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Expression of CD39 and CD73 Ectonucleotidases in Interferon-γ-treated Human Wharton's Jelly Mesenchymal Stem Cells

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ABSTRACT

Background: Mesenchymal stem cells (MSCs) exhibit substantial immunomodulatory properties. Interferon gamma (IFN-γ) exposure has been shown to enhance the immunoregulatory capacity of MSCs. This study aimed to evaluate the expression levels of ectonucleotidases CD39 and CD73, which generate adenosine, a potent immunosuppressant, in Wharton's Jelly-MSCs (WJ-MSCs) cultured in the presence or absence of IFN-γ.

Materials and Methods: MSCs isolated from human umbilical cord Wharton's jelly were cultured and propagated. Phenotypic characterization of the isolated cells was performed using flow cytometry to assess the expression of characteristic surface markers. The cultured MSCs were then treated with IFN-γ. After 24 hours of treatment, the expression levels of *CD39* and *CD73* genes were quantified in both IFN-γ-treated and untreated cells using real-time quantitative polymerase chain reaction.

Results: Exposure to IFN-γ resulted in a significant upregulation of *CD39* gene expression compared with untreated cells, while no statistically significant difference was observed in *CD73* expression between IFN-γ-treated and untreated groups.

Conclusion: The findings suggest that *CD39* upregulation may serve as a molecular integrator of inflammatory cytokine-mediated licensing of MSCs, contributing to their immunoregulatory capacity possibly through modulation of the expression of downstream target genes; however, further studies are required to indicate the inflammatory and immunosuppressive effects associated with *CD39* induction.

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Introduction

Mesenchymal stem cells (MSCs) are characterized by the ability to self-renew and to undergo multilineage differentiation [1, 2]. In addition, MSCs possess immunomodulatory functions mediated through both soluble and cell-bound factors, including interlukine-10 (IL-10), transforming growth factor-β1 (TGF-β1), prostaglandin E2, hepatocyte growth factor, indoleamine 2,3-dioxygenase (IDO), and programmed cell-death ligand 1 (PD-1) [3-6]. The therapeutic application of MSCs has gained considerable attention in the modulation of immune-mediated inflammatory conditions [7-9]. Recent evidence indicates that MSCs acquire immunomodulatory properties following exposure to inflammatory cytokines, such as interferon gamma (IFN-γ) alone or in combination with TNF-α, IL-1α, and IL-1β [10, 11]. IFN-γ, which is primarily produced by natural killer (NK) cells, CD4+(Th1) T cells, and CD8+ cells, is a key mediator of immune and inflammatory responses [12]. Considerably, MSC-mediated anti-proliferative effects are found to diminish in the absence of IFN-γ signaling, demonstrating the effect of IFN-γ licensing on MSC-mediated immunoregulation [13].

Numerous studies have established the importance of adenosine in immune regulation. During inflammation or tissue injury, extracellular adenosine levels are increased through the sequential enzymatic actions of CD39 and CD73 [14, 15]. CD39 (nucleoside triphosphate diphosphohydrolase [NTPDase-1]) hydrolyzes adenosine triphosphate (ATP) and adenosine diphosphate (ADP) to adenosine monophosphate (AMP) and CD73 (ecto-5-nucleotidase) converts AMP to adenosine. These ectonucleotidases shift an ATP-driven pro-inflammatory milieu to an adenosine-induced anti-inflammatory environment [16, 17]. The generation of adenosine by regulatory T cells (Tregs) and MSCs critically mediates the suppression of immune and inflammatory responses [18, 19]. Recent findings have found that these effects may be attributed to the downregulation of Th1 and Th17 cells, along with the upregulation of Th2 and regulatory T cells, thereby promoting a regulatory microenvironment [20, 21]. Ectonucleotidase-based regulation has been significantly implicated in tumor immune evasion [22]. With respect to humoral immunity, the germinal center B cells require adenosine signaling for the generation and maintenance of long-lived plasma cells [23]. This study examined whether IFN-γ modulates the expression of the ectonucleotidases CD39 and CD73 in Wharton's jelly-mesenchymal stem cells (WJ-MSCs). This investigation is based on the hypothesis that IFN-γ enhances the immunoregulatory capacity of MSCs.

