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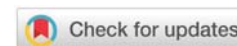
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Editorial

Non-alcoholic Fatty Liver Disease (NAFLD) and Mesenchymal Stem Cell-derived Extracellular Vesicles: Current Status and Perspective

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Abstract

Intrahepatocyte triglyceride buildup and concurrent immune system activation, followed by histological alterations, tissue destruction, and clinical manifestations, are signs of Non-alcoholic Fatty Liver Disease (NAFLD). One promising method of treating diabetes is cell-based therapy. In regenerative medicine, Mesenchymal Stem Cells (MSCs), which can be isolated from various tissue sources, such as bone marrow, adipose tissue, umbilical cord, and mobilized peripheral blood, have gained increasing significance. Mesenchymal Stem Cell (MSC)-derived Extracellular Vesicles (EVs) (MSC-EVs) are novel cell-free carriers with minimal immunogenicity that might inhibit harmful immune responses in tissues that are inflamed. EVs may reduce inflammation in liver conditions. Advancement in the clinical translation of EVs necessitates enhanced interdisciplinary collaboration between EV researchers, nanomedicine specialists, regulatory agencies, and clinical institutions is required. However, further in vitro and in vivo studies are required for better understanding cross talk between EVs and immune cells to clarify the potency and mechanisms of action of this novel potential therapeutic tool.

Intrahepatocyte triglyceride buildup and concurrent immune system activation, followed by histological alterations, tissue destruction, and clinical manifestations, are signs of Non-alcoholic Fatty Liver Disease (NAFLD). Hepatic fibrosis, cirrhosis, and hepatocellular carcinoma are among the possible outcomes that range from isolated excessive hepatocyte triglyceride accumulation and simple steatosis (Non-alcoholic Fatty Liver, or NAFL), to parenchymal inflammation and hepatocyte damage (non-alcoholic steatohepatitis, or NASH) [1].

Stable blood glucose levels are largely dependent on the liver's ability to metabolize glucose [2]. Impaired insulin regulation leads to an inappropriate elevation of glucagon in patients with type 2 diabetes mellitus (T2DM), which increases the breakdown of liver glycogen and causes hyperglycemia [3].

Furthermore, high blood cholesterol levels are risk factors for atherosclerosis and the advancement of diabetes [4]. Thus, enhancing hepatic glucose and lipid metabolism represents a key strategy in diabetes management.

One promising method of treating diabetes is cell-based therapy [5]. In regenerative medicine, Mesenchymal Stem Cells (MSCs), which can be isolated from various tissue sources, such as bone marrow, adipose tissue, umbilical cord, and mobilized peripheral blood, have become more and more significant [6,7]. Human umbilical cord-derived MSCs (HucMSCs) exhibit greater proliferative capacity and a lower immunogenicity, making them the perfect option for the treatment of diabetes [8-10]. There is growing evidence that MSCs primarily use paracrine signaling to achieve their therapeutic actions [11]. Exosomes, a key mediator of paracrine signaling, have been

viewed as a potentially effective cell-free treatment because of their numerous bioactivities and intercellular communication capabilities [12,13].

Mesenchymal Stem Cell (MSC)-derived Extracellular Vesicles (EVs) (MSC-EVs) are novel cell-free carriers with minimal immunogenicity that might inhibit harmful immune responses in tissues that are inflamed [14]. EVs have shown potential in reducing inflammation in liver-related conditions. Because they can deliver medicines, miRNA, siRNA, and other payloads steadily and are easily absorbed by liver cells, they are considered a promising therapeutic modality for the treatment of by delivering anti-fibrotic miR-223-3p and subsequently suppressing E2F1 Nonalcoholic Fatty Liver Disease (NAFLD), opening the door for EV-based therapy [14].

Delivery of anti-fibrotic miR-223-3p by ADSC-EVs leads to E2F1 suppression, Adipose-derived MSC (ADSC)-EVs slowed the evolution of NAFLD, which may indicate that miR-223-3p-loaded ADSC-EVs are a viable treatment option for NAFLD [15].

Because of their high capacity for tissue repair and anti-inflammatory properties, Human Umbilical Cord Mesenchymal Stem Cells (hUC-MSCs) are being investigated more and more in end-stage liver disease clinical trials [16]. hUC-MSC exosomes are spherically shaped vesicles that are released by their parent cells. The fact that exosomes have a substantially smaller diameter than hUC-MSCs suggesting they may serve as a safer alternative to mesenchymal stem cell-based therapies. Given that exosomes and hUC-MSCs are proposed to exert similar biochemical effects [16]. UC-MSC-derived exosomes have been shown to alleviate MCD-induced NASH in murine models by modulating macrophage anti-inflammatory phenotypes and by reversing PPAR α protein expression in liver cells, which suggests promising therapeutic potential for NASH treatment [16].

The hostile environment that the pathological conditions in several GI illnesses, as well as NAFLD, produce for EVs and their parents increases the risk of MSC apoptosis and senescence, which reduces the yield of MSC-EVs and limits their large-scale uses [17]. Because MSC-EVs adapt to the adverse microenvironment to which they are exposed, preconditioning with pharmacological agents or biological mediators may enhance their therapeutic efficacy [17].

Insulin resistance (IR) plays a central role in the development of both Non-alcoholic Fatty Liver Disease (NAFLD) and Metabolic Dysfunction-associated Steatotic Liver Disease (MASLD). Both conditions are frequently associated with metabolic syndrome and obesity, which serve as key risk factors. IR occurs when the body's cells become less responsive to insulin, a hormone that helps regulate blood sugar levels. In response, the pancreas produces more insulin to compensate and maintain euglycemia. However, over time, this contributes to multiple metabolic disturbances, notably hepatic lipid accumulation, which is a hallmark of MASLD. While mesenchymal stem cell-derived EVs may reduce metabolic abnormalities and may represent a novel therapeutic

approach for MASLD, adipose tissue-derived EVs contribute to insulin resistance and progression across MASLD stages [18,19].

A complex metabolic syndrome with major clinical problems is Diabetes Mellitus with Nonalcoholic Fatty Liver Disease (DM-NAFLD). Recently, it was demonstrated that circ-Tulp4 is delivered into hepatocytes via UCMSC-derived EVs, where it inhibits the HNRNPC/ABHD6 axis, attenuating pyroptosis and alleviating DM-associated MASLD [20].

Advancing the clinical translation of EVs requires enhanced collaboration between EV researchers, nanomedicine specialists, regulatory agencies, and clinical institutions is required. However, further in vitro and in vivo studies are required for better understanding cross talk between EVs and immune cells to clarify the efficacy and mechanisms of action of this novel potential therapeutic tool.

In conclusion, the amount of relevant research is steadily increasing, laying the groundwork for the potential therapeutic applications of EVs in the treatment of MASLD.

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