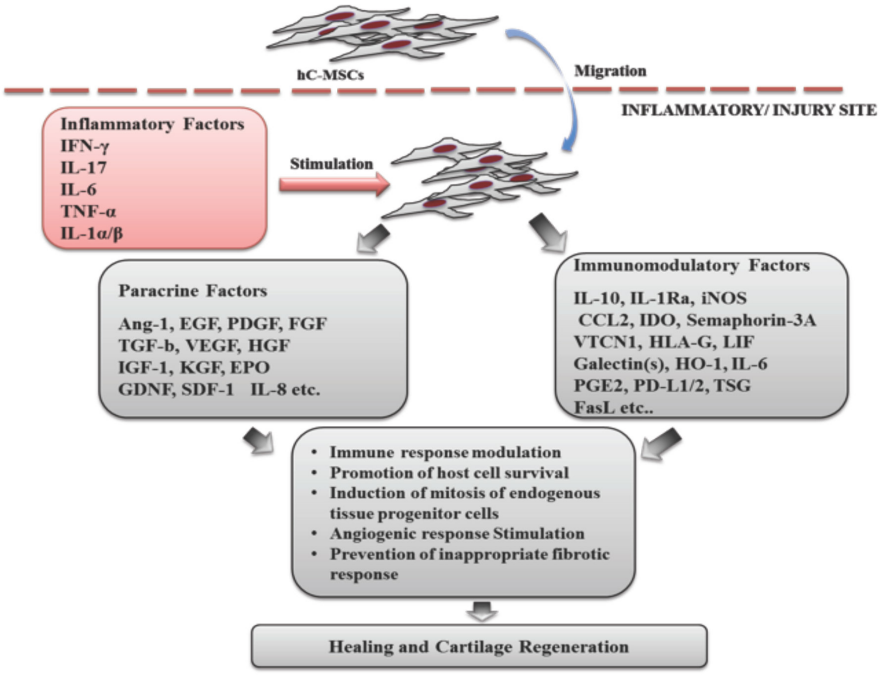

Figure 3: Interplay between MSCs, inflammatory cytokines and paracrine factors in cartilage tissue repair. The hC-MSCs move to the site of inflammatory injury in response to stimulation by inflammatory cytokines (TNF-α, IL-1α/β, and IFN-γ). The stimulated MSCs release paracrine factors (Ang-1, angiopoietin-1; EGF, epidermal growth factor; PDGF, platelet-derived growth factor; FGF, fibroblast growth factor; VEGF, vascular endothelial growth factor; TGF-b, transforming growth factor b; HGF, hepatocyte growth factor; IGF, insulin growth factor-1; KGF, keratinocyte growth factor; EPO, erythropoietin; GDNF, glial cell line-derived neurotrophic factor; IL-8, interleukin-8 and SDF -1, stem cell-derived factor-1) as well as immunomodulatory factors (IL-10, Interleukin-10; IL-Ra, Interleukin-1 receptor antagonist; iNOS, inducible nitric oxide synthase; CCL2, chemokine ligand 2; IDO, indoleamine 2,3-dioxygenase; Semaphorin-3A; VTCNT1, V-set domain-containing T-cell activation inhibitor 1; HLA-G, human leukocyte antigen G; LIF, leukemia inhibitory factor; Galectin(s); HO-1, heme oxygenase-1; IL-6, Interleukin-6; PGE2, prostaglandin E2; PD-L1/2, programmed cell death 1 ligand1/2; TSG, TNF-α stimulated gene/protein and FasL, Fas ligand). These factors' concerted effect promotes trophic and regenerative processes which lead to healing and tissue repair. Compiled using information sourced from (42, 48).

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