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Hypoxic MSCs Secretome Modulates IL-18-Mediated Inflammatory in Type 2 Diabetes Mellitus via AP-1 Regulation

Fajar Amansyah[1], Iffan Alif [2]*, Risky Chandra Satria Irawan[3]

*Correspondence: iffanalif@gmail.com

[1]Department of Postgraduate Medical Science, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia

[2]Department Biotechnology, Institut Karya Mulia Bangsa, Semarang, Indonesia

[3]Department Biomedical Science, Institut Karya Mulia Bangsa, Semarang, Indonesia

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ABSTRACT

Background : Chronic inflammation is central to the pathophysiology of Type 2 Diabetes Mellitus (T2DM), contributing to the progression of metabolic dysfunction characterized by hyperglycaemia and insulin resistance. This study aims to investigate the therapeutic potential of the hypoxic MSCs secretome (SH-MSCs) in reducing inflammation of a T2DM rat model. **Methods:** T2DM was induced in Wistar rats through a high-fat diet (HFD) followed by streptozotocin (STZ) administration. A total of 24 healthy male Wistar rats were randomly assigned to five groups: healthy control, T2DM, T2DM + metformin, T2DM + SH-MSCs. **Results:** SH-MSCs significantly reduced IL-18 mRNA expression, a key indicator of proinflammation, and suppressed the expression of AP-1 mRNA, a crucial proinflammatory transcription factor. **Conclusion:** These findings highlight the therapeutic potential of SH-MSCs as an alternative approach to alleviate inflammation in T2DM.

Keywords : AP-1, Hypoxic MSCs, IL-18, Secretome, T2DM.

INTRODUCTION

Diabetes Mellitus type 2 (T2DM) is a chronic metabolic disorder characterized by hyperglycaemia caused by insulin resistance and pancreatic β cells dysfunction.[1] Various lifestyle factors, including poor dietary habits, lack of physical activity, alcohol consumption, and smoking have been implicated in the development insulin resistance. An imbalance between energy intake and expenditure leads to increased adipose tissue, resulting in obesity and visceral fat accumulation.[2] The accumulation of visceral fat induces adipose tissue hypertrophy, hypoxia in the endoplasmic reticulum of cells, adipocyte death and infiltration of pro-inflammatory type 1 macrophages (M1).[3] Persistent exposure to these condition triggers the release of proinflammatory cytokines from M1 such as interleukin (IL)-6, IL-12, IL-18 and TNFα which will eventually result in local and systemic inflammation that will interfere with insulin signalling.[4]

The presence of chronic inflammation triggered by the release of cytokines from M1 can result in insulin resistance and damage to pancreatic β cells. Visceral obesity perpetuates continuous destruction of adipose tissue where this condition causes M1 to be present in the body while limiting the production of anti-inflammatory type 2 macrophages (M2), which play a key role in mitigating

inflammation.[5] Regulation of M1 and M2 macrophage polarization is influenced by Activator Protein-1 (AP-1), which is an important transcription factor in controlling gene expression related to inflammation, oxidative stress, and immune system activation.[6] AP-1 consists of a complex of c-Jun, c-Fos, ATF, and MAF proteins, which are activated through the MAPK pathway (JNK, ERK, p38 MAPK) in response to lipopolysaccharide (LPS), hypoxia, and metabolic stress that occurs in obese adipose tissue.[6,7]

In T2DM, AP-1 plays a role in increasing IL-18 production by M1 macrophages.[8] IL-18 enhances the AP-1 response through MAPK pathway[9], leading to increased production of pro-inflammatory cytokines, such as IL-6, IL-8, and TNF- α that recruits more leukocytes to tissues that have experienced metabolic dysfunction, which then promotes M1 infiltration into adipose tissue and worsens inflammation.[4] In addition, AP-1 also interacts with NF-κB, which further enhances the expression of pro-inflammatory cytokines and worsens insulin resistance.[7] Therefore, chronic inflammation triggered by AP-1 and IL-18 causes a disruption in the balance between M1 (pro-inflammatory) and M2 (anti-inflammatory) macrophages, so that the inflammatory condition continues and inhibits the mechanism of pancreatic tissue repair and the insulin signalling pathway[9,10]. Prolonged visceral obesity causes continuous destruction of adipose tissue, resulting in M1 dominance in the tissue and decreased production of M2, which should play a role in reducing inflammation.[2] Therefore, targeting the AP-1 and IL-18 pathways may be a potential therapeutic strategy to reduce inflammation and improve insulin sensitivity in T2DM patients.