Materials and Methods

Isolation and culture of WJ-MSCs

Umbilical cords (UCs) were collected from term deliveries and aseptically transferred to the laboratory for further processing. Then, umbilical cord-derived cells were isolated using a tissue culture method. In brief, UCs were rinsed in Hanks' balanced salt solution and cut into small pieces (approximately 2 cm) to remove blood vessels and isolate Wharton's jelly. The tissue was then minced into small fragments, and the resulting explants were transferred into 25-cm² culture flasks and cultured in low glucose dulbecco's modified eagle medium (DMEM) (Gibco, UK) containing 20% fetal bovine serum (Gibco, UK), 1% penicillin/streptomycin (Gibco, UK), and amphotericin B (Sigma, USA) at 37 ˚C under a 5% carbon dioxide (CO_2) atmosphere. The culture flasks were maintained in an incubator for 10 days to allow the migration of MSCs from the tissue explants. Subsequently, the tissue fragments were removed to promote the expansion of adherent cells. The culture medium was replaced every 3 to 4 days. When the cell density reached 75-80% confluence, the adherent cells were detached using 0.25% trypsin-ethylenediaminetetraacetic acid (EDTA) (Gibco, UK) and passaged into new flasks.

Flow cytometry analysis of wharton's jelly stem cells

To confirm the identity of the isolated MSCs, immunophenotyping analysis was performed to evaluate the expression of CD34, CD44, CD45, CD73, CD90, and CD105 surface markers. For this purpose, a cell suspension at a 1-2×10^6 cells/mL were prepared, followed by incubation with antibodies against the indicated surface markers according to the manufacturer's protocol. Similarly, isotype control antibodies were used to assess the background fluorescence. The cells were finally analyzed by FACSCalibur® flow cytometer (BD Biosciences, USA), and the data analysis was performed using FlowJo software.

RNA isolation and cDNA synthesis

The experimental groups consisted of WJ-MSCs (0.5×10^6 cells/mL) treated with IFN-γ (20 ng/mL) for 24 hours and untreated MSCs [24]. The IFN-γ dose was determined according to previously reported MSC immunomodulation studies [25, 26]. Previous studies have demonstrated that short-term exposure to the pro-inflammatory cytokine IFN-γ, as mimicked by 24-hour licensing, enhances the immunomodulatory capacity

of cultured human MSCs without inducing apoptosis [27]. Total ribonucleic acid (RNA) was extracted from IFN-γ-treated and untreated cells using the ONE STEP-RNA reagent (BIO BASIC) kit according to the manufacturer's procedures. The extracted RNA samples were treated with DNase I (Thermo Fisher Scientific, USA) to eliminate genomic DNA contamination and quantified using the 260/280 nm absorbance ratio, followed by confirmation of RNA integrity by agarose gel electrophoresis. The extracted RNA samples were then diluted for complementary DNA (cDNA) synthesis using a PrimeScriptTM RT Reagent Kit (Takara, Japan) according to the manufacturer's protocol. Each target gene was amplified in triplicate by polymerase chain reaction (PCR) in which the reaction mixture contained 0.5 µL of each forward and reverse primer (10 pmol), 10 µL of master mix, 2 µL of cDNA, and 7 µL of double-distilled water to a final volume of 20 µl under the following conditions: 10 minutes at 95 ˚C followed by 35 cycles of 95 ˚C for 30 seconds, an annealing temperature for 30 seconds, and a final extension for 5 minutes at 72 ˚C. The same program was applied for the amplification of glyceraldehyde-3-phosphate dehydrogenase (*GAPDH*) gene, except that the annealing temperature was changed. Then, PCR products were subsequently electrophoresed on a 1.5% agarose gel and visualized by a safe nucleic acid staining reagent.

