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Original Article

Mesenchymal stem cells treated with Interleukin-1 beta for mediation of an inflammatory response in human tissues

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Abstract

The present study examined the functional activities of the human bone marrow mesenchymal stem cells (hBM-MSCs) under the effects of various concentrations of the inflammatory mediator interleukin 1 beta (IL-1β). The effects of IL-1β on the functional properties of hBM-MSCs were measured using functional assays (adhesion, proliferation, and migration). hBM-MSCs expressions of colony-stimulating factors 1 and 2 (CSF1, CSF2), C-C chemokine receptor type 2 (CCR2), C-X-C chemokine receptor type 1 and 3 (CXCL1, CXCL3), were examined using real-time polymerase chain reaction (RT–PCR). The pro-inflammatory cytokine IL-1β did not disrupt hBM-MSCs adhesion, but it improved proliferation and migration only up to 50 ng/ml. However, in response to 100 ng/ml IL-1β, cell growth, proliferation, and migration were reduced significantly. The expression of CSF1, CCR2, CXCL3, and IL-1β genes increased with the increase in the concentration of IL-1β. CSF2 and CXCL1 gene expression increased in the 50ng/ml group compared with the 10ng/ml group to be higher than the control group in the 100ng/ml IL-1β group which might facilitate the differentiation, and homing of MSCs to the site of injury and augment their activities in the inflamed microenvironment. The study corroborates the advantages of prior stimulation of mesenchymal stem cells (MSCs) with the cytokine IL-1β, demonstrating an upregulation of key chemokines and cytokines. This upregulation potentially enhances MSCs' ability to differentiate and migrate to injury sites, while also augmenting their functional role within an inflamed microenvironment, thereby amplifying their therapeutic potential.

Keywords: IL-1β, hBM-MSCs, CSF1, CCR2, CXCL3.

1. Introduction

Mesenchymal stem cells (MSCs) possess the ability to self-renew and differentiate into diverse cell types, including muscle, fat, cartilage, bone, and the supportive tissue in bone marrow. These versatile cells reside in various tissues of both adult organisms and developing embryos, including bone marrow, adipose tissue, the umbilical cord, and the placenta [1].

The immunomodulatory characteristics of MSCs make them excellent candidates for cell-based therapeutic agents against immune-mediated diseases. They modulate immune responses by interacting with various immune cells, including T and B cells, monocytes, and macrophages, through the secretion of multiple inflammatory mediators and other signaling molecules Therefore, MSCs can be preconditioned with several elements to resist oxidative stress [2-5].

MSCs are remarkably adept at aiding in tissue repair and regeneration, making them invaluable in the treatment of inflammation-associated diseases. In environments characterized by high levels of oxidative stress and inflammation—essentially, conditions that are detrimental to most cells—MSCs retain their ability to function and contribute to tissue repair [2, 3]. MSCs demonstrated remark-

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able resilience in the harsh oxidative environment induced by high concentrations of hydrogen peroxide (H_2O_2). Preconditioning MSCs with H_2O_2 not only enhanced their functional activities but also modulated the expression of genes involved in crucial cellular processes. This suggests that preconditioning with H_2O_2 could potentially improve the therapeutic efficacy of MSCs in regenerative medicine applications [6].

Also, MSCs have been shown to possess remarkable protective effects on endothelial cells, shielding them from the detrimental effects of H_2O_2 and monocytes. This property makes them promising candidates for cell-based therapies in inflammation-associated diseases [7, 8]. Treating mesenchymal stem cells (MSCs) with interleukin-1 beta (IL-1β) has been shown to enhance their therapeutic potential by increasing their production of anti-inflammatory and pro-growth factors. Additionally, IL-1β appears to bolster the ability of MSCs to modulate the immune system, potentially improving the success of stem cell transplantation therapies [9].

This study investigated the response of human bone marrow mesenchymal stem cells (hBM-MSCs) to varying concentrations of IL-1β, a cytokine known to mediate stress responses within the body [10]. The effects of these IL-1β concentrations on the cells' release of key molecules involved in regulating immune defense and inflammatory reactions were also tested. Additionally, the study studied how this inflammatory microenvironment influences hBM-MSC activities such as adhesion, proliferation, and migration.

