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Hypoxia-Conditioned Mesenchymal Stem Cell-Derived Exosomes Reduce NF-κB and STAT3 Gene Expression in a Type 2 Diabetes Mellitus Rats

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ABSTRACT

Background: Chronic low-grade inflammation is a key contributor to insulin resistance and progressive β-cell dysfunction in type 2 diabetes mellitus (T2DM). Nuclear factor-kappa B (NF-κB) and signal transducer and activator of transcription 3 (STAT3) are central regulators of inflammatory signaling implicated in metabolic dysfunction. Exosomes derived from hypoxia-conditioned mesenchymal stem cells (EH-MSCs) have emerged as promising cell-free therapeutics with potent immunomodulatory properties. **Aim:** This study evaluated the effects of EH-MSC-derived exosomes on pancreatic NF-κB and STAT3 gene expression in a streptozotocin–nicotinamide-induced rat model of T2DM. **Methods:** Umbilical cord-derived mesenchymal stem cells (UC-MSCs) were isolated, characterized according to International Society for Cellular Therapy criteria, cultured under 5% O_2 for 24 h, and exosomes were collected by tangential flow filtration. Twenty-eight male Wistar rats were randomly assigned to healthy control, T2DM+NaCl, T2DM+metformin, and T2DM+EH-MSC groups (n=7/group). Diabetes was induced using nicotinamide and streptozotocin. Metformin was administered orally for 14 days, whereas EH-MSC-derived exosomes (500 µL) were administered three times over 7 days. Pancreatic NF-κB and STAT3 mRNA expression was quantified by quantitative real-time PCR. **Results:** STZ induction successfully established T2DM, increasing fasting blood glucose from approximately 111 to 334 mg/dL. Diabetic rats exhibited marked upregulation of both NF-κB and STAT3 compared with healthy controls. EH-MSC-derived exosome treatment significantly reduced NF-κB and STAT3 expression (both $p<0.05$), restoring their expression toward physiological levels. In contrast, metformin produced only a modest reduction in NF-κB expression and a less pronounced effect on STAT3, indicating inferior suppression of inflammatory signaling compared with EH-MSC-derived exosomes. **Conclusions:** EH-MSC-derived exosomes effectively attenuated pancreatic inflammatory signaling by simultaneously suppressing NF-κB and STAT3 expression in experimental T2DM.

Keywords: *Type 2 Diabetes, Inflammation, NF-κB, STAT3, Exosome.*

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a global metabolic disorder characterized by insulin resistance progressive pancreatic β-cell dysfunction, and chronic low-grade inflammation (1). Persistent inflammatior plays a central role in the development and progression of T2DM by exacerbating peripheral insulir resistance, impairing β-cell function, and contributing to diabetes-related complications (2). Chronic hyperglycemia further promotes excessive production of reactive oxygen species (ROS) while reducing endogenous antioxidant defenses, resulting in oxidative stress that aggravates metabolic

dysfunction (3). The combined effects of oxidative stress and inflammation activate several intracellular signaling pathways, leading to sustained production of pro-inflammatory mediators and further deterioration of insulin signaling. Among these pathways, nuclear factor-kappa B (NF-κB) and signal transducer and activator of transcription 3 (STAT3) are recognized as key regulators of inflammatory responses and metabolic homeostasis. Persistent activation of these transcription factors amplifies inflammatory cytokine production and contributes to the vicious cycle of chronic inflammation and insulin resistance in T2DM. Therefore, therapeutic strategies that target inflammatory signaling pathways may provide additional benefits beyond conventional glucose-lowering therapies.

