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Research Article

Bone Marrow Mesenchymal Stem Cell Secretome from Acute Patients Reveals a Distinct Signature

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Abstract

Objective: Stem cells play a pivotal role in wound healing. Understanding the interplay of chemical signals governing wound healing in different settings could inform on novel strategies to improve outcomes. Before examining wound responses to targeted supplementation of anti-inflammatory or pro-angiogenic treatments, components of the wound secretome should be analyzed at various phases of healing. This study aimed to evaluate the differences in the wound secretome produced by MSCs from severe knee Osteoarthritis (kOA) versus acutely inflamed patients (infections and trauma requiring amputations). We hypothesized that bone marrow-derived Mesenchymal Stem Cells (MSCs) from patients requiring amputation would secrete a higher level of pro-inflammatory cytokines compared to MSCs from patients with chronic diseases such as kOA.

Methods: Bone marrow was processed with density-gradient centrifugation. MSCs phonetypes were confirmed by surface CD34, CD45, CD73, CD90 and CD105 expressions using flow cytometry. Supernatants were collected after 40 hours of cell culture. Milliplex Human Cytokine/Chemokine/Growth Factor Panel A kit was used to measure pro-inflammatory (IL1β, IL6, IL8, IL17A and MCP1); anti-inflammatory (IL4 and IL10); immunomodulatory (FGF-2) and pro-angiogenic (VEGF) factors. Data were analyzed with Bioplex200 Manager and Mann-Whitney U tests performed with α=0.05.

Results: A total of 12 patients were enrolled in this IRB-approved study with 7 (58%) who had undergone Total Joint Replacement (TJR) for kOA and 5 (42%) who had non-limb salvageable injuries from acute traumatic or infectious etiologies requiring below or above-the-knee amputations. The mean age and BMI were 68.1 ± 7.6 years and 30.8 ± 2.9 kg/m^2 for the kOA group and 56.2 ± 9.42 years and 32.8 ± 7.3kg/m^2 for the acute group. 29% of patients in the kOA group were male compared to 80% of the trauma group. Similarly, 70% and 60% of patients in the kOA and trauma groups identified as White respectively. Compared to MSCs from kOA patients, significantly higher concentrations of the pro-inflammatory IL-6, IL-8, IL-17A and MCP-1 and anti-inflammatory IL-10 were secreted into the culture media by MSCs from the acutely ill patients.

Conclusion: MSCs from acutely injured and infected patients produced significantly higher concentrations of four pro-inflammatory cytokines (IL-6, IL-8, IL-17A, MCP-1) and one potent anti-inflammatory cytokine, IL-10. These findings can provide insight into targeted regulation of acute inflammation and the healing response.

Key Messages: Cytokines, chemokines and growth factors are drivers of inflammatory process guiding wound healing and tissue repair. The secretomes of Mesenchymal Stem Cells (MSCs) derived from tibial bone marrow of patients with acute injuries requiring amputation and patients with end-stage knee Osteoarthritis (kOA) undergoing Total Joint Replacement (TJR) were evaluated in this study to better understand the mechanisms influencing wound healing in acute versus chronic inflammatory settings.

Keywords: Mesenchymal; Trauma; Knee Osteoarthritis; Cytokines; Bone Marrow; Stem Cells

Introduction

The bone marrow produces and supports a variety of cells, including Mesenchymal Stem Cells (MSCs), hematopoietic cells and progenitors of bone and cartilage [1]. These cells are known to secrete a diverse array of bioactive factors that are critical for tissue repair and the regulation of inflammatory responses. Bone marrow-derived Mesenchymal Stem Cells (BMSCs) have shown promise in regenerative medicine for their role in tissue repair and wound healing in both chronic diseases and acute injuries. Recent studies have focused on profiling factors secreted by MSCs in various pathological contexts to better understand their roles in modulating the inflammatory environment in efforts to identify interventions promoting tissue regeneration.