Real-time quantitative PCR (qPCR)

The expression levels of *CD39* and *CD73* genes were quantified in both IFN-γ-treated and untreated samples using the SYBR Premix Ex TaqII kit (Takara, Japan) according to the manufacturer's procedures. The real-time PCR was carried out in a final reaction volume of 20 µL containing 10 µL of SYBER master mix, 0.5 µL of each forward and reverse primers, and 2 µL of template cDNA. The thermal cycling conditions consisted of 95 ˚C for 10 minutes, followed by 45 cycles of 95 ˚C for 10 seconds, annealing at the appropriate temperature for 30 seconds, and 72 ˚C for 20 seconds. The melting temperature cycle was performed from 55 ˚C to 95 ˚C to confirm the product specificity. All reactions were performed in duplicate for each gene using a Rotor-Gene 6000 Thermocycler (Qiagene, Netherlands). The threshold cycle (Ct) values were used to analyze gene expression levels via the $2^{-\Delta\Delta Ct}$ method. The *GAPDH* transcripts were used as the internal reference for normalization. A negative control was also analyzed under the same procedure. Table 1 presents the primer sequences used in this study.

Statistical analysis

Statistical analyses were performed using the GraphPad Prism software, version 5/04. The data were analyzed using Mann–Whitney test and presented as Mean±SD. A $P<0.05$ was considered statistically significant.

Results

Morphology and immunophenotype of WJ-MSCs

Following the planting of Wharton's jelly explants for 10 days, cell buds began to grow and fibroblast-like stromal cells appeared around the tissue fragments. After the removal of tissue pieces, the adherent cells were allowed to further expand and monitored during the culture period using an inverted microscope. The cells were passaged into several culture flasks when 80% confluence was achieved. Figure 1 shows representative images of MSCs derived from the primary culture of human umbilical cord Wharton's jelly. Flow cytometric analysis also showed the expression of surface markers CD44, CD90, CD105, and CD73 in WJ-MSCs, whereas hematopoietic specific markers, such as CD34 and CD45, were not significantly expressed in the cells (Figure 2) [28].

Real-time PCR(RT-PCR) results

IFN-γ-treated and untreated WJ-MSCs were compared regarding *CD39* and *CD73* gene expression. For this purpose, both the quantity and quality of the extracted RNA were assessed by the optical absorption measurement and agarose gel electrophoresis prior to cDNA synthesis. Specifically, RT-PCR was performed to amplify *GAPDH*, *CD39*, and *CD73* transcripts. All PCR amplicons were checked by gel electrophoresis to verify the expected product size and confirm the absence of non-specific amplification. In the gel electrophoresis analysis, distinct bands corresponding to 218 bp, 180 bp, and 105 bp were observed for the respective targets (Figure 3). After that, the synthesized cDNA was used for quantitative PCR (qPCR) to assess the relative expression of *CD39* and *CD73* genes in IFN-γ-treated and untreated cells, with *GAPDH* serving as the internal reference gene. The results demonstrated a significant upregulation of *CD39* in IFN-γ-treated cells compared to the untreated control group ($P\leq0.05$), whereas no statistically significant difference was observed in *CD73* expression between the two groups (Figure 4).

Table 1. Primer sequences used for RT-PCR and qPCR assays

Gene	Primer Sequence (5'-3')
CD39	F:AAGTGAAGAGTTGGCAGACAG R: GGGACTATGCTGAACCACC
CD73	F: TGTGGGAATCGTTGGATA R: TCTACTTCAGGTTGTAATGC
GAPDH	F: GAAGGTGAAGGTCGGAGT R: GAAGATGGTGATGGGATTTC

Discussion

Accumulating evidence indicates that MSCs exhibit low immunogenicity and possess significant immunomodulatory properties [29]. Advances in understanding the molecular mechanisms underlying immune regulation have further supported the effective application of MSCs in both experimental and clinical settings. This study examined the impact of the inflammatory cytokine IFN-γ on the expression levels of ectonucleotidases CD39 and CD73 in WJ-MSCs. Given the key role of adenosine signaling in the modulation of immune and inflammatory responses, IFN-γ–induced alterations in CD39 and CD73 expression may contribute to the effector mechanisms underlying MSC-mediated immunoregulation within an inflammatory microenvironment.