2. Material and methods

2.1. Cultivation of human Bone Marrow Mesenchymal Stem Cells

Immortalized hBM-MSCs served as a model for primary hBM-MSCs in this study. The hBM-MSCs were obtained from Lonza Group Ltd. These immortalized cells have been extensively characterized, exhibiting characteristics comparable to primary hBM-MSCs [11]. The cells were grown in Dulbecco's Modified Eagle Medium (DMEM) with added 0.25 mol/L D-glucose, 10% fetal bovine serum (FBS, US origin), 1x penicillin-streptomycin, and a mix of NAA (all from Gibco-Invitrogen, USA). The cells were grown to 70-80% confluence in DMEM at 50,000 cells/ml density (Figure 1).

2.2. Enhancement of hBM-MSC adhesion and proliferation in response to IL-1β stimulation

The research involved four distinct treatment groups for hBM-MSCs, as detailed in Table 1. To evaluate the adhesion and growth of hBM-MSCs, the investigators utilized the xCELLigence system, a real-time cellular analysis instrument from Roche Diagnostics, based in Mannheim, Germany [Real-Time Cell Analysis dual purpose (RTCA DP)]. This instrument continuously monitors and records changes in electrical impedance, which are subsequently represented as a cell index value [12].

In this study, a population of 20,000 hBM-MSCs was cultured using a complete hBM-MSCs growth medium, adhering to the previously established protocol. The control batch and three experimental batches were exposed to incremental levels of IL-1β (100, 50, and 10 ng/ml) within the wells of a 16-well cell culture nanochip-plate (E-Plate 16, Roche Diagnostics, catalog number 05469813001). These culture plates were then installed in the xCELLigence system, which was maintained at approximately 37°C. The progression of the hBM-MSC cell index was meticulously monitored using the xCELLigence system. Initial cell adhesion was observed immediately after cell introduction to the culture wells, followed by cell proliferation observed over a period of 24 to 72 hours.

Data collection and analysis were performed using methodologies consistent with those outlined in previous scholarly articles. The xCELLigence system was employed to dynamically evaluate the attachment and growth of hBM-MSCs. The cells were cultured in varying levels of IL-1β, with their activity continuously monitored through the xCELLigence system's ongoing electrical impedance recordings. This method enabled the research team to investigate the impact of IL-1β on hBM-MSCs over a defined timeframe, generating data that were subsequently processed following established analytical protocols [12].

Table 1. hBM-MSCs treatment groups.

Groups	Description
1	hBM-MSCs cultured alone (Control group)
2	hBM-MSCs cultured with IL-1β 10 ng/ml
3	hBM-MSCs cultured with IL-1β 50 ng/ml
4	hBM-MSCs cultured with IL-1β 50 ng/ml

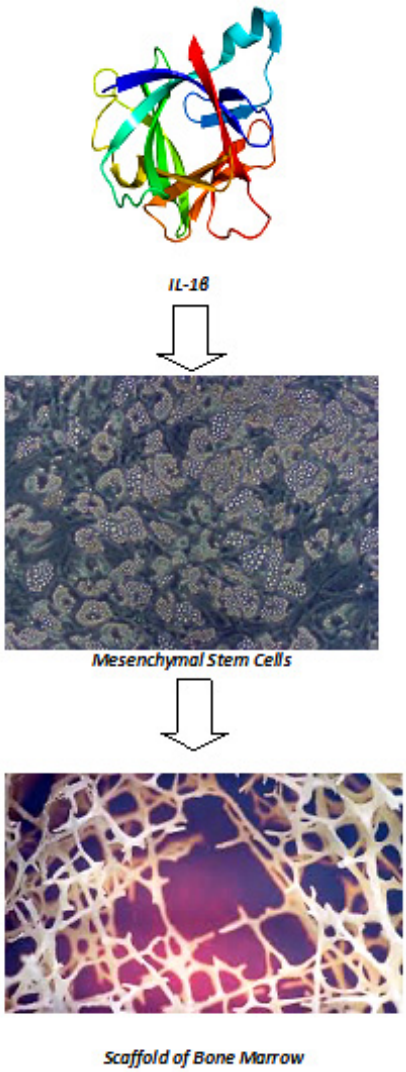

Fig. 1. Enhancing therapeutic efficacy: IL-1β primed human bone marrow mesenchymal stem cells (hBM-MSCs)

