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MINIREVIEWS

Emerging role of engineered exosomes in nonalcoholic fatty liver disease

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Abstract

Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease worldwide. NAFLD comprises a continuum of liver abnormalities from nonalcoholic fatty liver to nonalcoholic steatohepatitis, and can even lead to cirrhosis and liver cancer. However, a well-established treatment for NAFLD has yet to be identified. Exosomes have become an ideal drug delivery tool because of their high transmissibility, low immunogenicity, easy accessibility and targeting. Exosomes with specific modifications, known as engineered exosomes, have the potential to treat a variety of diseases. Here, we review the treatment of NAFLD with engineered exosomes and the potential use of exosomes as biomarkers and therapeutic targets for NAFLD.

Key Words: Nonalcoholic fatty liver disease; Nonalcoholic steatohepatitis; Exosome; Engineered exosome; Targeted therapy

Core Tip: Nonalcoholic fatty liver disease (NAFLD) is the fastest growing chronic disease in the world. As the disease progresses, NAFLD can lead to liver fibrosis, cirrhosis and even liver cancer. However, a well-established treatment for NAFLD has yet to be identified. Exosomes are small extracellular vesicles secreted by cells. Owing to their high delivery efficiency and biocompatibility, exosomes are expected to become a new means of drug delivery and precise treatment for a variety of diseases, including NAFLD.

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a metabolic disease that is prevalent worldwide affecting at least a quarter of the population[1]. NAFLD is a continuum of liver abnormalities from nonalcoholic fatty liver (NAFL) to nonalcoholic steatohepatitis (NASH) that can even lead to cirrhosis and liver cancer. NAFL is reversible, whereas NASH with cirrhosis is difficult to reverse[2]. Therefore, it is critical to explore the pathogenesis of NAFLD and identify therapeutic targets to treat or prevent its development. Exosomes are extracellular vesicles with a particle size of 30-150 nm that play a crucial role in communication between cells[3]. Some macromolecules such as RNA or proteins in exosomes are associated with the occurrence and development of liver-related diseases and can be used as potential molecular markers in the diagnosis of NAFLD[4]. Processed and modified exosomes (known as engineered exosomes) may also facilitate the study of NAFLD and the development of new therapeutic strategies[5]. In this review, the mechanism and function of engineered exosomes in the development of NAFLD are reviewed (Figure 1).

ENGINEERED EXOSOMES AND LIPID METABOLISM

The liver is the largest metabolic organ and a hub of lipid metabolism. Abnormal changes in lipid metabolism in the liver lead to the development of metabolic diseases[6]. A research team found that the release of exosomes in cultured astrocytes from apolipoprotein E knockout mice was significantly reduced compared to wild-type controls, and a PI3K inhibitor (LY294002) rescued the release of exosomes. They confirmed that the release of exosomes was regulated by cellular cholesterol through stimulation of the PI3K/Akt signalling pathway[7].

Li *et al*[8] systematically screened for microRNA expression using high-throughput small RNA sequencing and found that miR-199a-5p was significantly upregulated in adipose tissue in a mouse model of high-fat diet (HFD). Further studies confirmed that exosomal miR-199a-5p promoted lipid accumulation in the liver through induction of macrophage stimulating 1 (MST1) expression and fatty acid metabolism. Cheng *et al*[9] found that exosomal miR-627-5p reversed insulin resistance, prevented liver injury, normalized glucose and lipid metabolism and reduced lipid deposition in a rat model of NAFLD.

Brown adipose tissue (BAT) strongly promotes energy expenditure and shows good potential in the treatment of obesity. Zhou *et al*[10] treated HFD-fed mice with engineered exosomes derived from the serum of young healthy mice or from BAT. They found that treatment with BAT exosomes significantly promoted oxygen consumption in recipient cells, thus alleviating metabolic syndrome in HFD-fed mice.

Li *et al*[11] used a low-density lipoprotein receptor-deficient mouse (Ldlr mouse) as a model for hypercholesterolemia. Ldlr mRNA was encapsulated into exosomes by overexpression of Ldlr in donor AML12 mouse hepatocytes. The authors found that engineered exosomes loaded with Ldlr mRNA could restore the expression of Ldlr in the livers of Ldlr-deficient mice and rescue hypercholesterolemia. This study suggests that engineered exosomes may be an effective therapy for patients with hypercholesterolemia.