Oral antihyperglycemia drugs and insulin therapy are commonly prescribed for patients with type 2 DM (4). Although these therapies are effective in controlling hyperglycemia, they do not adequately address the underlying mechanism of the disease, namely insulin resistance and chronic inflammation (5). Studies have shown that elevated TNFa levels can alter the insulin signaling pathway and downregulate the expression of glucose transporter type 4 (GLUT4), a key regulator of insulin-dependent glucose uptake (6). Two major transcription factors involved in these processes are nuclear factor kappa B (NF-kB), particularly the subunit P65 (RelA), and signal tranducer and activator of transcription 3 (STAT3), which regulate numerous pro-inflammation responses (7). Activation of NF-kB (P65) induces the expression of cytokines and chemokines that exacerbate systemic inflamation. In contrast, dysregulation of STAT 3 affects insulin sensitivity, gluconeogenesis, and cell survival pathway (8). Together, alterations in NF-kB and STAT3 activity contribute to metabolic dysfunction in patients with type 2 DM.

Exosomes derived from mesenchymal stem cell (MSC) have emerged as promising cell-free therapeutic agents due to their ability to carry various bioactive molecules, such as protein, microRNAs and lipids (9). These biomolecules play essential roles in modulating inflammation and promoting tissue regeneration. Exosome isolated from MSCs cultured under hypoxic conditions have been reported to possess greater therapeutic potential than those derived from normoxic MSCs because of their higher content of anti-apoptotic and pro-regenerative molecules (10). Several studies have demonstrated that hypoxia-derived MSC exosomes reduce inflammation and improve insulin sensitivity in diabetic animal model (11). However, the molecular mechanism underlying this mechanism is not yet fully understood.

Therefore, there is need for novel therapeutic approaches that not only focus on blood glucose control but also target inflammation and metabolic dysfunction. This study aims to evaluate the NF-kB and STAT3 expression in type 2 diabetes model induced by streptozotocin and nicotinamide. The results are expected to provide a better understanding of how hypoxic-derived MSC exosomes improve insulin resistance and regulate the glucose metabolism in type 2 DM.

MATERIALS AND METHODS

Rats UC-MSCs Isolation and Characterization

Umbilical cords were harvested from 19-day pregnant Wistar rat fetuses under general anesthesia. Blood vessels were removed, and the umbilical cord tissue was minced into small explants and cultured in DMEM (Sigma-Aldrich, St. Louis, MO, USA) supplemented with 10% fetal bovine serum (FBS; Gibco, NY, USA) and 1% penicillin–streptomycin at 37°C in a humidified atmosphere containing 5% CO_2. The culture medium was replaced every 3 days, and cells were passaged upon reaching approximately 80% confluence. Passage 4–5 UC-MSCs were used for subsequent experiments. The immunophenotype of passage 4 UC-MSCs was characterized by flow cytometry using fluorochrome-conjugated antibodies against CD90, CD29, CD45, and CD31, with corresponding isotype controls. Cells were analyzed using a BD flow cytometer (BD Biosciences, San Jose, CA, USA). The multilineage differentiation potential of

passage 4 UC-MSCs was evaluated by culturing the cells in osteogenic and adipogenic induction media for 21 days. Osteogenic and adipogenic differentiation were confirmed by Alizarin Red and Oil Red O staining, respectively, and examined under an inverted microscope.

EH-MSC Preparation and Characterization

UC-MSCs at approximately 80% confluence were cultured under hypoxic conditions (5% O_2) in a hypoxia chamber for 24 h at 37°C. The conditioned medium was collected and sequentially centrifuged at 300 × *g* for 5 min to remove cells and 2,000 × *g* for 30 min to eliminate cellular debris. The resulting supernatant was concentrated using tangential flow filtration (TFF) with a sterile 300-kDa polyethersulfone hollow-fiber membrane to obtain EH-MSCs. EH-MSCs were characterized by flow cytometry. Briefly, EH-MSC samples were incubated with capture beads overnight at room temperature, followed by staining with anti-CD9 antibody f or 1 h at 2–8°C in the dark. After washing, samples were resuspended in assay buffer and analyzed using a flow cytometer to confirm the expression of the exosomal marker CD9.