Trauma is the leading cause of mortality for the younger population of United States and the systemic response to severe injuries often includes suppression of bone marrow cell production, complicating the healing process. Conversely, over 6.5 million adults in the US live with chronic wounds and these numbers are expected to rise in a population that lives with an increasing number of comorbidities [2]. The delicate balance of chemical signals that orchestrate the inflammatory response to trauma is pivotal for timely recovery; dysregulation can either result in poor healing due to an inadequate response or cause organ damage from excessive inflammation. Notably, a considerable portion of risk factors that hinder wound healing are preventable [3]. A closer look at the dynamic chemical signals guiding wound healing after trauma injuries can help us employ informed treatment strategies to improve outcomes. While MSCs have been identified as modulators of wound healing in trauma, the specific secreted factors and cytokines that contribute to differential outcomes in acute versus chronic conditions remain inadequately characterized. This study aimed to evaluate and compare the cytokine profiles secreted by injury site-specific BMSCs from acutely injured patients with those from patients with chronic inflammation, specifically chronic knee Osteoarthritis (KOA). We hypothesize that BMSCs isolated from acutely ill patients will exhibit distinct cytokine signatures compared to BMSCs from patients with chronic degenerative conditions, thereby providing insights into the differential mechanisms governing inflammation and tissue regeneration in these two cohorts. Understanding these differences could lead to improved therapeutic strategies for optimizing wound healing and tissue regeneration in diverse clinical scenarios.

Methods

Tissue Harvest

Bone marrow was collected from the tibial bones of 7 patients who underwent total joint replacement for kOA and from 5 Emergency (EM) patients who underwent leg amputation due to traumatic injuries or infection. Approximately 10 mL of unfractionated bone marrow were collected, purified and cultured according to Pierini, et al., with some modifications [4]. Bone marrow aspirates were transferred into 50 ml conical tubes, layered with equal volumes of Ficoll-Paque density gradient media and further processed via density-gradient centrifugation. The suspension was centrifuged at 1560xg rcf - rpm would be different for different centrifuges for 30 minutes at room temperature followed by collection of the buffy coat into a 50 mL conical tube and layering it with three times the volume of Phosphate Buffered Saline (PBS). The tube was then mixed vigorously and subsequently centrifuged at 1500 rpm for 10 minutes at room temperature. The supernatant was discarded and the cell pellets were resuspended in 5 mL media preheated to 37oC and filtered using a 100 μm cell strainer.

MSC Culturing

The cells were cultured in Gibco™ Dulbecco's Modified Eagle Medium (DMEM) supplemented with GlutaMAX™ (Thermo Fisher Scientific, Waltham, MA, USA), 10% fetal bovine serum and 1% penicillin/streptomycin at 37°C in a humidified incubator with 5% CO_2. The isolated MSCs were then assessed for the surface expression of CD45, CD73, CD90 and CD105 via flow cytometry using a Cytek® Northern Lights (Cytek Biosciences, Fremont, CA, USA) machine. Supernatants were subsequently collected from the EM and kOA-derived MSCs after 40 hours (about 3 days) of culture in DMEM.

Multiplex Analyses

Analyses were performed on the supernatants, assessing for IL-1beta, IL-6, IL-8, IL-4, IL-17A, MCP-1 (Monocyte Chemoattractant Protein-1), IL-10, Fibroblast Growth Factor-2 (FGF-2) and Vascular Endothelial Growth Factor (VEGF) secretion using a Bio-Plex 200 Systems - Luminex System (Bio-Rad, California, USA). The Multiplex assay kit was purchased from Fisher Scientific (Biomatik, Cat#EKC32642, USA), with the assay performed by introducing 25 μl of MSC culture supernatant into the wells of the assay plate. The plates were further processed according to the manufacturer's protocol.

Statistical Analysis

Univariate analyses were performed to compare the two cohorts (EM vs kOA) with all outliers removed. The data were collected with Bioplex200 Manager (BioRad) and Mann-Whitney U tests were performed using GraphPad Prism version 10.0.0 for Windows (GraphPad Software, Boston, MA, USA) with α=0.05.