2.3. hBM-MSCs migration in response to IL-1β

Migration of hBM-MSCs was evaluated using the xCELLigence system in a CIM plate (Roche Diagnostics GmbH), adhering to protocols established in previous studies. Initially, 20,000 hBM-MSCs from the first group were seeded alone in the upper chamber. For the remaining three groups, 100 µL of hBM-MSCs culture medium was added to the upper chamber, and IL-1β was introduced into the lower chamber. Following a 30-minute incubation at room temperature to allow cell attachment to the membrane, the xCELLigence system commenced tracking cell migration [12]. Results were recorded as cell index values at the 24-hour mark. A 10% FBS solution served as the positive control for migration, while a 1% FBS solution acted as the negative control.

2.4. Analysis of gene expression with real-time quantitative PCR (RT-qPCR)

Expression levels of genes related to cytokines, chemokines, and adhesion molecules—including colony-stimulating factors 1 and 2 (CSF1, CSF2), C-C chemokine receptor type 2 (CCR2), C-X-C chemokine receptor type 1 and 3 (CXCL1, CXCL3), and IL-1β—were investigated in hBM-MSCs after a 24-hour IL-1β induction at varying concentrations. Complete RNA was extracted from the hBM-MSCs, converted to cDNA, and used with a set of primers (Table 2). The expression analysis was carried out using a qRT-PCR Via VII system (ABI, USA) in three replicates. Data interpretation followed previously established methods, and the relative gene expression was reported as fold changes using the $2^{-\Delta\Delta CT}$ calculation method.

2.5. Statistical analysis

We systematically organized and evaluated the collected data using the Kruskal-Wallis nonparametric test in SPSS software version 22. A P-value less than 0.05 was considered statistically significant.

3. Results

A similar adhesion pattern, of hBM-MSCs in all groups, to the plastic surface, was detected. The attachment of the hBM-MSCs was not affected by the different concentrations of IL-1β as they were attached at almost the same rate as the control group. An inverse relationship between increased IL-1β concentrations and cell growth was observed. The highest IL-1β concentration (100 ng/ml) showed the highest doubling time and lowest growth (Figure 2).

The hBM-MSCs proliferated differently in the four groups and the proliferation was altered by high concentrations of IL-1β. Proliferation improved after stimulation with IL-1β with 10 and 50 ng/ml. Yet, when exposed to 100 ng/ml of IL-1β, there was a significant decrease in proliferation compared to the control group (Figure 3).

hBM-MSCs exhibited no migration when cultured in 1% FBS serum. However, migration was significantly increased in cells treated with 10% FBS serum and IL-1β (Figure 3). Exposure of hBM-MSCs to 10 ng/ml of IL-1β induced the most prominent enhancement of migration compared to the control. A dose of 50 ng/ml of IL-1β also promoted a moderate improvement in hBM-MSCs migration. Conversely, treating hBM-MSCs with 100 ng/ml of

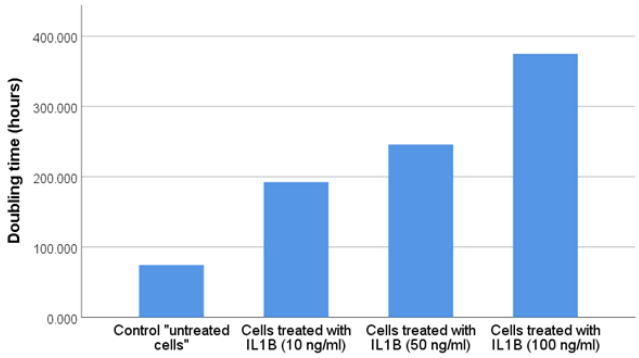

Fig. 2. hBM-MSCs doubling time in response to IL-1β run on real-time cell analysis dual purpose (RTCA-DP) system.