Experimental Animals and T2DM Induction

Twenty-eight male Wistar rats (8–10 weeks old, 200–250 g) were acclimatized for 7 days under standard laboratory conditions with ad libitum access to food and water. The animals were randomly assigned to four groups (n = 7/group): healthy control, T2DM + NaCl, T2DM + metformin, and T2DM + EH-MSCs. Type 2 diabetes mellitus (T2DM) was induced in all groups except the healthy control by intraperitoneal injection of nicotinamide (230 mg/kg body weight), followed 15 min later by streptozotocin (55 mg/kg body weight). Fasting blood glucose levels were measured 7 days after induction, and rats with blood glucose levels ≥180 mg/dL were considered diabetic and included in the study. The T2DM + metformin group received metformin (300 mg/kg body weight/day) orally for 14 consecutive days, whereas the T2DM + EH-MSCs group received 500 µL EH-MSCs three times over a 7-day period, followed by a 7-day observation period. The healthy control and T2DM + NaCl groups received normal saline. At the end of the experiment, rats were anesthetized with a ketamine–xylazine–acepromazine cocktail and euthanized. Pancreatic tissues were harvested for subsequent molecular analyses.

NFκB and STAT-3 Gene Expression

RNA of pancreas tissue samples was extracted by adding RNA Iso Plus and sonicated. cDNA synthesis was conducted using RNA sampel. Gene expression of NFκB and STAT-3 were analyzed using quantitavie *Real Time-Polymerase Chain Reaction* (qRT-PCR) with primers. Primer NFκB F: 5'-AACACTGCCGAGCTCAAGAT-3' and R: 5'-CATCGGCTT GAGAAAAGGAG-3'. Primer STAT-3 F: 5'-TTCTTTGAGTTCGGTGGGGTC-3' and R: 5'- TGCATATTTGTTTGGGGCAGG-3'. Primer *housekeeping* gene GAPDH F: 5'-ATGTGTCCGTCGTGGATCTGAC-3' and R: 5'-AGACAACCTGGTCCTCAGTGTAG-3'. PCR conducted using temperature: 95°C (5 minutes), 95°C (15 minutes), 60°C (1 minutes), 40 cycles.

Data Analysis

Relative gene expression was calculated using the comparative Ct (2^−ΔΔCt) method with GAPDH as the reference gene. Statistical analyses were performed using R version 4.6.1 (R Foundation for Statistical Computing, Vienna, Austria). Differences among groups were analyzed using one-way ANOVA on ΔCt values followed by Tukey's HSD post hoc test. Assumptions of normality and homogeneity of variance were evaluated using the Shapiro–Wilk and Levene's tests, respectively. Given the small sample size (n = 3 per group), the findings were confirmed using the Kruskal–Wallis test as a sensitivity analysis. Effect sizes are presented as partial eta-squared (η^2p). Statistical significance was defined as $p < 0.05$.

RESULTS

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MSCs Characterization

The isolated cells displayed the typical spindle-shaped, fibroblast-like morphology characteristic of mesenchymal stem cells (MSCs) (Figure 1A). Flow cytometric analysis confirmed their mesenchymal phenotype, demonstrating high expression of the positive MSC markers CD90 (98.7%) and CD29 (99.9%), together with low expression of the hematopoietic marker CD45 (0.40%) and the endothelial marker CD31 (3.92%) (Figure 1D). The multipotent differentiation potential of the isolated cells was further evaluated through osteogenic and adipogenic induction. After 21 days of culture in lineage-specific induction media, osteogenic differentiation was confirmed by the deposition of calcium-rich mineralized matrix, as indicated by positive Alizarin Red staining (Figure 1B). Adipogenic differentiation was demonstrated by the accumulation of lipid droplet, visualized by positive Oil Red O staining (Figure 1C). Together, these findings confirm that the isolated cells satisfy the minimal criteria for mesenchymal stem cell identification established by the International Society for Cellular Therapy (ISCT) (12).