Cell-based therapy offers a new paradigm in the management of T2DM by creating a cell source that functions as both an immunosuppressor and immunomodulator, enhancing immune function, reducing inflammation, and improving pancreatic β-cell function.[11] Mesenchymal stem cells (MSCs) cultured in liquid media under hypoxic conditions can increase the secretion of various soluble molecules or secretomes containing anti-inflammatory cytokines such as IL-10 and regenerative growth factors such as TGF β, PDGF, and VEGF.[12] Tangential flow filtration technology makes it possible to isolate the hypoxic MSCs secretome (SH-MSCs) containing anti-inflammatory cytokines and regenerative growth factors.[13] The SH-MSCs can be an active molecule that can be stable at a temperature of 2-8ºC for a long time.[14] This causes the SH-MSCs to have several advantages compared to stem cells, where the use of hypoxic MSCs therapy based on biologically active factors secreted by stem cells and progenitor cells can significantly reduce the risks associated with direct MSCs injection.[15] In addition, proteomic analysis of the SH-MSCs showed an increase in various biologically active molecules such as anti-inflammatory cytokines, mRNA and growth factors that play an important role in tissue regeneration.[16]

Study on the potential application of SH-MSCs in improving inflammation through AP-1 and IL-18 regulation in T2DM is still inadequate. Therefore, this study aims to investigate the role of the SH-MSCs in reducing inflammation, as indicated by the decreased expression of AP-1 and IL-18 in a T2DM rat model.

MATERIAL AND METHODS

Research Design and Ethical Clearance

This post-test-only experimental study was carried out at the Stem Cell and Cancer Research (SCCR) Laboratory, located in Semarang, Central Java, Indonesia, between January and February 2025. The study used Wistar rats (*Rattus norvegicus*) weighing 150–200 g as an animal model for T2DM. All

procedures involving animals adhered to the ethical standards and guidelines established by the I Institutional Research Bioethics of Universitas Islam Sultan Agung, under approval number 16/I/2025/Komisi Bioetik.

Preparation, phenotyping, and differentiation analysis of MSCs

Mesenchymal stem cells (MSCs) were isolated following established protocols.[13] The cells were cultured in Dulbecco's Modified Eagle Medium (DMEM; Gibco, NY, USA) supplemented with 10% fetal bovine serum (FBS; Gibco), 1.5% penicillin/streptomycin (Gibco), and 0.25% amphotericin B (Gibco) at 37°C under 5% CO_2 conditions. The culture medium was replaced every three days. UC-MSCs at passage 5 were used for all subsequent experiments. Flow cytometry analysis was conducted to characterize surface markers on UC-MSCs at passage 5. Cells were stained with rat anti-CD90-FITC, CD29-PE, CD31-perCP, and CD45-APC antibodies (BD Bioscience, CA, USA). Analysis was performed using a BD Accuri C6 Plus flow cytometer and accompanying software (BD Bioscience). Adipogenic and osteogenic differentiation potential of UC-MSCs at passage 5 was assessed using standard differentiation media under conditions of 37°C and 5% CO_2. Adipogenic and osteogenic differentiation basal media (MesenCult™; Stem Cell Technologies, Singapore) were supplemented with specific differentiation supplements (Stem Cell Technologies), 1% L-glutamine (Gibco), 1% penicillin (Gibco), and 0.25% amphotericin B (Gibco). Media changes were performed every three days. After 21 days of differentiation, lipid deposits were visualized using Oil Red O staining, while calcium deposits were identified using Alizarin Red staining (Sigma-Aldrich, MO, USA).

Induction of Hypoxic Environment for MSCs

To simulate hypoxic conditions, UC-MSCs at approximately 80% confluence were transferred to a hypoxia chamber (Stem Cell Technologies). The chamber's oxygen concentration was maintained at 5% using an oxygen controller (BioSpherix, Lacona, NY, USA), which continuously monitored the partial oxygen pressure (pO_2). The cells were incubated under these conditions for 18 hours at 37°C with 5% CO_2. After the incubation period, the culture medium was collected for subsequent analyses.

