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# EFFECTS OF TGF-B AND DIM ON THE SECRETION OF GROWTH FACTORS INTO THE CULTURE MEDIUM BY UMBILICAL CORD - DERIVED MESENCHYMAL STEM CELLS

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## ABSTRACT

*Purpose: Mesenchymal stem cells (MSCs) and their secretome have been demonstrated to play an important role in regenerative medicine. In particular, the secretome, which consists of soluble factors and extracellular vesicles, including microvesicles and exosomes, is emerging as a promising cell-free alternative to MSCs because it is considered safer than cells while retaining comparable efficacy. However, the composition of this secretome is highly sensitive and influenced by multiple factors, including the type and source of the secreting cells, their physiological state, and the stimulating factors during cell culture. This study evaluates the expression of several growth factors secreted into the conditioned medium by umbilical cord-derived MSCs (UCMSCs) under stimulation with TGF-β and 3,3'-diindolylmethane (DIM).*

*Subjects and methods: UCMSCs were cultured at passage 5 (P5) and primed with TGF-β, DIM, and a combination of TGF-β and DIM. Conditioned media were collected and analyzed for the levels of key growth factors, including fibroblast growth factor-2 (FGF-2), hepatocyte growth factor (HGF), platelet-derived growth factor-BB (PDGF-BB), and vascular endothelial growth factor-A (VEGF-A), using Luminex assays.*

*Results: Results showed that FGF-2 and HGF expression remained consistent across all groups, with no significant differences, except that the HGF level in the TGF-β and DIM-primed group is greater than that in the from TGF-β-primed group. In contrast, TGF-β significantly increased the secretion of PDGF-BB and VEGF-A by USMCS compared with the control group ($p < 0.05$), highlighting its strong modulatory effect. DIM did not significantly alter growth factor levels. Additionally, the combination of TGF-β and DIM did not produce synergistic effects and even attenuated PDGF-BB secretion compared with TGF-β.*

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***Conclusion:*** *These findings demonstrate that TGF-β is a potent regulator of UCMSC secretome, enhancing the release of growth factors associated with tissue regeneration and angiogenesis, whereas DIM alone exerts minimal influence. Additionally, the absence of synergistic effects between TGF-β and DIM suggests a complex interplay between cellular signaling pathways. This study underscores the potential of TGF-β preconditioning as a strategy to optimize UCMSC secretome for regenerative medicine applications.*

***Keywords:*** *Umbilical cord-derived mesenchymal stem cells (UCMSCs), secretome, conditioned medium, stimulation, TGF-β, 3,3'-diindolylmethane (DIM), growth factors.*

## 1. BACKGROUND

Cell therapy, particularly mesenchymal stem cells (MSCs), is emerging as a potential, safe, and effective approach in regenerative medicine [1, 2]. The therapeutic effects of MSCs are not only attributed to their ability to differentiate into target functional cells but also to biologically active components in their secretome, such as epidermal growth factor (EGF), fibroblast growth factor (FGF), insulin-like growth factor (IGF), platelet-derived growth factor (PDGF), transforming growth factor beta (TGF-β), and vascular endothelial growth factor (VEGF) [3]. These components have been shown to promote wound healing, angiogenesis, and anti-inflammatory responses, and they may even substitute for MSCs in clinical applications [3, 4].

Among MSC sources, umbilical cord-derived mesenchymal stem cells (UC-MSCs) have attracted greater attention due to their superior biological properties and minimal ethical concerns [1, 5]. The secretome of UC-MSCs contains soluble proteins, cytokines, chemokines, and extracellular vesicles (EVs) such as exosomes and microvesicles [6]. Evidence suggests that this secretome promotes wound healing by enhancing fibroblast and keratinocyte proliferation, stimulating angiogenesis, and exhibiting anti-inflammatory and antioxidant activities [5]. Under inflammatory conditions, UC-MSC-derived secretome can regulate immune cell activity, reduce pro-inflammatory cytokines, and promote the synthesis of anti-inflammatory factors [1, 7]. Several preclinical studies have demonstrated that UC-MSC-derived secretome shows potential in treating acute lung injury, respiratory inflammation, and neurodegenerative diseases through anti-inflammatory and tissue regeneration mechanisms [2, 8-10]. Notably, clinical trials have reported the efficacy of UC-MSC-derived secretome in treating osteoarthritis, with significant pain reduction, improved functional indices, and modulation of biomarkers such as MMP-3 and TGF-β1, without severe adverse effects [4]. Collectively, these findings indicate that UC-MSC-derived secretome represents a promising cell-free therapy for regenerative and immunomodulatory applications.