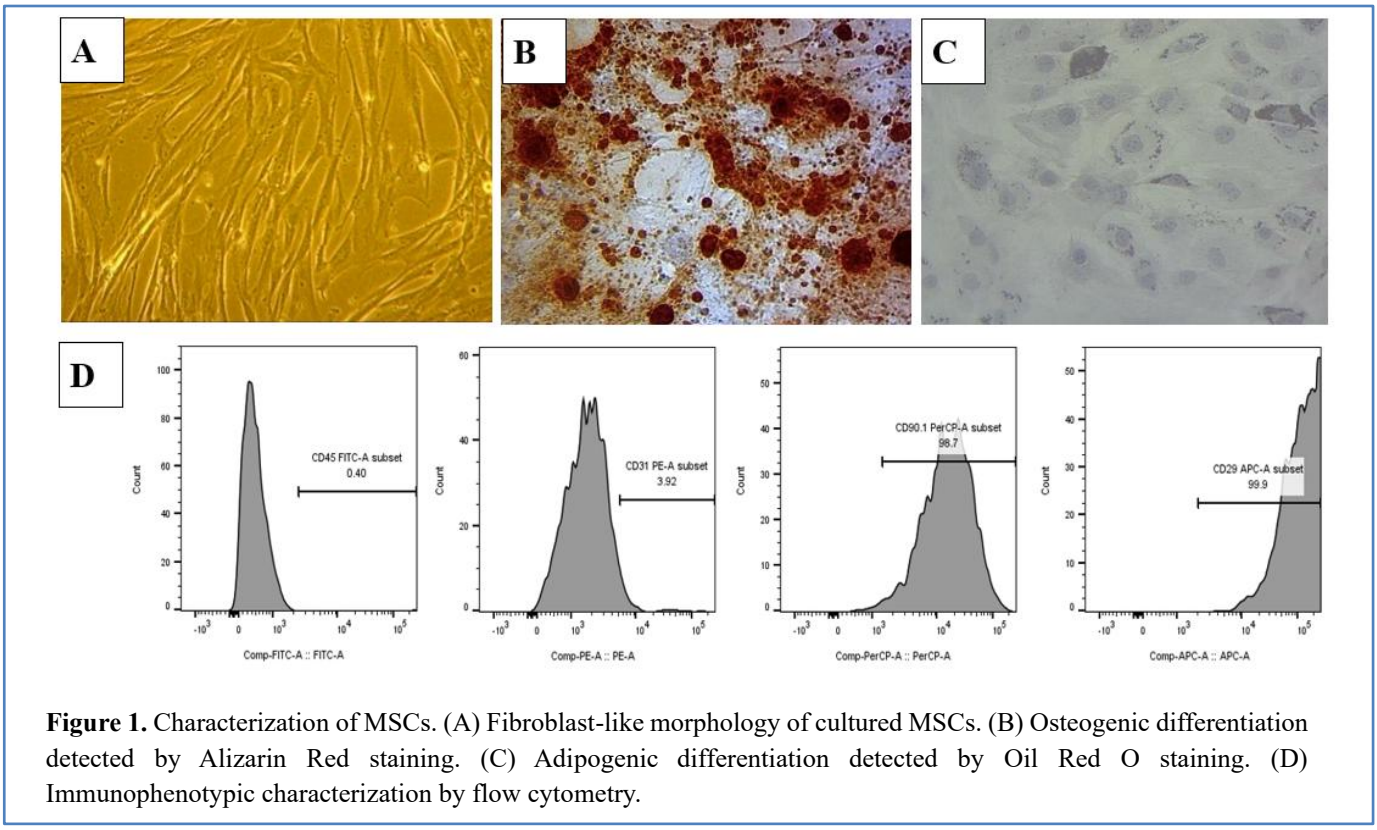


Figure 1. Characterization of MSCs. (A) Fibroblast-like morphology of cultured MSCs. (B) Osteogenic differentiation detected by Alizarin Red staining. (C) Adipogenic differentiation detected by Oil Red O staining. (D) Immunophenotypic characterization by flow cytometry.