ENGINEERED EXOSOMES AND INSULIN RESISTANCE

Insulin resistance is now believed to play a key role in the onset and progression of NAFLD[12]. A HFD reduces insulin sensitivity. Kumar *et al*[13] found that feeding a HFD changed the lipid composition of intestinal exosomes. These exosomes were found to be absorbed by macrophages and hepatocytes, resulting in inhibition of the insulin signalling pathway. Castaño *et al*[14] found that obesity can alter the

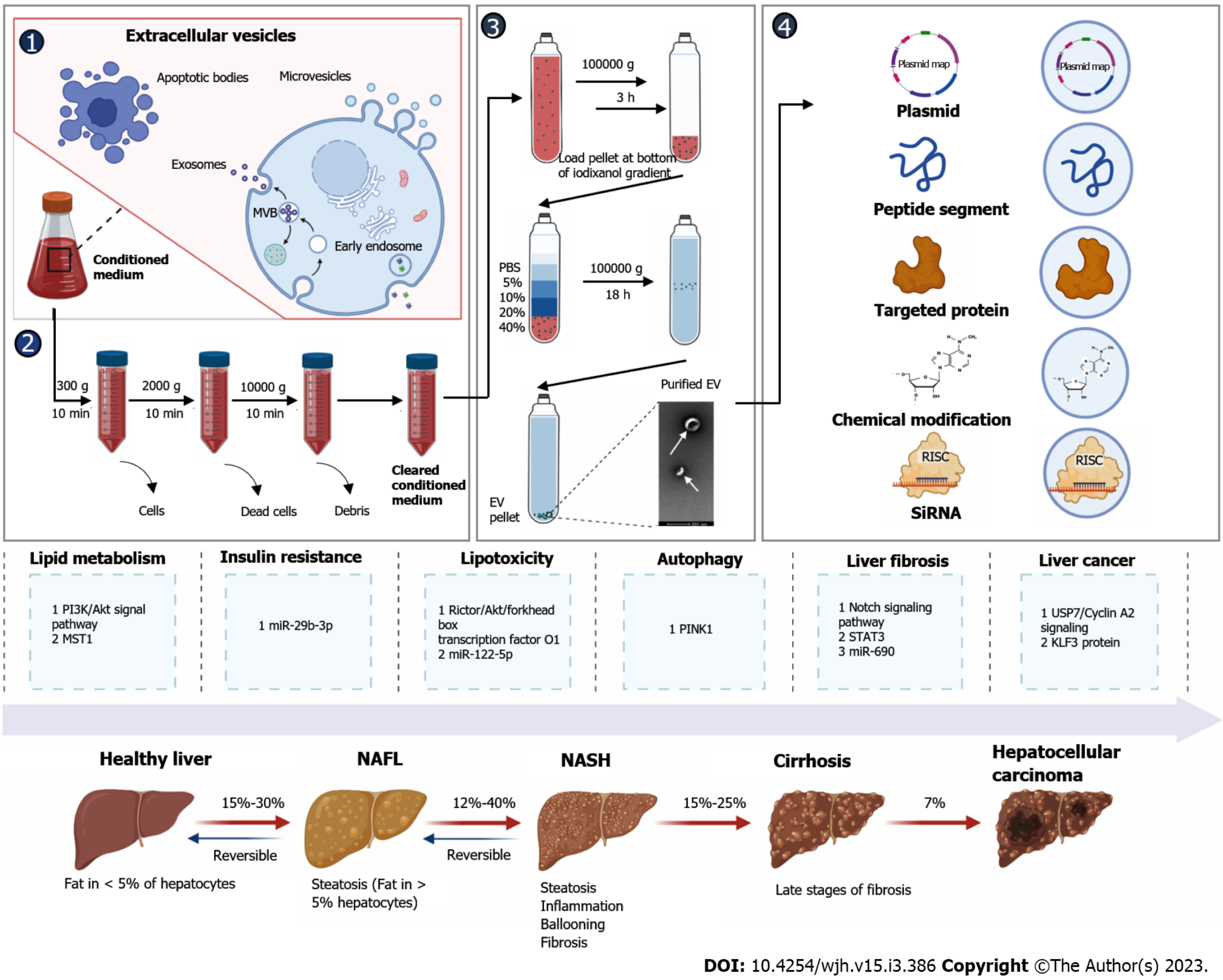

Figure 1 Diagram shows the correlation between nonalcoholic fatty liver disease and engineered exosome. MVB: Multivesicular body; EV: Extracellular vesicles; NASH: Nonalcoholic steatohepatitis; NAFL: Nonalcoholic fatty liver; STAT3: Signal transducer and activator of transcription 3; RISC: RNA-induced silencing complex; MST1: Mammalian STE20-like kinase 1; USP7: Ubiquitin specific peptidase 7; KLF3: Kruppel-like factor 3; PINK: PETN induced kinase 1; PI3K: Phosphatidylinositol-4,5-Bisphosphate 3-Kinase; Akt: Protein kinase B.

expression and composition of miRNAs in mouse plasma exosomes. Ying *et al*[15] found that miR-690, an exosome-derived miRNA from M2-polarized macrophages, improved insulin sensitivity in obese mice. Su *et al*[16] found that exosomes derived from the bone marrow mesenchymal stem cells (BM-MSCs) of aged mice could be ingested by fat, muscle and liver cells, leading to insulin resistance *in vivo* and *in vitro*. The authors found that the amount of miR-29b-3p in exosomes released by BM-MSCs was significantly increased in aged mice. Furthermore, they found that inhibition of miR-29b-3p with an aptamer-mediated nanocomposite delivery system improved insulin resistance in aged mice.

ENGINEERED EXOSOMES AND LIPOTOXICITY

Lipotoxicity promotes proinflammatory M1 polarization of liver macrophages during the development of NAFLD[17,18]. Liu *et al*[19] found that miR-192-5p-rich hepatocyte-exosomes induced by lipotoxic injury promoted macrophage M1 polarization and liver inflammation through Rictor/Akt/forkhead box transcription factor O1 signalling. Zhao *et al*[20] found that