SH-MSCs preparation

The conditioned medium (CM) from hypoxia MSCs was collected and centrifuged at 13,000 × g for 10 minutes at 4°C to eliminate cellular debris. The isolation of the SH-MSCs was conducted using a tangential flow filtration (TFF) system (Formulatrix, MA, USA), following the methodology established in our previous study. The fractionation process utilized molecular weight cut-off (MWCO) filter cassettes ranging from 10–100 kDa, effectively enriching bioactive molecules within the SH-MSCs fraction. The purified SH-MSCs were stored at −80°C for subsequent analyses, including enzyme-linked immunosorbent assays (ELISA), and were used in downstream experimental procedures.

SH-MSCs profilling

The cytokine and growth factor profiles of SH-MSCs were analyzed using enzyme-linked immunosorbent assays (ELISAs) following the manufacturer's instructions (Invitrogen, CA, USA). The concentrations of vascular endothelial growth factor (VEGF), interleukin 10 (IL-10), and stromal cell-derived factor-1 (SDF-1) were measured at room temperature. Absorbance was recorded at 450 nm using a microplate reader (Bio-Rad, CA, USA), and the obtained data were processed to characterize the secretory profile of SH-MSCs.

Generation of T2DM animal model

Following the acclimatization period, the healthy rats was maintained on a standard pellet diet, while the experimental groups were fed a high-fat diet (HFD) for eight weeks to induce metabolic disturbances. The composition of the HFD included 50% ground standard pellet, 25% wheat flour, 10% mutton fat, 5% egg yolk, 1% coconut oil, and 10% sodium chloride (NaCl). Body weight measurements were recorded weekly to monitor metabolic changes. To induce type 2 diabetes mellitus (T2DM), nicotinamide (120 mg/kg body weight; Sigma-Aldrich, MO, USA) was administered intraperitoneally, followed by streptozotocin (STZ) (60 mg/kg body weight; Santa Cruz Biotechnology, TX, USA) after a 15-minute interval. The STZ solution was freshly prepared and utilized within five minutes to ensure stability. Healthy rats received intraperitoneal injections of phosphate-buffered saline (PBS, Elabscience, USA) and 0.05 M sodium citrate buffer (pH 4.5) as vehicle controls in place of nicotinamide and STZ.

After seven days post-STZ administration, all rats underwent a six-hour fasting period before measuring fasting blood glucose, insulin levels and HOMA-IR to confirm diabetes onset. Rats were classified as diabetic if fasting blood glucose levels exceeded 15 mmol/L and HOMA-IR exceeded 2.4. The diabetic rats (n = 6 per group) were then randomly assigned to three different treatment groups, and therapeutic interventions were conducted over 21 days. Except for the healthy rats, all diabetic rats continued the HFD throughout the study period. The positive control group received metformin at a dose of 45 mg/kg body weight, administered once a week for three weeks. Treatment group received 500 µL of hypoxic MSC via intravenous injection once a week for three weeks.

Sample collection

On day 21, the rats were anesthetized via intramuscular injection using a combination of ketamine (60 mg/kgBW) and xylazine (20 mg/kgBW) to ensure proper sedation. Following anaesthesia, dorsal skin tissue samples were carefully harvested. The collected tissue samples were preserved in RNA later (Sigma-Aldrich) for subsequent qPCR analysis to ensure RNA integrity. Additional samples were fixed in 10% buffered formalin for histological evaluation. Remaining tissue samples were snap-frozen and stored at -80°C for intracellular enzyme-linked immunosorbent assay (ELISA) to quantify protein expression levels.