However, the MSC secretome is highly variable depending on the cell source and culture conditions, such as low physiological oxygen levels, cytokine stimulation, or exposure to bioactive compounds. One study showed that hypoxic conditions increased VEGF secretion from UC-MSCs, highlighting the feasibility of modulating secretome composition and concentration through

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external factors [11]. Stimulation of UC-MSCs with TGF-β enhanced fibroblast migration and extracellular matrix protein production (particularly elastin) via exosomal signaling [3, 12]. Moreover, TGF-β signaling regulates MSC proliferation through the FAK-Akt-mTOR pathway, suggesting that exposure to TGF-β may induce broader functional changes that affect secretome composition [13]. Similarly, activation of UC-MSCs with 3,3′-diindolylmethane (DIM), a dietary indole compound, increased the release of exosomes containing Wnt11 and activated an autocrine β-catenin signaling loop, thereby improving wound healing efficacy *in vivo* [14]. In UC-MSCs, DIM stimulation also enhanced the secretion of several paracrine mediators, including GM-CSF, IL-6, MCP-1, and VEGF, demonstrating the potential of using small molecules to control MSC secretome activity [14].

Although previous studies have examined the effects of TGF-β and DIM individually in stimulating MSC secretion with promising outcomes [3, 14], no direct comparison has been made regarding their effects on the secretome expression of UC-MSCs. Furthermore, no study has evaluated the combined influence of these two factors on MSC-derived secretome. Therefore, we conducted this study to assess the effects of TGF-β1, DIM, and their combination on the expression of selected growth factors in the conditioned medium of UC-MSC cultures.

## 2. MATERIALS AND METHODS

### 2.1. Study location

This study was conducted at the Vinmec-VinUni Institute of Immunology and Vinmec High-Tech Center.

**** Umbilical cord-derived mesenchymal stem cell (UC-MSC) cultures***

UC-MSCs at passage 3 (P3) were provided by the Extracellular Vesicle (EV) group of the Vinmec-VinUni Institute of Immunology. The cells were thawed and seeded at a density of 5,000 cells/cm² in the culture flasks. The cells (P4) were maintained in DMEM/F12 medium (Gibco, USA) supplemented with 5% PLT (Mill Creek, USA). The culture flasks were incubated at $37^0$C with 5% $CO_2$. When cell confluence reached approximately 80%, subculturing was performed.

**** UC-MSC subculture procedures***

The supernatant was removed, and the cells were washed with PBS. After discarding PBS, CTS™ TrypLE™ enzyme (Thermo Fisher Scientific, USA) was added to the culture flask (2 mL per T75 flask) and incubated at 37°C for 3 minutes. The flask was gently tapped to detach the cells from the surface, and the enzyme was neutralized with an equal volume of culture medium. The cell suspension was centrifuged at 400 × g for 4 minutes at $20^0$C to remove residual enzyme. The cell pellet was resuspended in 3 mL of culture medium.

A 10 µL aliquot of the cell suspension was mixed with 10 µL Trypan Blue, and viable cells were counted using a hemocytometer. Cells were reseeded at a density of 5,000 cells/cm² in prepared culture flasks and maintained at $37^0$C, 5% $CO_2$.

At the fifth passage (P5), UC-MSCs were harvested for surface marker analysis and collection of conditioned medium to evaluate the growth factors secreted into the culture medium.

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### 2.2. Surface marker analysis of UC-MSCs

The surface markers of UC-MSCs at P5 were analyzed by flow cytometry using the Human MSC Analysis Kit (BD Biosciences, USA). Cells were stained with positive antibodies (anti-CD73 APC, anti-CD90 PerCP-Cy5.5, anti-CD105 FITC) and negative antibodies (anti-CD45 PE, anti-CD34 PE, anti-CD11b/CD19 PE, and HLA-DR PE). Data were acquired and analyzed using a Beckman Coulter flow cytometer integrated with Navios software version 3.2.