EH-MSCs Characterization

EH-MSCs were characterized by flow cytometry to determine their surface marker expression. The results demonstrated that the isolated EH-MSCs expressed the exosomal marker CD9 at 9.1% (Figure 2), confirming the presence of extracellular vesicles enriched with exosomal characteristics (13).

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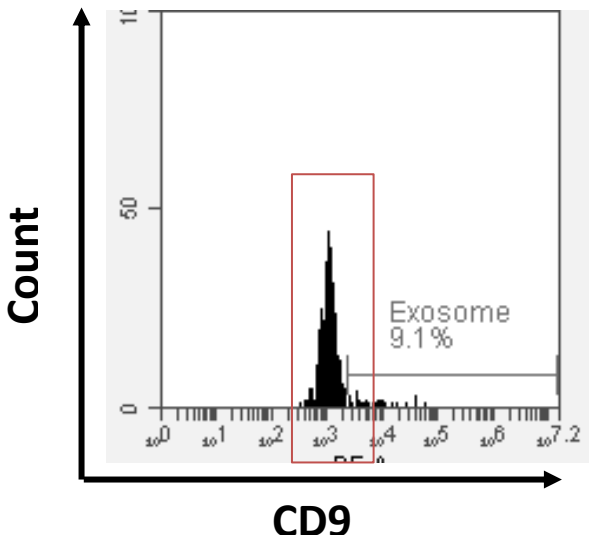


Figure 2. Characterization of the CD9 Marker in EH-MSCs by Flow Cytometry

T2DM Rat Model Validation

The T2DM rat model was validated by comparing fasting blood glucose levels between healthy control rats and streptozotocin (STZ)-induced rats. STZ induction resulted in a marked increase in blood glucose levels, with diabetic rats exhibiting a mean glucose concentration of 334 mg/dL compared with 111 mg/dL in healthy controls (Figure 3). These findings confirmed the successful establishment of the T2DM rat model.

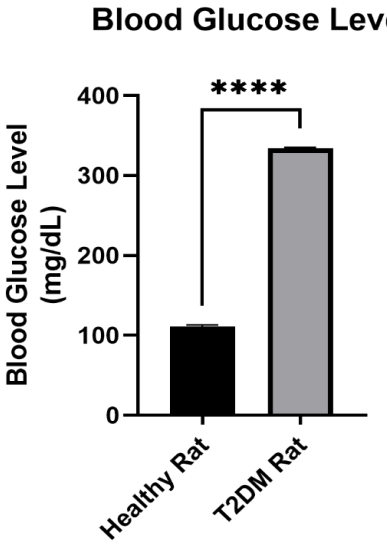


Figure 3. Validation of the STZ-induced T2DM rat model. Fasting blood glucose levels of healthy control and STZ-induced T2DM rats.

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NFκB and STAT-3 Gene Expression

The effects of metformin and EH-MSC-derived exosome treatment on NF-κB and STAT3 gene expression were evaluated by qRT-PCR (Figure 4). NF-κB expression was markedly elevated in the diabetic control (DM + NaCl) group compared with the healthy control group. Treatment with EH-MSC-derived exosomes significantly reduced NF-κB expression compared with the diabetic control ($p < 0.05$), restoring its expression to a level comparable to that of healthy rats. In contrast, metformin treatment resulted in a modest reduction in NF-κB expression, which did not differ significantly from the diabetic control group (Figure 4A).

Similarly, STAT3 expression was substantially increased in diabetic rats receiving NaCl compared with healthy controls. EH-MSC-derived exosome treatment significantly decreased STAT3 expression relative to the diabetic control group ($p < 0.05$). Notably, EH-MSC-derived exosomes produced a greater suppressive effect than metformin, reducing STAT3 expression to a level approaching that of the healthy control group (Figure 4B).