The immunomodulatory capacity of MSCs is well established to be acquired in response to signals from the surrounding microenvironment and immune cells. In this context, modulation of adenosine production mediated by the CD39/CD73 pathway at the MSC-T cell interface has been identified as a key mechanism underlying MSC-mediated anti-proliferative immune responses

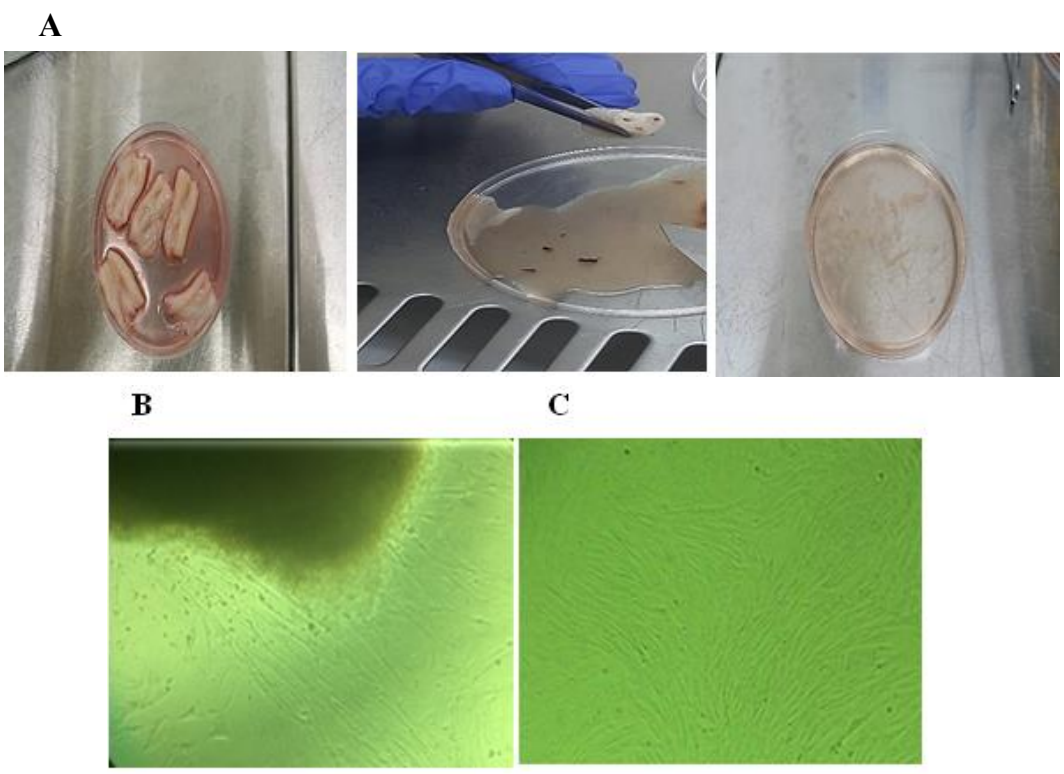

Figure 1. Human umbilical cord dissection and isolation of cells

Note: Minced human umbilical cord tissue was cultured to allow the migration and outgrowth of mesenchyme stem cells from Wharton's jelly. A: The Morphological characteristics of WJ-MSCs. B: Cell buds observed around Wharton's jelly tissue fragments after 10 days of primary culture (40×). C: After the cells were passaged, adherent fibroblast-like MSCs exhibited a high proliferative capacity and formed a confluent monolayer (40×).