Results

Patient Demographics

The mean age and BMI for the kOA group were 68.1 ± 7.6 years and 30.8 ± 2.9 kg/m^2 and for the acute inflammation group, 56.2 ± 9.42 years and 32.8 ± 7.3kg/m^2. In the kOA group, 29% of patients were male compared to 80% in the trauma group. Similarly, 70% and 60% of patients in the kOA and trauma groups self-identified as White, respectively. Patient demographics are presented in Table 1. The most common reasons requiring emergency amputations in the acutely ill patient cohort were: trauma, necrotizing soft tissue infection and burn injury.

Stem Cell Characterization

MSCs were negative for surface expression of CD34 and CD45, positive for CD73 and CD90 when analyzed using Flow Cytometry (Fig. 1). CD105 surface expressions varied (Fig. 1).

Cytokine Levels

Following 40 hours of incubation under culture conditions, 8 of the 10 analyzed cytokines were secreted at levels detectable by the multiplex assay (Table 2, Fig. 2). Concentrations of all detectable cytokines were higher from the analytes in the MSCs from the acute inflammation cohort, however, the differences in FGF-2 and VEGF concentrations between cohorts were not statistically significant. IFN-γ and IL-4 concentrations were undetectable in both groups. IL-6 was the most abundant cytokine secreted by the MSCs isolated from kOA patients (60 pg/mL). On the other hand, IL-8 (3691 pg/mL) and MCP-1(4007 pg/mL) were the cytokines detected at the highest concentration secreted by MSCs isolated from acute patients. Compared with kOA patient MSCs,acute cohort MSCs secreted significantly higher concentrations of pro-inflammatory IL-6 (p= 0.018), IL-8 (p= 0.004), IL-17A (p= 0.013) and MCP-1 (0.004) and anti-inflammatory IL10 (0.004).

	kOA MSCs (n=7)	EM MSCs (n=7)	p-value
Male, n (%)	2 (29)	6 (86)	0.1026
Age, avg (SD)	68.1 (7.6)	58.57 (5.58)	**0.0169**
BMI, avg (SD)	30.8 (2.9)	28.03 (9.23)	0.535
White, n (%)	5 (71)	3 (43)	0.5921
AA, n (%)	1 (14)	4 (57)	0.2657

Table 1: Donor (patient) characteristics.

Cytokine	kOA MSCs (n=7)	EM MSCs (n=7)	p-value
IFNy	-	-	-
IL-6	60.27 (158.99)	982.87 (1184.21)	**0.0175**
IL-1-Beta	0.51 (0.50)	14.07 (19.05)	**0.0274**
IL-8	13.63 (15.80)	3691.14 (3671.01)	**0.0041**
IL-4	0.17 (0.26)	0.27 (0.06)	0.197
IL-17A	0.28 (0.59)	1.28 (0.51)	**0.0126**
IL-10	0.42 (0.09)	78.88 (135.24)	**0.0035**
FGF-2	25.46 (4.37)	35.19 (24.78)	0.2727
MCP-1	19.54 (39.33)	4007.44 (4402.54)	**0.0041**
VEGF	4.38 (7.03)	8.11 (1.81)	0.1649

Table 2: Statistical analysis of secreted cytokines.