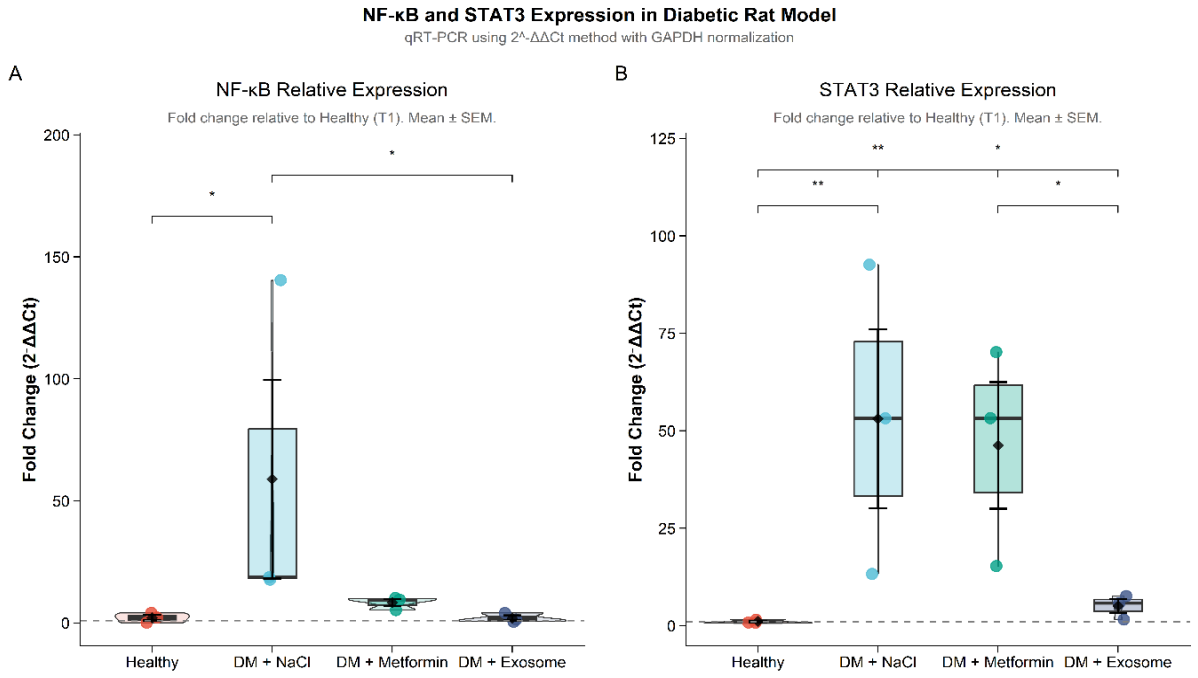


Figure 4. Effects of EH-MSC-derived exosomes on inflammatory gene expression in diabetic rats. (A) Relative NF-κB gene expression. (B) Relative STAT3 gene expression. Gene expression was quantified by qRT-PCR using the 2^−ΔΔCt method and normalized to GAPDH. Data are presented as the mean ± SEM. Statistical significance was determined using one-way ANOVA followed by Tukey's multiple comparisons test. $p < 0.05$.

DISCUSSION

The present study aimed to compare the molecular effects of MSC-derived exosome therapy and metformin on inflammatory signaling pathways in a Wistar rat model of type 2 diabetes mellitus (T2DM), focusing on the relative expression of STAT3 and NF-κB, two central transcription factors that orchestrate chronic inflammation and insulin resistance. The principal findings demonstrated that diabetic rats exhibited marked upregulation of both STAT3 and NF-κB compared with healthy controls.

While metformin reduced NF-κB expression, its effect on STAT3 remained relatively modest. In contrast, treatment with MSC-derived exosomes significantly suppressed both STAT3 and NF-κB expression, approaching levels observed in healthy animals. These findings suggest that MSC-derived exosomes may exert broader immunomodulatory effects than metformin by modulating multiple interconnected inflammatory signalling pathways implicated in T2DM.