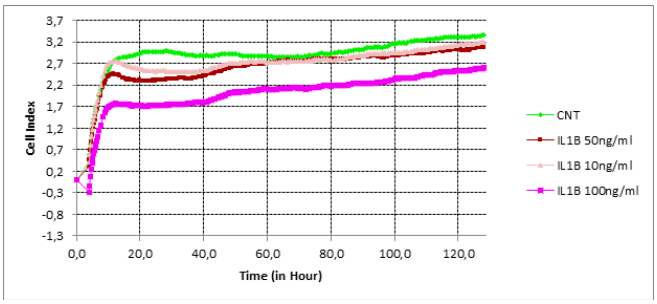

Fig. 3. Cell proliferation of hBM-MSCs in presence of different concentrations of IL1B.

Table 2. The forward and backward primer sequences used during the RT-qPCR.

Gene		Primer sequences
CSF1	Forward Primer	5'-GCTGCCAGGCTTTCTTCGTGG-3'
	Reverse Primer	5'-CGGTGCAGTTCTCCACCTGTCT-3'
CSF2	Forward Primer	5'-TGGGATTCCATGGCCAAGTCC-3'
	Reverse Primer	5'-AGGCTCGTGGGCTTCAGGGTT-3'
CCR2	Forward Primer	5'-TGGCTCAAGGCTGTCCACACT-3'
	Reverse Primer	5'-AGGTCTTGCTGGAGTTGGCTG-3'
CXCL1	Forward Primer	5'-GGCATAGCAGTACGAGTCTTG-3'
	Reverse Primer	5'-TGGACATTTTGCTGGCTTG-3'
CXCL3	Forward Primer	5'-TTCACCTCAAGAACATCCAAAGTG-3'
	Reverse Primer	5'-TTCTTCCCATTCTTGAGTGTGGC-3'
IL1B	Forward Primer	5'-GCACGATGCACCTGTACGAT-3'
	Reverse Primer	5'-CACCAAGCTTTTTTGCTGTGAGT-3'

IL-1β resulted in a substantial reduction in migration compared to the control group (Figure 4).

The expression of CSF1 and CCR2 genes increased in parallel with higher concentrations of IL-1β compared to the control group. Conversely, CSF2 gene expression exhibited a significant reduction at the lower IL-1β concentration of 10 ng/ml when compared to the control. However, its expression increased when the concentration was raised to 50 ng/ml, surpassing the control group level. At the 100 ng/ml IL-1β concentration, CSF2 expression again declined, falling below the control group level (Figure 5).

Gene expression levels of CXCL3 and IL-1β showed a rising trend alongside the increasing concentrations of IL-1β when compared to the control group. Notably, CXCL1 gene expression significantly decreased at a lower concentration of IL-1β (10 ng/ml) relative to the control group. However, this expression escalated when the concentration was adjusted to 50 ng/ml and exceeded control levels upon reaching 100 ng/ml of IL-1β **(**Figure 6**).**

4. Discussion

Mesenchymal stem cells (MSCs) have been demonstrated to be an effective therapeutic approach for managing inflammatory diseases with a variable influence [13-15]. Stem cells can receive and respond to environmental changes and actively react to them [16]. In addition, MSCs can secrete chemokines, cytokines, and growth factors, promoting their anti-inflammatory effects in a paracrine manner. These factors can also enhance the proliferation and the immunomodulatory effects of the injured tissues. Therefore, many preconditioning approaches have been investigated to enhance their poor migration [9, 17, 18].

The current study sought to elucidate the genetic responses of MSCs to inflammatory environments and investigate the effects of preconditioning MSCs on their functional activities (adhesion, proliferation, and migration). The study evaluated the impact of varying concentrations of IL-1β on MSCs functions in vitro. It revealed that this treatment had no significant effect on MSCs adhesion but significantly decreased their proliferation at the high concentration of 100 ng/ml IL-1β. However, it was reported that the adhesion of MSCs to human umbilical vein endothelial cells was enhanced with the IL-1β through LFA-1/ICAM-1 interaction [19]. Furthermore, in another study, the two low doses of IL-1β did not affect proliferation and induced migration, adhesion, and leucocyte recruitment through an NF-κβ-mediated pathway [20].