### 2.3. Total protein quantification using the BCA assay

The conditioned medium was thawed and kept at $4^0$C for total protein quantification using the Pierce BCA Protein Assay Kit (Thermo Fisher Scientific, USA). Nine wells were prepared for the nine standard concentration points, and additional wells were used for the test samples. A volume of 25 µL of each sample (thawed) or standard solution was pipetted into designated wells, followed by the addition of 200 µL of Working Reagent to each well. The plate was shaken for 30 seconds, covered, and incubated at $37^0$C for 30 minutes. After cooling to room temperature, absorbance was measured at 562 nm using a Glomax spectrophotometer (Promega, USA). Based on the absorbance values and known standard concentrations, a standard curve ($y = ax + b$) was generated to determine protein concentration.

### 2.4. Growth factor analysis using Luminex technique

Growth factor concentrations in the UC-MSC conditioned medium were analyzed using the Luminex multiplex immunoassay technique, specifically the ProcartaPlex™ 4-Plex Assay Kit (Thermo Fisher, USA). The analyzed growth factors included FGF-2, HGF, PDGF-BB, and VEGF-A.

Magnetic beads coated with specific antibodies for each growth factor were added to the wells and captured at the bottom using a magnetic plate. Subsequently, the conditioned medium samples were added and incubated for two hours before washing to remove unbound components. The procedure was performed according to the manufacturer's protocol. Fluorescent signals were detected and quantified using the Luminex™ 100/200™ system integrated with xPONENT 3.1 software.

### 2.5. Statistical analysis

All data were expressed as mean ± standard deviation (SD) from at least three biological replicates and presented in tables and graphs. Statistical analyses and figure plotting were performed using GraphPad Prism 10 (GraphPad Software, California, USA). One-way ANOVA was used to compare differences among groups, and $p < 0.05$ was considered statistically significant.

## 3. RESULTS

### * Characteristics of UC - MSCs

UC-MSCs were cultured to passage 5 (P5) and characterized based on their morphology and surface marker expression. The results showed that P5 UC-MSCs exhibited a fibroblast-like and spindle-shaped morphology (Figure 1A). Flow cytometry analysis of surface markers revealed that positive markers (CD73, CD90, and CD105) were expressed at levels exceeding 95%, while negative markers (CD45, CD34, CD11b/CD19 PE, and HLA-DR) were expressed below 2% (Figure 1B). These results are consistent with the typical characteristics of UC-MSCs provided by the EV group and align with previously published findings [15].

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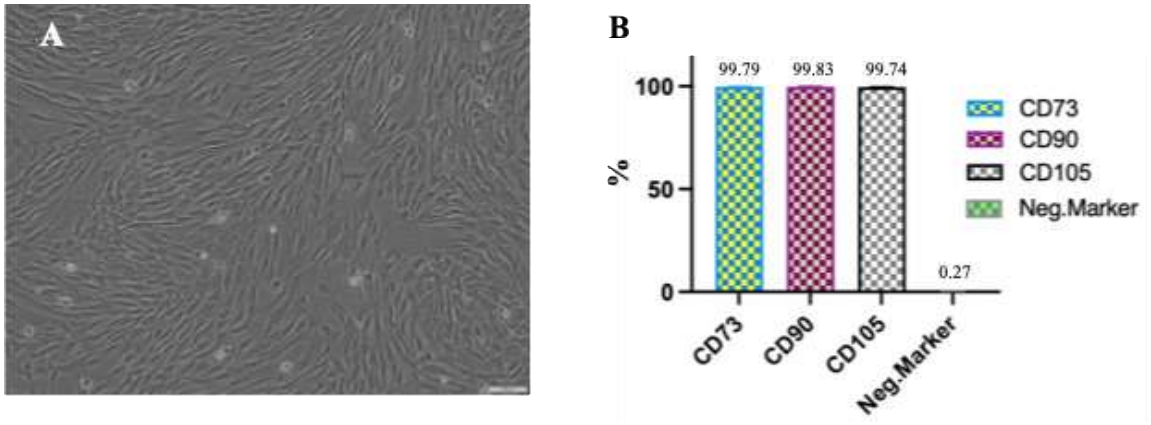


**Figure 1: Morphological and immunophenotype characterization of UC-MSCs at passage 5 (P5). (A) Morphology of UC-MSCs. (B) Surface marker expression of UC-MSCs**