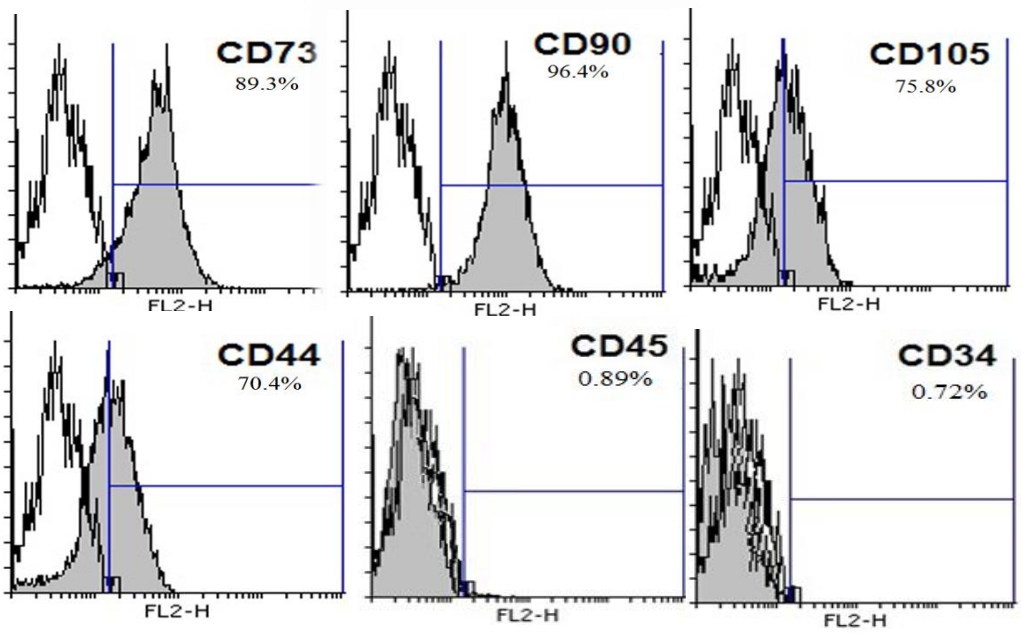

Figure 2. Immunophenotyping results of WJ-MSCs

Note: White-filed histogram and grey-filled histogram represent fluorescence intensity (log) of cells stained with isotype control and specific antibodies, respectively. Representative histograms illustrate that WJ-MSCs were positive for stem cell specific markers including CD44, CD105, CD73 and CD90, but they were negative for the expression of hematopoietic specific markers such as CD45 and CD34.

[15]. Recent studies have further demonstrated that the upregulation of CD73 on MSC co-cultured monocytes promotes their polarization toward an anti-inflammatory M2-like phenotype and amplifies the sustained immunomodulatory effects of MSCs [30]. Additionally, experimental evidence indicates that human bone marrow-derived MSCs significantly attenuate IL-17A/IFN-γ secretion in Th17 cells via up-regulation of CD39 expression [31]. Consistently, human gingival tissue-derived MSCs have been shown to suppress inflammatory responses and invasion behavior of rheumatoid fibroblast-like synoviocytes in a CD39/CD73-dependent manner [32]. The results obtained from the coculturing of naïve T cells with both cancer and normal adipose tissue-derived MSCs have demonstrated the induction of IL-10- and TGF-β-producing regulatory T cells (Tregs), as well as IL-17-producing Tregs, which exert enhanced immunosuppressive effects, are potentially attributable to the co-expression of CD73 and CD39 [33]. In line with these findings, a recent study has reported that tumor-infiltrating PD-1+T cells with elevated expression of CD39 and CD73 contribute to T cell dysfunction in synergy with tumor-derived immunosuppressive factors, particularly TGF-β [34]. Similarly, cervical cancer-derived MSCs expressing high levels of CD73 and CD39 ectonucleotidases have been shown to suppress cytotoxic T lymphocyte activity and promote the establishment of an immunosuppressive tumor microenvironment [35]. Moreover, CD39-dependent inhibition of inflammation mediated by hematopoietic stem cells has been reported to promote liver regeneration following hepatectomy [36].

Recent studies have suggested that the exposure of MSCs to IFN-γ enhances their immunomodulatory effects on immune cell responses, mediated in part through cellular interactions and adenosine production [37, 38]. However, evidence indicates that IFN-γ licensing may not fully restore the reduced immunosuppressive capacity of MSCs in mixed lymphocyte reactions, highlighting the context-dependent nature of MSC immunoregulation [39].

Our findings showed a significant upregulation of *CD39* gene expression in WJ-MSC following 24 hours of IFN-γ treatment compared to untreated control cells, while no statistically significant difference was observed in the expression levels of *CD73* gene between the two groups. In agreement with our results, Prasana et al. reported no alteration in *CD73* expression in bone marrow-derived MSCs and Wharton's jelly following treatment with IFN-γ or TNF-α [40]. The lack of CD73 modulation