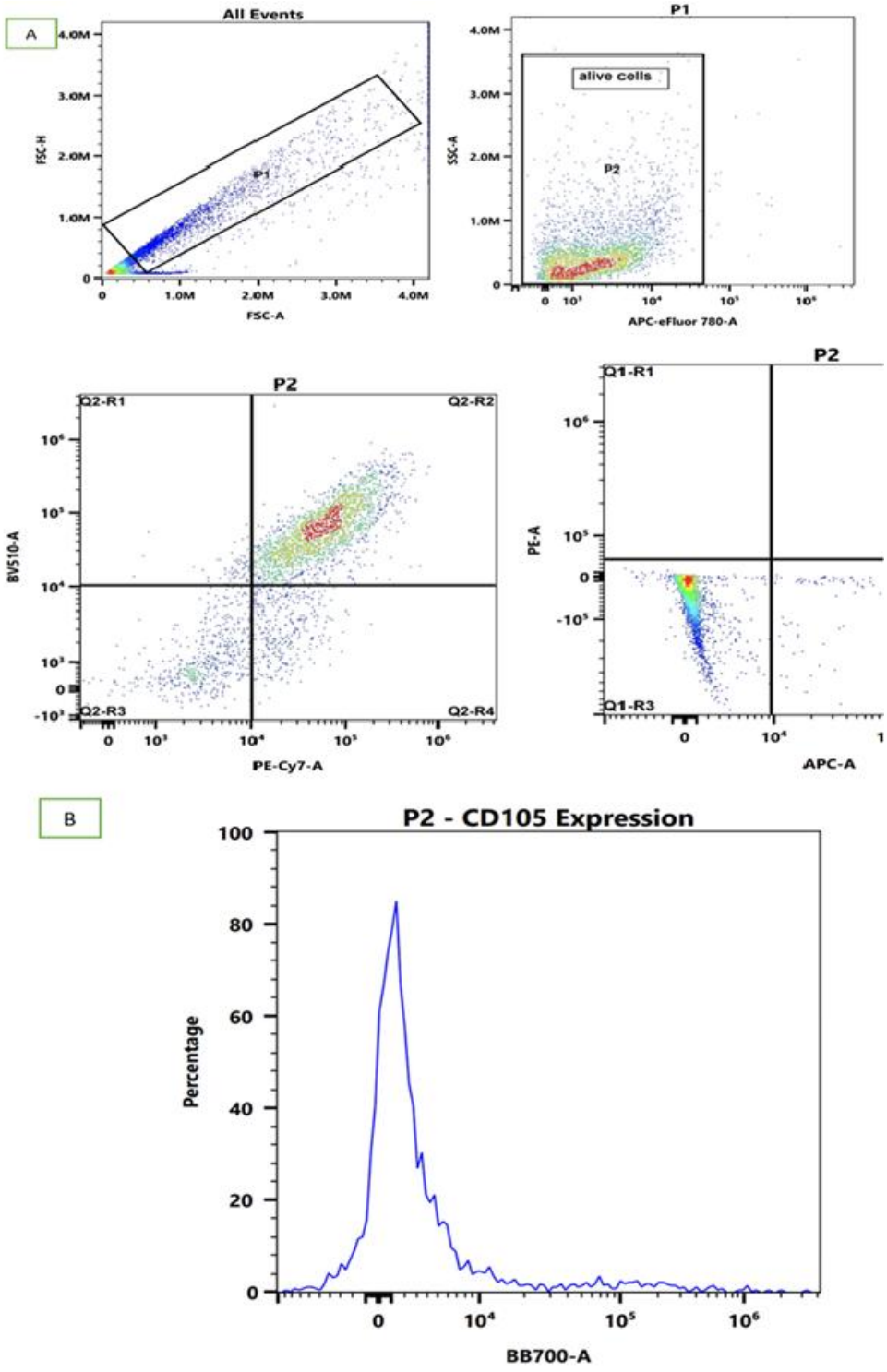

Figure 1: Flow cytometry plots of a representative sample obtained using a Cytek® Northern Lights (Cytek Biosciences, Fremont, CA, USA) machine, analyzed with SpectroFlo (Cytek Biosciences, Fremont, CA, USA) software. FSC-H: Forward Scatter-Height; FSC-A: Forward Scatter-Area, SSC-A: Side Scatter-Area, APC-eFluor780: viability dye, BV510: CD90, PE-Cy7: CD73, PE: CD34, APC: CD45, BB700: CD105, P1 gate represents single cells, P2 gate represents alive cells.