mRNA expression analysis

Total RNA was extracted from rats pancreas collected on day 21 using TRI Reagent (Sigma-Aldrich), following the manufacturer's protocol. Complementary DNA (cDNA) was synthesized using the Enhanced Avian First Strand cDNA Synthesis Kit (Sigma-Aldrich), adhering to the manufacturer's instructions. The reverse transcription reaction utilized oligo d(T) primers, with an incubation step at 70°C for 10 minutes, followed by 45°C for 15 minutes. Quantitative real-time PCR (qPCR) was performed in a two-step protocol using the Eco Real-Time PCR System (Illumina Inc., San Diego, CA, USA) and the KAPA SYBR® FAST Universal Kit (Sigma-Aldrich). A cDNA template of 3 ng was used for each reaction. The expression levels of AP-1 were assessed, with GAPDH serving as the reference gene. The primer sequences were as follows: IL18 forward: 5'- GAC AAA AGA AAC CCG CCT G -3', IL18 reverse: 5'- ACA TCC TTC CAT CCT TCA CAG -3', AP1 forward: 5'-CGG GCT GTT CAT CTG TTT GT-3', AP1 reverse: 5'-CCG GGA CTT GTG AGC TTC TT-3', GAPDH forward: 5'-GCG ACA GTC AAG GCT GAG AAT G-3', GAPDH reverse: 5'-TCT CGC TCC TGG AAG ATG GTG A-3'. The thermocycling conditions included an initial denaturation step at 95°C for 3 minutes, followed by 40 cycles of 95°C for 10 seconds and 60°C for 30 seconds. Gene expression levels were quantified using the ΔΔCt method, analysed through the Eco Study Software (Illumina), and normalized to the β-actin housekeeping gene.

Intracellular ELISA

Tissue lysates were prepared from the extracted samples using a lysis buffer containing RIPA, PMSF, NaF, and a protease inhibitor cocktail. The lysates were centrifuged at 4°C for 10 minutes, and the supernatants were collected for analysis. Protein concentrations were determined using UV-Vis spectrophotometry at 260 nm and 280 nm to ensure sample quality and consistency. Equal volumes of protein from each sample were loaded into ELISA wells. The intracellular levels of IL-18 were measured using a specific ELISA kit (Elabscience, Texas, USA) according to the manufacturer's protocol. Standard curves were generated for each assay to calculate IL-18 concentrations. Colorimetric absorbance was recorded at a wavelength of 450 nm using a microplate reader. All measurements were conducted in triplicate to ensure the reliability and reproducibility of the results.

Statistical analysis

All statistical analyses were conducted using SPSS version 26 (IBM, New York, USA). For data following a normal distribution, one-way analysis of variance (ANOVA) was performed, followed by Tukey's post-hoc test to assess pairwise group differences. For non-normally distributed data, the Kruskal-Wallis test was employed, followed by Mann-Whitney U tests for pairwise comparisons. Results are expressed as mean ± standard deviation (SD). A p-value of less than 0.05 was considered statistically significant.

RESULTS

The Hypoxic MSCs Characterization

Medium contained of hypoxic MSCs was collected after 24 hours of incubation in hypoxic environment. Using molecular weight cut-off strategies, we separated the cytokines and growth factors present in the hypoxic MSCs to isolate pure secretome-derived from the medium. Tangential flow filtration (TFF) was employed, with 10-100 kDa filter cassette to isolate selectively the soluble molecules. The levels of growth factor and cytokines in the secretome were evaluated using ELISA. Table 1 showed the summarized of concentration of each soluble molecule identified in hypoxic MSCs secretome.