cholesterol-induced lysosomal dysfunction increased exosome release from hepatocytes, leading to M1 polarization and macrophage-induced inflammation in a miR-122-5p-dependent manner. Human umbilical cord mesenchymal stem cells (HUC-MSCs) are increasingly being studied in clinical trials of end-stage liver disease due to their excellent tissue repair and anti-inflammatory effects. Shi *et al*[21] found that HUC-MSC-derived exosomes could protect against methionine- and choline-deficient L-amino acid diet (MCD)-induced NASH.

Lipotoxicity can damage mitochondria and induce oxidative stress during the progression of NAFLD [22,23]. Studies have shown that adipocytes respond to mitochondrial stress by rapidly and vigorously releasing exosomes[24]. Similarly, exosomes derived from chemically induced human hepatic progenitors inhibit cell death induced by oxidative stress[25].

ENGINEERED EXOSOMES AND AUTOPHAGY

Autophagy is a process in which cells degrade and metabolize their own damaged organelles or protein aggregates that plays a key role in maintaining liver homeostasis[26]. Increasing evidence suggests that autophagy plays a very important role in lipid metabolism. Autophagy mainly protects cells and regulates inflammation in NAFLD[26]. Because autophagy and exosomal biogenesis share common elements, some studies have found that plasma exosomal levels are higher in NAFLD patients than in healthy controls[27]. Luo *et al*[28] found that miR-27a inhibited mitochondrial autophagy and promoted NAFLD-associated liver fibrosis by negatively regulating PINK1 expression *via* lipotoxic hepatocyte exosomes. A research team established a model of hepatocyte injury and apoptosis induced by D-galactosamine and lipopolysaccharide (D-GalN/LPS) to study the protective effect of bone marrow mesenchymal stem cell (BMSC)-derived exosomes on liver injury. They found that BMSC-derived exosomes attenuated D-GaIN/LPS-induced hepatocyte apoptosis by activating autophagy *in vitro*[29]. Similar studies have shown that upregulation of miR-96-5p in BMSCs and their exosomes ameliorated NASH *via* caspase-2[30].