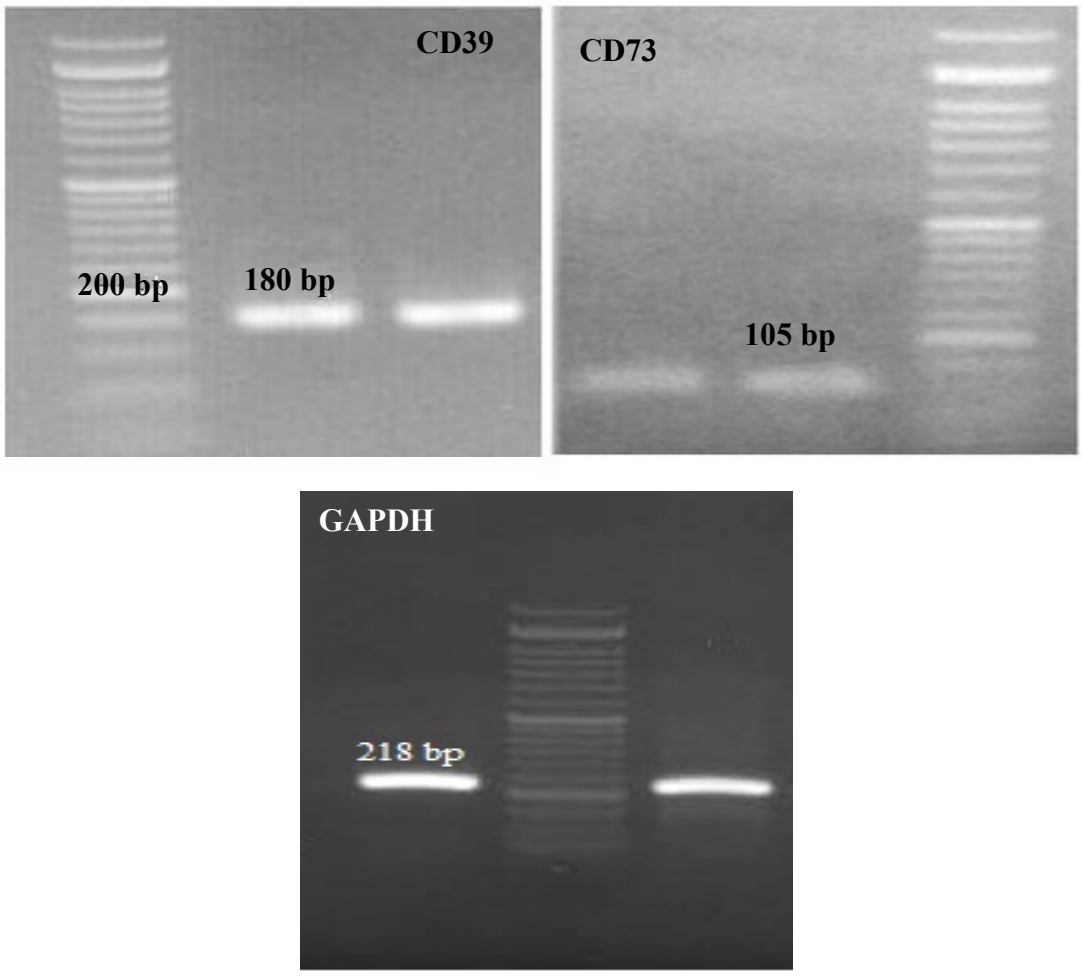

Figure 3. Gel electrophoresis of RT-PCR amplification products in WJ-MSCs

Note: PCR products amplified using gene-specific primers were run on 1.5% agarose gel. All amplicons were analyzed by gel electrophoresis to verify the expected product size and to confirm the absence of nonspecific amplification. Distinct bands corresponding to the target genes *CD39* and *CD73*, as well as the housekeeping gene *GAPDH*, were observed.

may be attributable to the low concentration of IFN-γ or the limited duration of cytokine exposure. Alternatively, IFN-γ alone may be insufficient to mimic the complex inflammatory milieu present in vivo that is required for CD73 expression. It is also possible that CD73 is not actively engaged in immune modulation under this experimental inflammatory condition, which needs to be investigated further. Notably, accumulating evidence highlights a critical role for CD73 in IFN-γ-mediated licensing of MSCs, particularly in the suppression of pro-inflammatory M1 macrophage polarization [13].