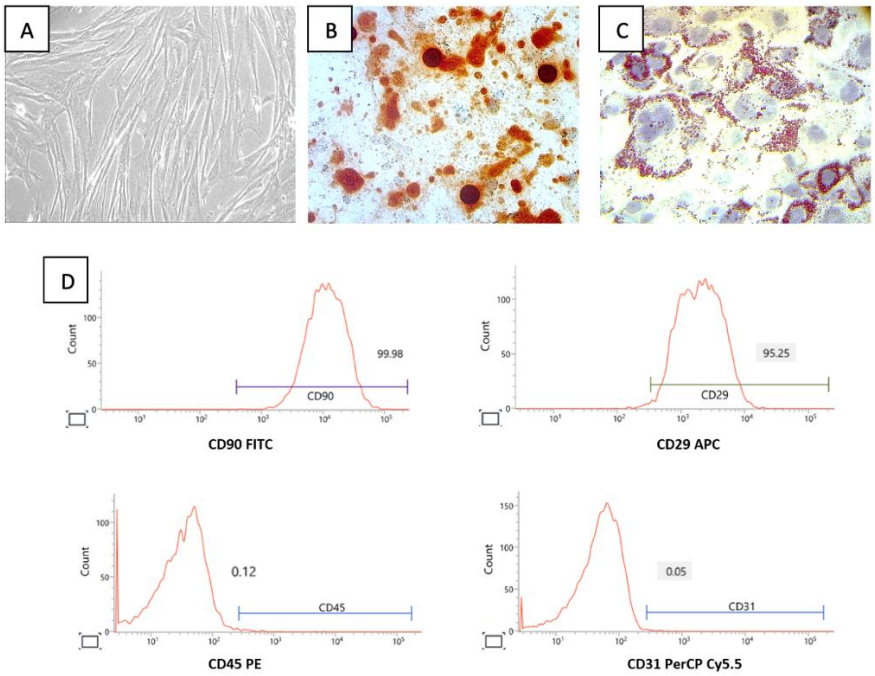

Figure 1. Validation Results of Hypoxic MSCs Formation. *Validation Results of Hypoxic MSCs Formation.* (**A**) MSCs culture after the 5th passage shows *spindle-like cell morphology* at the bottom of the flask, observed at *40x magnification*. (**B**) MSCs demonstrate the ability to *differentiate into osteocytes*. (**C**) MSCs also show the ability to *differentiate into adipocytes*. *Calcium and lipid deposits* are visible following *Alizarin Red* and *Oil Red O staining,* respectively, at *400x magnification*. (**D**) Validation using *flow cytometry* reveals the expression of characteristic *MSCs surface markers*. MSCs express *CD90 (99.98%)* and *CD29 (95.25%)*, with minimal expression of *CD45 (0.12%)* and *CD31 (0.05%)*.

Table 1. Validation of Hypoxic MSCs Secretome

Parameter	Results
VEGF	1064.74 pg/mL
SDF-1	7374.94 pg/mL
IL-10	523.23 pg/mL

The T2DM Rats Model Characterization

To determine whether T2DM induction occurred in the rat model, validation was performed by measuring HOMA-IR and fasting blood glucose levels (FBG). Measurements were taken after the T2DM group were subjected to a HFD and STZ treatment. One week after STZ injection, the FBG levels of the T2DM group showed a significant increase compared to healthy group. As shown in Table 2, the FBG levels in T2DM group exceeded 126 mg/dL, confirming the diabetic condition.[17] HOMA-IR value between 0.5–1.4 is categorized as normal, while a value of ≥1.9 indicates early-stage insulin resistance, and a value of ≥2.4 signifies the presence of insulin resistance.[18] Table 2 shows HOMA-IR value of T2DM group significance higher than healthy group.

Table 2. Validation of induction of T2DM modelled rats.

Group	Fasting blood Glucose (mg/dL) Mean±SD	HOMA-IR Mean±SD
Healthy	104.222±2.973	0.768±0.037
T2DM	458.200±36.267***	18.937±2.509***

Significance level = ***p<0.001

Effect of Hypoxic MSCs Secretome on AP-1 mRNA Expression

T2DM rats showed a significant increase in AP-1 expression compared to healthy rats ($p < 0.001$), reflecting increased inflammatory processes. Figure 2 shows the treatment of hypoxic MSCs secretome group resulted in significance decrease AP-1 expression compared to T2DM rats ($p < 0.05$), even lower than that observed with metformin treatment group. This finding highlights the potential of hypoxic MSCs secretome to more suppress AP-1 expression compared to standard therapy in male Wistar rats with the T2DM model.

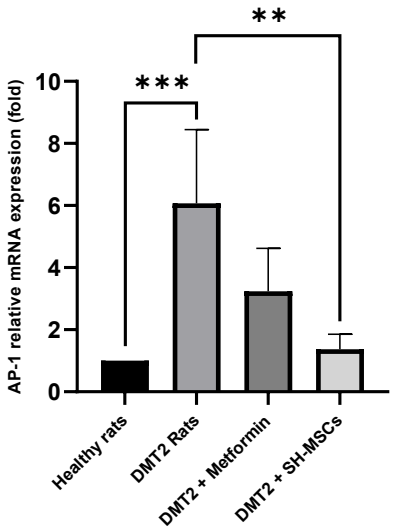

Figure 2. AP-1 Expression in T2DM Rat Model. T2DM rats showed a significant increase in AP-1 expression compared to healthy rats. Hypoxic MSCs secretome treatment rats group showed a significant low level in AP-1 expression compared to the T2DM rats and Metformin group. **: $p \leq 0.01$; ***: $p \leq 0.001$.