Also, in this study, the pro-inflammatory cytokine IL-1β was found to maintain MSCs adhesion without causing disruption and to enhance proliferation at concentrations up to 50 ng/ml. Yet, cell growth and proliferation experienced a notable decline with 100 ng/ml IL-1β. This observation aligns with earlier research where IL-1β was observed to limit the proliferation of umbilical cord-derived MSCs. This warrants a re-evaluation of IL-1β's role in the proliferation and adhesion processes of MSCs.

The study also revealed that at 10 ng/ml, IL-1β significantly increased migration, with 50 ng/ml also having beneficial effects. However, at 100 ng/ml, there was a substantial decrease in migration. Complementing these findings, Guo et al. identified that IL-1β facilitates MSC transmigration across HUVEC cells through engagement with the CXCR3 and its ligand, CXCL9. Additionally, IL-1β is known to enhance the migration capability of MSCs

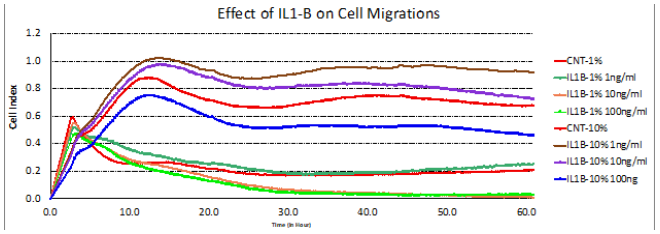

Fig. 4. Impact of different IL-1β concentrations on hBM-MSCs cellular migration over a 60-hour-period. The cell index, a quantitative measure of cell migration, is plotted against time. The control groups denoted as CNT-1% and CNT-10%, reflect baseline migration activity in the presence of 1% and 10% fetal bovine serum (FBS), respectively. Comparative migration patterns are observed in response to IL-1β at concentrations of 1ng/ml, 10ng/ml, and 100ng/ml, both in the 1% and 10% FBS environments. Notably, the CNT-10% group maintains higher cell index values indicative of greater migration, serving as a positive control. In contrast, the CNT-1% serves as a negative control with markedly lower migration. This data highlights the dose-dependent influence of IL-1β on hBM-MSCs migratory behaviour, providing insights into the cellular mechanisms modulated by this cytokine.

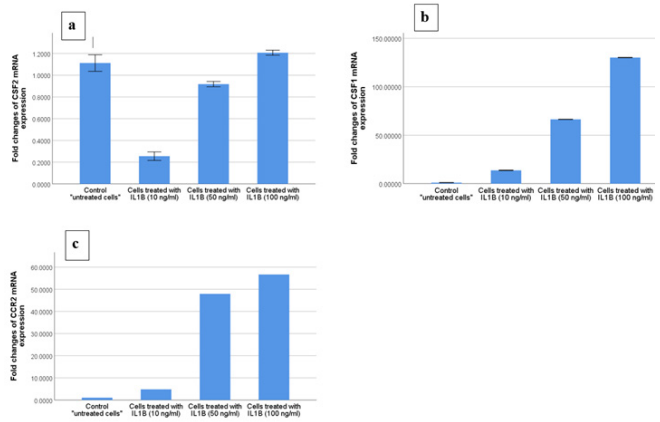

Fig. 5. Chemokines responsive gene expression after 24hrs induction of hBM-MSCs with different concentrations of IL-1β, **a:** colony-stimulating factor 1 **(CSF2)**, **b:** colony-stimulating factor 1 **(CSF1)**, and **c**: chemokine receptor type 2 **(CCR2).**