### ** Characteristics of conditioned media from UC-MSC cultures*

Conditioned media (supernatant) were collected when UC-MSCs (P5) reached approximately 80% confluence to access total protein concentration assessment prior to growth factor analysis. The results describing factors that affect the conditioned medium composition are summarized in Table 1. The total cell count at the time of conditioned medium collection ranged from 30.67 ± 0.30 × $10^6$ cells (lowest in the TGF-β + DIM group) to 33.47 ± 2.15 × $10^6$ cells (highest in the TGF-β group), with approximately 120 mL of conditioned medium collected per group. The total protein concentration was comparable across groups, ranging from 2606.81 ± 335.21 µg/mL to 2941.29 ± 146.62 µg/mL.

**Table 3.1. Cell counts and total protein concentration in conditioned media from UC-MSC cultures**

| Groups | Cell count (x $10^6$) (Mean ± SD) | Volume of conditioned medium (mL) | Total protein concentration (µg/mL) (Mean ± SD) |
|---|---|---|---|
| Control | 32.27 ± 2.12 | 120 | 2606.81 ± 335.21 |
| TGF-β | 33.47 ± 2.15 | 120 | 2941.29 ± 146.62 |
| DIM | 33.13 ± 2.82 | 120 | 2655.59 ± 354.50 |
| TGF-β + DIM | 30.67 ± 0.30 | 120 | 2665.87 ± 434.45 |

*Notes: TGF-β: Culture medium supplemented with TGF-β; DIM: Culture medium supplemented with DIM; TGF-β + DIM: Culture medium supplemented with both TGF-β and DIM; Mean (TB); SD: Standard deviation.*

### ** Expression levels of FGF-2 in UC-MSC conditioned medium*

Analysis of FGF-2 levels in conditioned media from UC-MSCs (P5) revealed that the TGF-β + DIM group (73.22 ± 7.92 pg/mL) was significantly higher compared to the TGF-β group (43.36 ± 20.47 pg/mL, $p < 0.05$) (Figure 2). There was not a statistically significant difference observed among the

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control (59.77 ± 15.53 pg/mL) and DIM (59.17 ± 11.48 pg/mL) groups. This suggests that the combination of TGF-β and DIM may stimulate UC-MSCs to secrete more FGF-2. However, FGF-2 concentrations across all experimental groups remained relatively low compared with those of HGF, PDGF-BB, and VEGF-A (Figures 3-5).

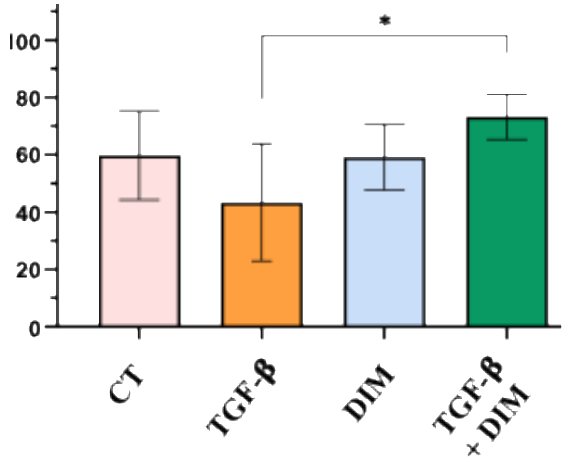


**Figure 2: Expression levels of FGF-2 in conditioned media from UC-MSC (P5) cultures**

CT: Control group; TGF-β: culture medium supplemented with TGF-β; DIM: culture medium supplemented with DIM; TGF-β + DIM: culture medium supplemented with both TGF-β and DIM; *: $p < 0.05$.

### * Stimulatory factors do not alter HGF levels in conditioned medium from UC-MSC cultures

Analysis of HGF levels in conditioned media from UC-MSCs (P5) revealed no statistically significant differences among the experimental groups (Figure 3). Specifically, HGF concentrations were 898.1 ± 107.02 pg/mL in the control group, 1180.00 ± 220.9 pg/mL in the TGF-β group, 1009.7 ± 296.1 pg/mL in the DIM group, and 1136.4 ± 239.9 pg/mL in the TGF-β + DIM group. These results suggest that the exogenous factors tested in this study did not significantly influence HGF secretion by UC-MSCs.