Effect of Hypoxic MSCs Secretome on IL-18 Level

The concentration level of IL-18, a crucial indicator of inflammation and immune response, was measured using ELISA after 21 days of treatment (Figure 3). T2DM rats showed a significant increase in IL-18 levels compared to healthy rats ($p < 0.001$), reflecting heightened inflammatory processes. Treatment with Metformin led to a reduction in IL-18 levels. Conversely, administration of 500 µL hypoxic MSCs secretome significantly reduced IL-18 levels ($p < 0.05$), produced the most substantial decrease in IL-18 even compared to Metformin treatment, indicating its potential to alleviate inflammation. The concentration level of IL-18 across the three treatment groups follows a similar pattern to the AP-1 expression in T2DM rats. As previously known, increased AP-1 expression influences the modulation of pro-inflammatory molecule expression.[9] Therefore, a reduction in AP-1 expression is followed by a decrease in IL-18 level.

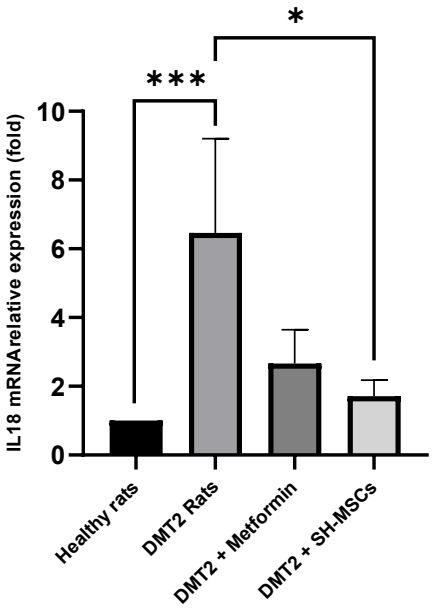

Figure 3. IL-18 Levels in T2DM Rat Model. *T2DM rats* showed a significant increase in *IL-18 levels* compared to healthy rats. *Hypoxic MSCs secretome treatment* rats group showed a significant low level in *IL-18 levels* compared to the *T2DM rats and Metformin group*. *: $p \leq 0.05$; ***: $p \leq 0.001$.

DISCUSSION

In Type 2 Diabetes Mellitus (T2DM), inflammation occurs due to visceral obesity, where adipocytes undergo hypertrophy, leading to tissue death and triggering the release of Damage-Associated Molecular Patterns (DAMPs).[19] This process stimulates M1 macrophages to secrete proinflammatory cytokines, such as IL-6 and IL-8.[20] The involvement of T cells, which regulated by nuclear factor of activated T-cell (NFAT) cooperated with the transcription factor AP-1, further drives M1 macrophages to continuously produce pro-inflammation cytokines, resulting in both local and systemic inflammation, which also contributes to inflammation in pancreatic β-cells.[5,21,22]

AP-1 as a transcription factor regulates pro-inflammatory production by macrophages through phosphorylation of its subunits, enabling it to bind to DNA and promote the expression of inflammatory genes.[20] AP-1 works synergistically with NF-κB and Signal Transducer and Activator of Transcription (STATs), particularly STAT1 and STAT3, to amplify pro-inflammatory cytokine expression.[23,24] AP-1 plays a crucial role in chromatin remodelling, loosening the chromatin structure and suggesting a facilitation of NF-κB binding to DNA.[25] Subsequently, NF-κB and STAT1/STAT3 sustain pro-inflammatory cytokine expression over time.[23] In parallel, NF-κB enhances the production of c-Jun and c-Fos[26], the primary subunits of AP-1, further strengthens AP-1 activity. Moreover, AP-1 and NF-κB directly induce STAT3 activation, maintaining chronic inflammation.[27,28] Additionally, STAT1, activated by IFN-γ, reinforces NF-κB expression[29,30], creating a positive feedback loop of inflammation that is difficult to control, as observed in T2DM. Breaking this inflammatory loop for instance, by inhibiting one of these transcription factors, such as AP-1 offers a promising strategy to mitigate chronic inflammation in T2DM.