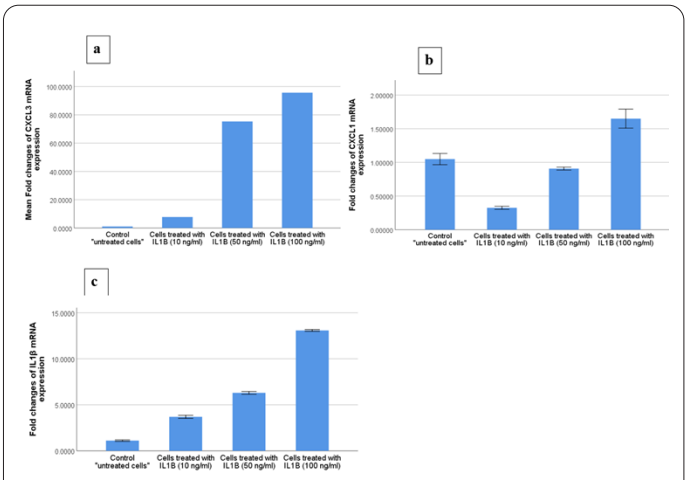

Fig. 6. cytokines responsive gene expression after 24hrs induction of hBM-MSCs with different concentration of IL-1β, **(a)** C-X-C chemokine receptor type 3 (CXCL3), **(b)** C-X-C chemokine receptor type 1 (CXCL1), and **(c)** interleukin 1 beta (IL-1β).

in a controlled environment. Furthermore, MSCs that were primed with IL-1β displayed an improved migration capacity to inflammatory sites within the gastrointestinal tract, which was evidenced by an increase in CXCR4 gene expression in response to dextran sulfate sodium-triggered colitis in mice, underlining the beneficial implications of the inflammatory milieu on MSC migration and localization [21].

MSCs exhibit a high degree of responsiveness to their environmental conditions. The process of priming or preconditioning MSCs, which involves exposure to hormones, chemokines, cytokines, hypoxic conditions, growth factors, biomaterials, and pharmaceutical agents, has been extensively studied with favorable outcomes. IL-1β preconditioning has been specifically noted to boost the immunomodulatory functions and overall efficiency of MSCs. It is also important to note that while the direct application of IL-1β on human umbilical cord-MSCs (HUVEC) did not affect their viability, the suppression of the IL-1R1 receptor through siRNA had a detrimental effect on MSC viability, irrespective of IL-1β's presence. This suggests that while IL-1β's signaling pathway is crucial for sustaining MSCs viability, it does not alter their fundamental structure or characteristics [21-23].

Colony-stimulating factor-1 (CSF1), or macrophage colony-stimulating factor, is an essential secreted cytokine that plays a pivotal role in advancing the release of pro-inflammatory chemokines and facilitating the differentiation of hematopoietic cells into macrophages. It serves as an essential agent for growth and differentiation within the macrophage family of cells. CSF1 is also recognized for its therapeutic potential, given its role in tissue regeneration across various types of tissue injuries [24, 25]. In this study, after inducing MSCs with IL-1β cytokine for a duration of 24 hours, an increase in CSF1 mRNA expression was observed that varied according to the dose administered. This aligns with the discovery of Sonomoto et al., in which they noted an IL-1β-induced boost in the differentiation of MSCs into osteoblasts. Furthermore, IL-1β was found to elevate CSF1 expression while reducing the release of inflammatory substances from MSCs [26, 27].

Granulocyte-macrophage colony-stimulating factor (GM-CSF or CSF2) is called both a pro-inflammatory cytokine and a hematopoietic growth factor. It governs the creation, differentiation, and functioning of granulocytes and macrophages. The protein functions extracellularly as a homodimer. The CSF2 gene is instrumental in fostering tissue inflammation and elevating cytokine levels. It also facilitates the shift from pro-inflammatory M1 macrophages to the M2 phenotype, mitigating apoptosis and emission with reactive oxygen species typically produced by M1 macrophages [28]. Previous reports have indicated that IL-1β secretion from dendritic cells is significantly reliant on CSF2 [29, 30]. Moreover, it has been demonstrated that CSF2 is actively secreted by MSCs following various cellular traumas, which correlates with enhanced migration and differentiation abilities [31]. In the present investigation, MSCs preconditioned with IL-1β showed a dose-responsive augmentation in CSF2 mRNA expression, indicating a potentially beneficial effect on the functional capabilities of MSCs.