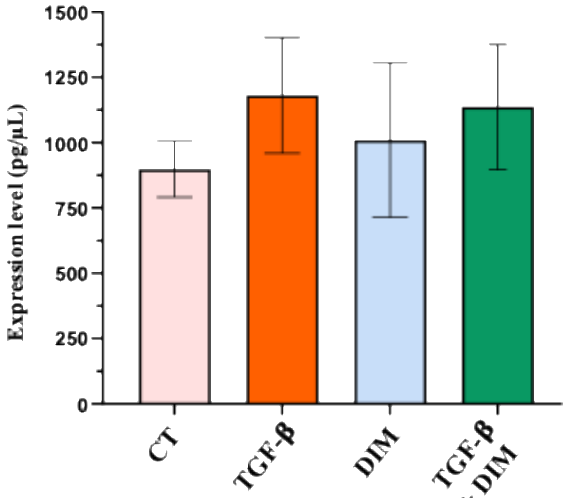


**Figure 3: Expression levels of HGF in conditioned media from UC-MSC (P5) cultures**

CT: Control group; TGF-β: culture medium supplemented with TGF-β; DIM: culture medium supplemented with DIM; TGF-β + DIM: culture medium supplemented with both TGF-β and DIM.

### * Expression levels of PDGF-BB Growth Factor in conditioned medium from UC-MSC cultures

For PDGF-BB, the highest concentration was observed in the conditioned medium of UC-MSCs stimulated with TGF-β (484.0 ± 60.08 pg/mL), significantly higher than in the control (244.7 ± 115.49 pg/mL, $p < 0.05$) and TGF-β + DIM (354.2 ± 97.4 pg/mL, $p < 0.01$). There was no statistically significant difference between the group primed with DIM (230.5 ± 88.4 pg/mL) and other groups. These results indicate that TGF-β effectively stimulates UC-MSCs to secrete PDGF-BB, while DIM alone does not have this stimulatory effect.

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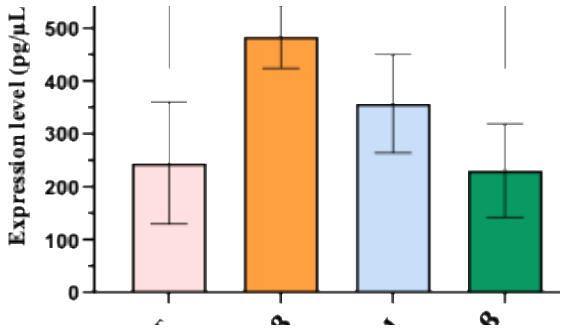


**Figure 4: Expression levels of PDGF-BB in conditioned media from UC-MSC (P5) cultures**

CT: Control group; TGF-β: culture medium supplemented with TGF-β; DIM: culture medium supplemented with DIM; TGF-β + DIM: culture medium supplemented with both TGF-β and DIM; *: $p < 0.05$, ***: $p < 0.001$.

### ** Exhibits the highest expression of VEGF-A in TGF-β-stimulated UC-MSCs*

Among the four analyzed growth factors, VEGF-A showed the highest expression level in the conditioned medium from the TGF-β group (651.44 ± 212.38 pg/mL, $p < 0.01$). No significant differences were observed among the other three groups: control (235.73 ± 24.49 pg/mL), DIM (283.08 ± 99.89 pg/mL), and TGF-β + DIM (242.81 ± 46.57 pg/mL). These findings suggest that TGF-β plays a prominent role in stimulating UC-MSCs to secrete growth factors, particularly VEGF-A.

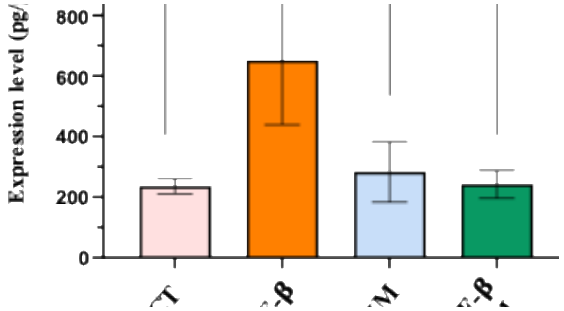


**Figure 5: Expression of VEGF-A in conditioned media from UC-MSC (P5) cultures**

CT: Control group; TGF-β: culture medium supplemented with TGF-β; DIM: culture medium supplemented with DIM; TGF-β + DIM: culture medium supplemented with both TGF-β and DIM; ***: $p < 0.001$, ****: $p < 0.0001$.