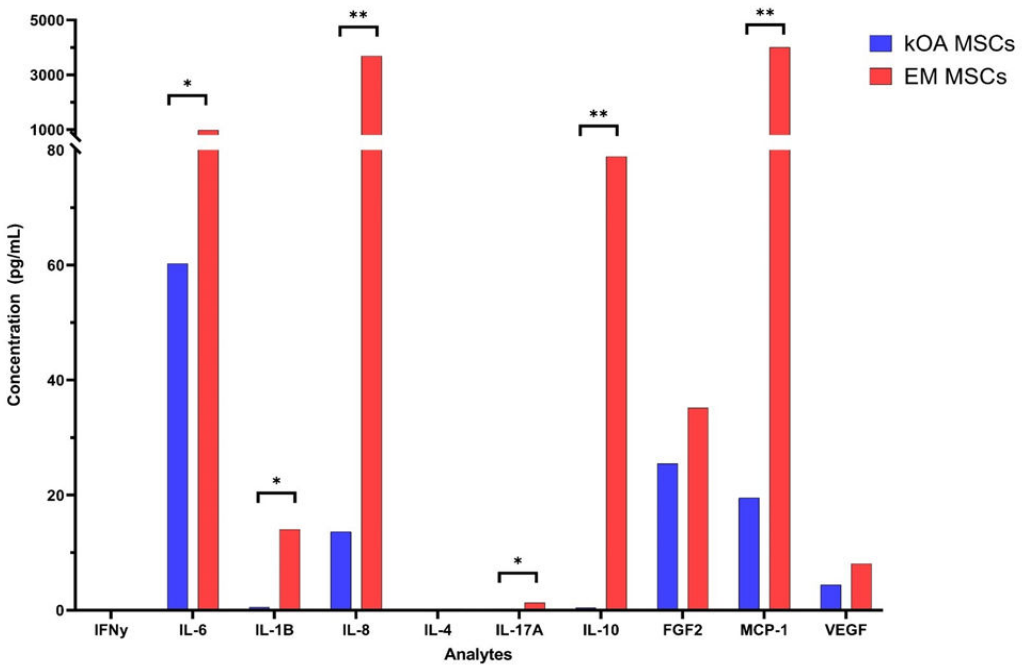

Figure 2: Secretion levels of human cytokines derived from the secretome of bone marrow-derived MSCs from emergency patients compared to kOA patients. Profile shows the mean concentration (pg/mL) of cytokines analyzed in triplicates. N=3, *p=0.01, **p=0.001.

Discussion

Cells in the bone marrow produce a variety of cytokines, chemokines and growth factors, collectively referred to as the 'secretome'; to regulate vital processes such as osteogenesis, hematopoiesis and stem cell regeneration [5]. Following trauma, BMSCs have been shown to migrate to the wound site in response to chemical signals, serving as progenitors of epidermal, dermal and endothelial cells that will be used to regenerate tissue [6,7]. The improved healing outcomes reported with BMSC transplantation in acute and chronic wounds have also been attributed to the autocrine and paracrine factors that constitute the "secretome" [16]. However, adoptive stem cell transfer poses several challenges including limited efficacy due to compromised cell viability and low engraftment after implantation [7,8]. Additionally, stem cells harvested from patients with a dysfunctional trauma response for auto-transplant can harbor the same disruptions that impair wound healing, thereby reducing treatment efficacy. However, despite the variable reports on the efficacy of adoptive transfer; there is promising data suggesting that MSC conditioned media alone can improve wound healing in *in-vitro* assays [7]. Identifying key elements, such as paracrine factors, of the MSC response to acute stressors such as trauma can guide tailored treatment strategies to overcome these challenges.