In experimental T2DM, STZ-induced β-cell damage is thought to trigger sustained hyperglycemia and oxidative stress, which together promote a chronic low-grade inflammatory milieu that contributes to insulin resistance and progressive β-cell dysfunction (15,16). Persistent metabolic stress induced by hyperglycemia, elevated free fatty acids, and oxidative stress activates pattern-recognition receptors such as Toll-like receptor-4 (TLR4), which subsequently stimulate the IκB kinase (IKK) complex (17). Activated IKK phosphorylates IκB, allowing NF-κB to translocate into the nucleus where it induces transcription of numerous pro-inflammatory mediators including TNF-α, IL-1β, IL-6, MCP-1, iNOS, and NLRP3 inflammasome components (18,19). These inflammatory mediators further impair insulin receptor substrate-1 (IRS-1) signaling through inhibitory serine phosphorylation, thereby aggravating insulin resistance and establishing a vicious cycle between chronic inflammation and metabolic dysfunction (20,21). Recent comprehensive reviews have emphasized that persistent activation of NF-κB represents one of the central molecular mechanisms linking hyperglycemia, oxidative stress, and diabetic complications (20,22,23). Consistent with this mechanism, the diabetic untreated group (DM + NaCl) exhibited the highest NF-κB expression, indicating sustained inflammatory activation in diabetic tissues. Interestingly, although metformin markedly reduced NF-κB expression, residual inflammatory activity remained detectable. This observation is biologically plausible because the anti-inflammatory action of metformin is largely indirect, occurring primarily through activation of AMP-activated protein kinase (AMPK), which suppresses NF-κB transcriptional activity by inhibiting IKK signaling and reducing oxidative stress (15,23). Consequently, this finding suggest that metformin mainly improves metabolic homeostasis and secondarily attenuates inflammation rather than directly regulating multiple inflammatory pathways.

In contrast, MSC-derived exosomes produced the significant reduction in NF-κB gene expression, nearly restoring physiological expression levels. This result may reflect the multifaceted biological cargo contained within MSC exosomes. Previous studies demonstrated that MSC may release nano-sized extracellular vesicle (EV) that containing several bioactive molecules including regulatory microRNAs (miR-146a, miR-21, miR-126, miR-181c, and miR-223), anti-inflammatory proteins, growth factors, and antioxidant enzymes (24,25). These bioactive molecules may act in a coordinated manner to modulate inflammatory signalling, potentially inhibiting the TLR4/MyD88 pathway, suppressing IKK activation, reducing NF-κB nuclear translocation, decreasing ROS generation, and limiting NLRP3 inflammasome activation (24,26). Consequently, the production of IL-1β, IL-6, TNF-α, and other inflammatory cytokines reduces substantially, interrupting the self-amplifying inflammatory cascade that characterizes diabetic tissues (27). Recent in vivo studies have consistently demonstrated that MSC-derived exosomes alleviate insulin resistance by suppressing NF-κB-dependent inflammation while simultaneously improving glucose utilization and preserving pancreatic β-cell viability (21,25).

In addition, the present study revealed a marked downregulation of STAT3 following MSC-derived exosome treatment. STAT3 is well recognized as the major downstream transcription factor of the IL-6/JAK/STAT signaling pathway, which is chronically activated in T2DM (26,27). Elevated circulating IL-6 may activate JAK2, resulting in phosphorylation and nuclear translocation of STAT3 (28). Activated STAT3 subsequently induces SOCS3, an inhibitor of insulin receptor signaling that promotes IRS-1 degradation and suppresses PI3K/Akt activation, thereby worsening insulin resistance (27). Furthermore, activated STAT3 positively interacts with NF-κB, enhancing inflammatory gene transcription and sustaining chronic cytokine production, particularly IL-6 itself, creating another