## 4. DISCUSSION

In this study, we collected conditioned medium (supernatant) from UC-MSCs at passage 5 (P5) to evaluate the levels of growth factors secreted during the cell culture. The results demonstrated that all UC-MSCs cultured in standard conditions exhibited the typical morphological and immunophenotypic characteristics of conventional MSCs. We then assessed the effects of TGF-β, DIM, and their combination on the secretion of selected growth factors by UC-MSCs at P5. The findings revealed different responses of individual growth factors to specific stimuli, reflecting the sensitivity of UC-MSCs to exogenous modulation.

Specifically, there was no significant difference in FGF-2 levels among experimental groups; however, its concentration was the lowest among the four analyzed growth factors (HGF, PDGF-BB, and VEGF-A). This finding is consistent with previous reports indicating that FGF-2 is typically maintained at baseline levels to support the fundamental growth capacity of stem cells [16]. Similarly, HGF levels showed no significant variation among stimulation groups, but its overall concentration was the highest compared with FGF-2, PDGF-BB, and VEGF-A. This suggests that HGF expression is relatively stable and less influenced by TGF-β or DIM. HGF plays a crucial role in tissue regeneration and antifibrotic activity; therefore, its elevated secretion compared to other factors implies a beneficial modulation of the UC-MSC secretome toward tissue repair and recovery [17, 18].

In contrast, PDGF-BB and VEGF-A were most highly expressed in the TGF-β-stimulated group, indicating that TGF-β strongly enhances the secretion of these

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angiogenic and tissue remodeling factors. On the other hand, DIM alone did not induce significant changes, although previous studies have shown that DIM can modulate exosome biogenesis and activate β-catenin signaling [14]. This discrepancy may be attributed to differences in MSC origin, culture conditions, exposure time, or specific factors being evaluated. For example, DIM has been reported to enhance the stemness of UC-MSCs and upregulate Wnt11 expression in their secreted exosomes [14]. Notably, the combined treatment of TGF-β and DIM did not produce synergistic effects; instead, it reduced PDGF-BB expression compared with TGF-β alone, suggesting complex interactions between the signaling pathways involved.

Overall, the results demonstrate that TGF-β effectively stimulates the upregulation of HGF, PDGF-BB, and VEGF-A, whereas DIM exerts no clear effect, and their combination does not yield a synergistic outcome. These findings are consistent with our previous study on the influence of cytokines and TGF-β on the expression of growth factors in MSC-derived exosomes [3]. This highlights the potential application of TGF-β as a regulatory agent for modulating UC-MSC secretome composition to optimize its therapeutic efficacy in regenerative medicine. In contrast, DIM has been reported to inhibit cell proliferation, induce apoptosis, and suppress cancer cell growth in both preclinical and clinical studies [19]. The mechanisms of DIM are primarily associated with modulation of NF-κB, Akt, Wnt, and PI3K/Akt/mTOR signaling pathways, which are known to regulate cell growth and survival [20]. This may explain why DIM did not enhance the secretion of growth factors analyzed in this study.

Despite the promising results, this study has several limitations, including (1) it focused only on a limited selection of growth factors, whereas the MSC secretome contains numerous cytokines, chemokines, and extracellular vesicles with diverse biological activities; (2) experiments were performed in vitro, which may not fully reflect the complex in vivo microenvironment; and (3) the relatively small sample size may have limited the ability to account for biological variability among MSC preparations.

## 5. CONCLUSION

This study demonstrates that TGF-β is more effective than DIM in stimulating umbilical cord-derived mesenchymal stem cells (UC-MSCs) to secrete growth factors, including HGF, PDGF-BB, and VEGF-A, into the culture medium. This indicates the potential of using TGF-β and DIM to modulating the components of UC-MSC's secretome. Although promising results were obtained, further research is required to provide a more comprehensive analysis about the effects of stimulating factors on the UC-MSC secretome, including the profiling of the entire protein and genetic material components, as well as investigations into the underlying mechanisms. Additionally, examining the influence of dosage, exposure duration, and sequential application of stimulatory agents may help optimize the stimulation protocol for improved outcomes.

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