Physiological response to trauma is characterized by a rise in IL-6, IL-10 and MCP-1 triggered by the release of Damage Associated Molecular Patterns, molecules like ATP released by dead or dying cells to trigger inflammation, within 12 hours, followed by a T-helper 17 predominant response secreting IL-17A evolving over the first 24 hours [9-11]. IL-6, initially identified as a B-cell differentiation factor, is one of the most widely studied cytokines of the acute trauma response and the rise in IL-6 following injury has been shown to correlate with the severity of the stressor [12,13]. There is a growing body of evidence to suggest that higher levels of IL-6 can be used to predict a dysregulated inflammatory response, including Multiorgan Dysfunction Syndrome (MODS) and Systemic Inflammatory Response Syndrome (SIRS) and its levels remain elevated as it regulates the transition of acute inflammation into a chronic state [14,15]. However, as the inflammatory state is sustained more local cells become sensitive to the effects of IL-6, hence less IL-6 will be needed to propagate the immune effects [16]. Studies have revealed higher synovial fluid concentrations of IL-6 in OA patients but reports on serum IL-6 levels vary between average and elevated, likely due to the variety of patient characteristics [17]. Our study demonstrated a significantly higher concentration of IL-6 secreted by the trauma cohort, which correlates with the existing literature.

IL-6, together with TGF- β and other cytokines, modulates the IL-17A response in acute and chronic inflammation. While initially identified by its role in chronic inflammation inducing neutrophilia, recruiting T cells and stimulating IL-6, IL-8 and MMP

production, emerging studies have identified critical roles for IL-17A in the acute response to trauma, hemorrhage and wound healing as well [18]. A study of 18 blunt trauma patients identified a prominent cytokine response from the pathogenic subset of Th17 cells that secrete IL-17A and inhibit IL-10 production in the non-survivor group which is in line with our data demonstrating higher levels of IL-17A and lower levels of IL-10 in trauma patients [19]. Additionally, the same study showed that the administration of an IL-17 antagonist to mice with hemorrhagic shock could dampen the organ damage. There are conflicting reports on the role of IL-17A in wound healing with some studies identifying it as a regulator of glycolysis promoting regeneration and others suggesting improved re-epithalization in mice when treated with IL-17A antagonists [20]. Considering the time and location limited functions of pleiotropic cytokines such as IL-17A, further studies are needed to identify the inflammatory stage specific roles of IL-17A and the potential benefits of its antagonists in modulating the trauma response.

IL-17A can also stimulate angiogenesis by promoting the production of VEGF [21,22]. Additionally, VEGF and IL-6 have been implicated in the inhibition of extracellular matrix type II collagen synthesis and in the pathogenesis of OA [23,24]. As IL-6 and VEGF both serve as essential regulators of wound healing, a dysregulated response can result in wound complications and fibrosis [25]. A study comparing the bone marrow secretome via RNA expression analysis from 52 blunt trauma patients with 33 patients undergoing elective hip replacement found a significant downregulation of VEGF expression in the trauma cohort [26]. Our study has not demonstrated a significant difference in VEGF secretion between the 2 groups and this discrepancy between studies might be explained by the different timeframes and levels of fold change required to observe differences in RNA expression, reported in the aforementioned study, versus levels of secreted cytokines, measured by our study.

IL-8 and IL-6 are signature biomarkers of traumatic injury as elevated levels of both can be used to distinguish trauma-related death from non-traumatic causes [27]. IL-8 is responsible for neutrophil, BMSC and macrophage recruitment, respectively, to the site of acute inflammation [28]. Studies have shown that IL-8 plays a pivotal role in endochondral bone formation following injury. Higher levels of IL-8 in our trauma cohort can be explained by the acute injury inducing its release to stimulate repair. While IL-8 has been implicated in OA pathogenesis via MMP regulation, only synovial concentrations, not plasma levels, have been associated with disease activity [29,30].