The C-C chemokine receptor type 2 (CCR2) functions as a G protein-coupled receptor specific to CCL2. These kinds of receptors are primarily found on monocytes/macrophages and play a pivotal role in guiding monocytes to sites of inflammation, thereby facilitating pro-inflammatory activities. In this study, MSCs pretreated with IL-1β exhibited an upregulation in CCR2 mRNA expression. CCR2-mediated signaling is essential for the release of monocytes from the bone marrow into circulation [32]. The observed elevation of CCR2 mRNA expression upon IL-1β treatment is suggestive of initiation of an inflammatory response, which typically involves the migration of monocytes to the affected region and the consequent release of growth factors. It was reported that CNS endothelial cells produce CSF2 in response to activation by IL-1β, which in turn transforms monocytes into antigen-presenting cells. Moreover, deficiencies in CCR2 and some of its ligands in animal models alter susceptibility to many experimental infections [33].

Chemokine C-X-C motif ligand-1 (CXCL1) acts as a potent chemoattractant for various immune cells, particularly directing the orchestrated migration and accumulation of neutrophils, as well as monocytes/macrophages, to specific sites requiring immune response or inflammation [34]. The present study assessed the gene expression of CXCL1 in MSCs following IL-1β treatment. Low doses of IL-1β reduced CXCL1 mRNA expression. However, higher doses returned CXCL1 mRNA expression to normal. The research noted that in human mesangial cells, initiating treatment with IL-1β before restimulation led to a decrease in the production of CXCL1 and CXCL2, which was regulated by the ubiquitin-editing enzyme known as A20 [35]. Additionally, starting treatments with IL-1α/β on various cell types spurred the creation of certain CXC chemokines and IL-8, along with other pro-inflammatory cytokines, including IL-1β itself [36]. The study at hand also observed that the intensities of IL-1β messenger RNA went up in a gradual manner when cells were induced with IL-1β beforehand. It suggests that to achieve a substantial increase in the production of these chemokines and cytokines within MSCs, higher doses of IL-1β might be necessary.

5. Conclusion

The study verifies the benefits of stimulating MSCs by the cytokine IL-1β. By exposing MSCs to IL-1β prior to their application, there was an upregulation in key chemokines and cytokines. This could potentially improve the MSCs' ability to differentiate and migrate to areas of injury, as well as boost their functional role within an inflamed microenvironment, thereby amplifying their healing properties.

Abbreviations

MSCs: human bone marrow mesenchymal stem cells, **hBM-MSCs:** human bone marrow mesenchymal stem cells, **IL-1β**: interleukin 1 beta, ***CSF:*** colony-stimulating factor*,* ***CCR:*** C-C chemokine receptor, ***CXCL:*** C-X-C chemokine receptor, **RT–PCR:** real-time polymerase chain reaction, H_2O_2: hydrogen peroxide, **DMEM**: Dulbecco's Modified Eagle Medium, **FBS**: fetal bovine serum, **US:** United States, **RTCA DP**: Real-time cell analysis dual purpose**, LFA:** lymphocyte function-associated antigen, **ICAM:** intercellular adhesion molecule, **HUVEC**: human umbilical cord-MSCs, **NF-κβ:** nuclear factor kappa light chain enhancer of activated B cells, **siRNA:** small interfering RNA

Conflict of interests
The author has no conflicts with any step of the article preparation.

Consent for publications.
The author read and approved the final manuscript for publication.

Ethics approval and consent to participate.
No human or animals were used in the present research.

Informed consent
The authors declare that no patients were used in this study.

Availability of data and material
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authors' contributions
Conceptualization, M.A., and M.AB.; methodology, M.A., O.A.R.., A.M., and M.E.; software, M.E., K.M.M., and A.E.S.; validation, M.A., K.M.M., O.A.R., and K.I.A.; formal analysis, K.M.M., M.E., and A.M.; investigation, M.A., M.E., A.M., and A.H.A.; resources, M.A.; data curation, M.A., A.H.A., K.I.A., and K.A.A.; writing—original draft preparation, M.A., O.A.R., K.M.M., and K.A.A; writing—review and editing, M.A., O.A.R., K.M.M., and K.A.A.; supervision, M.A.; project administration, M.A.; funding acquisition M.A. All authors have read and agreed to the published version of the manuscript.

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