The observed upregulation of CD39 expression in the presence of IFN-γ is consistent with previous reports indicating that concomitant elevation of IFN-γ and adenosine in chronic inflammatory conditions can modulate the inflammatory phenotype of macrophages exposed to IFN-γ [41]. Supporting this notion, studies in CD39-null mice have suggested that augmented Th1/IFN-γ responses are associated with more severe tissue damage in inflammatory bowel disease [41]. Conversely, microglia exhibiting elevated CD39 expression have been shown to attenuate IFN-γ production and IDO induction, thereby mitigating quinolinic acid-mediated neuronal injury in diabetic patients [42]. In this context, a previous study reported unchanged CD39 expression alongside a significant upregulation of CD73 on the surface of NK cells following co-culture with human umbilical cord-derived MSCs, suggesting that these cells may require exposure to MSCs for the conversion of AMP to adenosine [43].

The present study was limited to evaluating the expression of *CD39* and *CD73* genes in MSCs in the presence of IFN-γ, a key cytokine present at the inflammation site. However, the effects of IFN-γ on the production

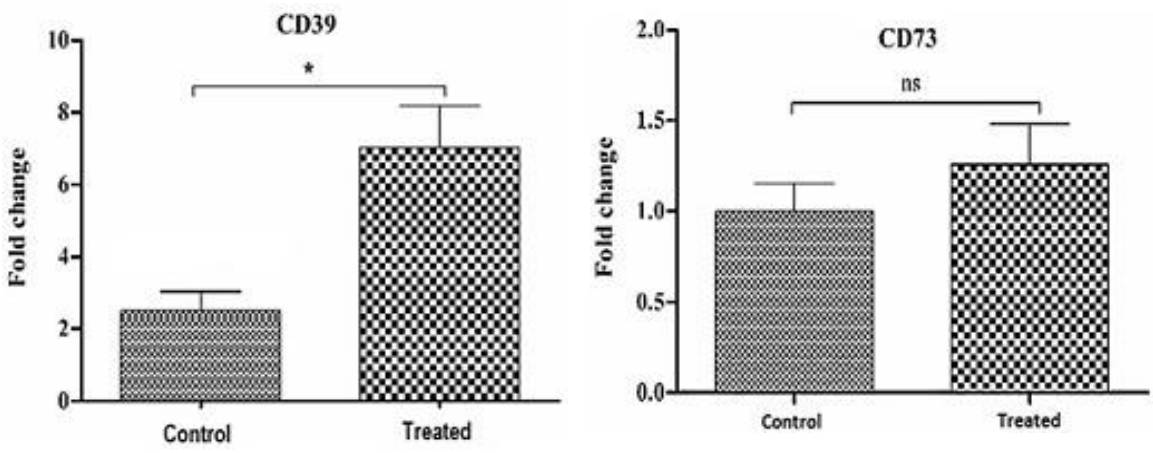

Figure 4. The expression level of *CD39* and *CD73* genes in untreated and IFN-γ-treated WJ-MSCs as determined by quantitative RT-PCR

Ns: Not significant.

*P≤0.05.

Note: Ct difference between the treated and control groups was calculated and normalized to the housekeeping gene *GAPDH*, and fold change expression of two different genes was determined using the $2^{-\Delta\Delta Ct}$ method. Data are presented as Mean±SD.

and functional activity of inhibitory mediators, including adenosine, remain to be elucidated and assessed particularly through quantitative measurement in culture supernatants. Furthermore, the contribution of CD39/CD73-mediated adenosine signaling to the immunoregulatory functions of MSCs, as well as the impact of MSC licensing by IFN-γ in combination with other inflammatory cytokines such as TNF-α, IL-1, and IL-17, should be investigated in the context of direct interactions with immune cells. Finally, determining the optimal dose and functional potency of cytokine-licensed MSCs in clinical settings remains an important area for future studies.

Conclusion

Given the inhibitory role of CD39 and CD73 ectonucleotidases in regulating various immune cells, the increased expression of CD39 in IFN-γ-treated WJ-MSCs may serve as a molecular indicator of MSC-mediated immunosuppressive capacity and a putative integrator of inflammatory cytokine licensing. Accordingly, further studies are needed to elucidate downstream targets of IFN-γ signaling and their functional consequences on the immunoregulatory activity of MSCs under diverse inflammatory conditions.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors contribution's

All authors equally contributed to preparing this article.

Conflict of interest

The authors declared no conflicts of interest.

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