Monocyte Chemoattractant Protein-1 (MCP-1), also referred to as Chemokine (CC-motif) Ligand-2(CCL-2), promotes the migration of monocytes and memory T-cells to the site of injury [30]. It is known to stimulate a Th2 response, signified by the production of IL-4 and IL-10 and triggers the release of active substances locally such as histamine from basophils and mast cells [27]. Therefore, MCP-1 plays a critical role in controlling local inflammation and it has been identified as one of the key factors driving synovial disruption in OA [31]. However, it is important to note that baseline levels of MCP-1 can vary due to a wide range of genetic polymorphisms [32]. Additionally, MCP-1 is known to promote endothelial regeneration and angiogenesis after injury while attracting leukocytes and enhancing the migration of monocytes to the subendothelium, contributing to an overall pro-thrombotic effect [32]. Notably, studies have shown an increased risk of venous thromboembolism in trauma patients with higher levels of IL6, IL8 and MCP-1, however it is not yet clear whether this could be the inciting factor or a confounder effect [33].Our results are in support of the view from the literature that MCP-1 levels can be a useful tool in cases of traumatic injury, but further research is needed to clarify its role [34].

As a cytokine with mostly anti-inflammatory effects that can inhibit IL-1, IL-6 and TNF- α; IL-10 plays a pivotal role in refining the immune response to trauma [27]. IL-6 is an important promoter of its synthesis, therefore, levels of IL-10 are elevated after acute injuries [35,36]. In contrast, serum IL-10 levels were found to be compromised in patients with osteoarthritis, possibly reflecting an inability to counter chronic inflammation [37]. Our findings are in line with data from the literature highlighting the critical role of IL-10 in the acute response to trauma.

IL-1 β can cause vasodilation, attract granulocytes, cause fever and stimulate a Th17 response [38]. Studies on IL-1 β deficient mice have failed to produce an acute phase response with a paucity of IL-6 production, nausea and fever [39,40]. These findings, in addition to our data, seem to highlight the critical role of IL-1 β as one of the initiators of the acute response to injury.

The cytokine response to tissue damage results in a highly dynamic serum cytokine profile with various cytokines such as IL-1 β demonstrating transient peaks due to low stability [33]. Therefore, it is important to evaluate the secretome over time to derive data that can guide clinical decisions. Future studies could assess how these cytokines, in addition to TGF- β and TNF- α, which

are known to play critical roles in injury response and tissue regeneration, change over time and differ according to patient characteristics including obesity and alcohol exposure, factors associated with a dysregulated inflammatory response [3,14,41]. Additionally, it is important to measure the changes in cytokine levels over time as baseline levels will vary according to patient characteristics; for example, older age and obesity are both associated with higher baseline levels of IL-6 [42].

Conclusion

In conclusion, Bone Marrow Stem Cells (BMSCs) are responsible for a majority of the chemical signals that regulate the acute response to injury. Our results underscore the significance of IL-1 β, IL-6, IL-8, IL-10, IL-17A and MCP-1 as key components of the cytokine signature associated with trauma. Additionally, our data suggests that there is a strong correlation between increased MSC pro-inflammatory cytokines levels and trauma, specifically IL-6: involved in acute phase-phase immune response, IL-1 beta: a potent stimulator for the release of other cytokines and immune cells, IL-8: a chemoattractant for neutrophils and IL-17A. Similarly, a correlation between decreased IL-10 - a potent anti-inflammatory cytokine that promotes tissue repair via suppression of pro-inflammatory cytokine expression and trauma was established. However, the specific role of these cytokines may vary depending on the presence of other factors. Further studies will be conducted to establish possible cytokine-cytokine interactions in both kOA and acute injuries. Interventions to modulate the activity of these cytokines can be used to prevent and treat complications associated with dysregulated trauma response. Further studies are needed to understand how these chemical signals can be manipulated to improve treatment outcomes.

Conflict of Interest

The authors report no conflicts of interest. AAS is a paid consultant for Aroa Biologics and on the advisory board for Prytime Medical. JEC is a stockholder for Permaderm, Inc. and SpectralMD and serves as a consultant for Avita and Polynovo Ltd. HAP serves as a consultant for Avita and SpectralMD. PG is a Consultant and paid speaker for Zimmer Biomet and MedExpert. The other authors declare no conflicts of interest.

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Consent for Publication

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