pathological positive-feedback loop (15,22). Recent mechanistic reviews describe STAT3 and NF-κB as mutually reinforcing signaling networks responsible for maintaining chronic inflammation in metabolic diseases (15,22,23). Interestingly, metformin only partially reduced STAT3 expression despite its substantial inhibition of NF-κB. This finding suggests that metformin predominantly targets metabolic signaling pathways and only indirectly modulates JAK/STAT signaling. Although AMPK activation may inhibit STAT3 phosphorylation under certain conditions, persistent IL-6 production originating from adipose tissue macrophages and inflamed pancreatic islets may continue to activate STAT3 independently of AMPK, thereby limiting the suppressive effect of metformin on this pathway.

In contrast, MSC-derived exosome treatment markedly reduced STAT3 expression toward levels observed in the vehicle group. MSC-derived exosomes may downregulate STAT3 via controlling IL-6 secretion from activated macrophages, promote macrophage polarization from the pro-inflammatory M1 phenotype toward the anti-inflammatory M2 phenotype, increase IL-10 production, and inhibit JAK2 phosphorylation (15,17,23). Other recent studies also shown that exosomal microRNAs such as miR-146a and miR-181c directly suppress upstream inflammatory mediators, thereby preventing sustained STAT3 activation (20,22,23). In addition, previous studies have shown that persistent STAT3 activation induces SOCS3 expression, which negatively regulates insulin receptor signaling by promoting IRS-1 degradation and suppressing PI3K/Akt activation (24,25). Accordingly, although these downstream mediators were not evaluated in the present study, the reduced STAT3 expression observed following MSC-derived exosome treatment may be consistent with improved insulin signaling reported in previous experimental models.

Another notable observation is that exosome therapy simultaneously suppressed both STAT3 and NF-κB, whereas metformin predominantly affected NF-κB. This distinction is mechanistically important because these pathways exhibit extensive molecular crosstalk (29,30). NF-κB stimulates IL-6 transcription, which subsequently activates STAT3 through JAK2 (30). Activated STAT3, in turn, further enhances NF-κB transcriptional activity, thereby maintaining persistent inflammatory signalling (31). Interrupting only one pathway may therefore incompletely resolve chronic inflammation (31,32)). The ability of MSC-derived exosomes to suppress both signaling cascades simultaneously suggests a broader systems-level mechanism that interrupts the reciprocal amplification between NF-κB and STAT3, producing a more profound anti-inflammatory response than conventional glucose-lowering therapy alone. Collectively, these findings indicate that MSC-derived exosomes act beyond glycemic control by directly modulating the molecular drivers of chronic inflammation in T2DM. Through coordinated suppression of the NF-κB–IL-6–JAK/STAT3 signaling axis, exosome therapy may reduce inflammatory cytokine production, alleviate insulin resistance, preserve pancreatic β-cell function, and ultimately slow the progression of diabetes-associated tissue injury.

This study is limited by the use of an experimental animal model and the evaluation of only two inflammation-related genes, *NF-κB* and *STAT3*. Additional studies incorporating protein-level validation, downstream signaling analyses, and functional metabolic assessments are needed to comprehensively elucidate the mechanisms underlying the therapeutic effects of MSC-derived exosomes. Despite these limitations, our findings provide preliminary mechanistic evidence supporting the anti-inflammatory potential of MSC-derived exosomes in T2DM and establish a basis for future translational research.

CONCLUSION

Hypoxia-conditioned mesenchymal stem cell-derived exosomes significantly decreased NF-κB and STAT3 gene expression in experimental type 2 diabetes mellitus, indicating their potential to modulate inflammation-associated gene expression.

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Authors' contributions

All authors contributed to the discussion of results, reviewed the final manuscript, and approved the submitted version.

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None.

Conflict of interest

The authors declare that there are no conflicts of interest related to this work.

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