In this study, the expression of the transcription factor AP-1 was observed to be increased in T2DM model rat compared to healthy group. Meanwhile, the AP-1 expression observed downregulated in T2DM model rats that given hypoxic MSCs secretome treatment compared to both negative and positive control groups, suggesting that hypoxic MSCs attenuate inflammation by suppressing AP-1 expression. This lower expression of AP-1 is likely mediated by the anti-inflammatory properties of the hypoxic MSCs secretome, which modulates oxidative stress through the secretion of cytokines such as IL-10.[12] IL-10 exerts its inhibitory effect on AP-1 activation through multiple pathways. IL-10 inhibits the phosphorylation of MAPK signalling components, particularly JNK and p38[31,32], preventing the activation of key AP-1 subunits, c-Jun and c-Fos, thereby reducing AP-1 transcriptional activity.[23,32,33] IL-10 also induces the expression of Suppressor of Cytokine Signalling 3 (SOCS3), which negatively regulates upstream signalling, consequently impeding AP-1 complex formation on the DNA.[34,35] Additionally, IL-10 modulates NF-κB activity by preventing the degradation of Inhibitor of κB (IκB)[36], thereby retaining NF-κB in the cytoplasm and indirectly suppressing AP-1 activation due to their synergistic role in promoting pro-inflammatory gene expression. Moreover, IL-10 reduces the production of ROS, thereby limiting the release of DAMPs and suppressing MAPK pathway activation, further mitigating AP-1 signalling.[37] Collectively, the findings indicate that IL-10 derived from the hypoxic MSCs secretome plays a crucial role in downregulating AP-1 expression through the modulation of multiple inflammatory pathways, thereby contributing to reduced inflammation in T2DM model rats.

Targeting AP-1 as the main therapeutic focus for T2DM can be achieved by regulating IL-18. IL-18 is a pro-inflammatory cytokine that stimulates the production of interferon-gamma (IFN-γ) by natural killer (NK) cells and T cells.[38] In T2DM, IL-18 activates AP-1 through the MAPK pathway.[39] Upon binding to its receptor IL-18R on the cell surface, IL-18 triggers the recruitment of the adaptor protein Myeloid Differentiation Primary Response 88 (MyD88). This activation leads to the recruitment and activation of TNF Receptor-Associated Factor 6 (TRAF6), a key signalling molecule that serves as the central node for the activation of MAPK pathways.[40] The combined activation of AP-1 creates a pro-inflammatory environment that drives chronic inflammation, one of the primary factors in T2DM pathogenesis.[22,28] Therefore, regulating IL-18 offers a promising strategy to decrease AP-1 activation and mitigate inflammation in T2DM. This study shows that IL-18 expression was elevated in T2DM model rats compared to healthy control. Treatment with hypoxic MSC secretome in T2DM model rats showed a reduction in IL-18 levels compared to both positive and negative controls. The ability of the hypoxic MSC secretome to reduce IL-18 expression already shows in previous study.[41] This is likely due to the TGF β-1-mediated regulatory pathway.[38] TGF β-1 is reported to have anti apoptotic activity and could restored skewed Treg/Th17 induced by LPS and hypoxia.[38,42] TGF β also reported can alter the activation, maturation, and differentiation of macrophages, thus reducing IL-18 productivity.[43]

The use of hypoxic MSC secretome to mitigate chronic inflammation in T2DM, which contributes to insulin resistance, demonstrates potential in regulating inflammation through the modulation of the AP-1 transcription factor. The regulation of AP-1 showed by the decreased expression of the pro-inflammatory cytokine IL-18. Regulating AP-1 may help reduce chronic inflammation and prevent complications in T2DM, ultimately improving patient's quality of life. Further studies are required to determine the optimal dosage and long-term effects of hypoxic MSC secretome. Additionally, further investigation is needed into its potential role in pancreatic regeneration. As this study was conducted in animal models, future research is necessary to evaluate its efficacy and safety in clinical studies.

CONCLUSIONS

Current study highlights the therapeutic potential of hypoxic MSCs secretome as an alternative approach to alleviate inflammation and oxidative stress in T2DM. The therapy demonstrated reduction in AP-1 expression and IL-18 levels, the pro-inflammatory pathways. This proposes that hypoxic MSCs secretome, can effectively decrease the inflammatory processes associated with T2DM, contributing to improved metabolic conditions and potentially reducing the risk of T2DM-related complications. Furthermore, the anti-inflammatory and antioxidative mechanisms underlying the detected therapeutic effects highlight the promise of this strategy for the management of T2DM. Future studies focusing on optimal dosing, long-term efficacy, and in-depth mechanistic insights are warranted to fully establish the clinical applicability of this novel therapeutic treatment.

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Competing Interests

The authors declare that there is no conflict of interest.

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