ENGINEERED EXOSOMES AND LIVER FIBROSIS

It is generally believed that during the development of NAFLD, liver-related cells are replaced by fibrotic scar tissue, giving rise to liver fibrosis or cirrhosis, which are associated with poor prognosis and mortality in patients with NASH[2]. The Notch signalling pathway is a key mediator of cellular differentiation, proliferation and apoptosis[31]. We designed hairpin-type decoy oligodeoxynucleotides (ODNs) for RBP-J to inhibit the activation of Notch signalling. ODNs were loaded into HEK293T-derived exosomes by electroporation. Furthermore, we observed that tail vein-injected exosomes were mainly taken up by hepatic macrophages in mice with hepatic fibrosis. RBP-J decoy ODNs delivered by exosomes efficiently inhibited Notch signalling in macrophages and ameliorated liver fibrosis in mice [32].

Hou *et al*[33] found that myeloid cell-specific IL-6 signalling promoted miR-223-enriched exosome production and attenuated NAFLD-associated fibrosis. Tang *et al*[34] found that exosomes embedded with siRNAs or antisense oligonucleotides targeting signal transducer and activator of transcription 3 (STAT3) could attenuate liver fibrosis. Gao *et al*[35] showed that Kupffer cells produced endogenous miR-690 and shuttled this miRNA to other hepatocytes through exosomal secretion. Treatment with miR-690 inhibitors reduced fibrosis and steatosis in a NASH model. Wang *et al*[36] found that miR-6766-3p-rich 3D human embryonic stem cell (hESC) exosomes could ameliorate liver fibrosis by targeting the TGFβ RII-SMADS pathway in hepatic stellate cells. Ji *et al*[37] developed an exosome-liposome hybrid loaded with clodronate-nintedanib that impaired hepatic fibrosis by reducing the activation of Kupffer cells.

CRISPR-Cas9 gene editing has become a powerful therapeutic technology. However, there is a lack of safe and effective *in vivo* delivery systems for CRISPR-Cas9, especially for tissue-specific vectors[38]. Luo *et al*[39] used exosome-mediated CRISPR/dCas9-VP64 delivery to reprogram hepatic stellate cells to construct engineered exosomes for the treatment of liver fibrosis. Similarly, Wan *et al*[40] delivered exosome-mediated Cas9 ribonucleoprotein complexes for tissue-specific gene therapy in liver disease.

ENGINEERED EXOSOMES AND LIVER CANCER

Without timely intervention, NAFLD inevitably results in liver cancer[41]. Liver cancer is the fourth leading cause of cancer-related death worldwide and occurs in patients with various chronic liver diseases[42]. To date, the exact pathogenesis of NAFLD-induced liver cancer is not fully understood, but may involve DNA damage responses, inflammation, autophagy, and disruption of the gut microbiota [41].

Adipose tissue is known to play a role in energy storage and metabolic regulation by secreting adipokines[43]. Studies have demonstrated that exosomal circRNA secreted by adipocytes promotes tumour growth by inhibiting miR-34a and activating the USP7/Cyclin A2 signalling pathway[44].

An acidic microenvironment has been shown to promote the release of exosomes, which are considered to be cell-to-cell communication agents involved in cancer progression and metastasis[45]. Tian *et al*[46] found that exosomal miR-21 and miR-10b induced by the acidic microenvironment in liver cancer could promote cancer cell proliferation and metastasis and be used as prognostic molecular markers and therapeutic targets for liver cancer.

Macrophage-derived exosomes play multiple roles in cancer initiation and progression[47]. Zhang *et al*[48] found that exosomes derived from RBP-J overexpressing macrophages inhibited the progression of liver cancer by miR-499b-5p/JAM3. M2 macrophages can influence tumour development by secreting various cytokines, including exosomes. Some studies suggest that M2 macrophage-derived exosomes modified by miR-660-5p-related oligonucleotides enhanced the development of hepatocellular carcinoma by regulating KLF3[49].

ENGINEERED EXOSOMES INVOLVED IN THE DIAGNOSIS OF NAFLD

Exosomes can be derived from healthy and stressed cells to provide a snapshot of the cell of origin under physiological and pathological conditions. Hepatocyte-derived exosomes released from stressed/injured hepatocytes have been identified as a partial cause of liver disease progression and liver injury, so circulating exosomes may serve as biomarkers of NAFLD. Nanopasmon-enhanced scattering of gold nanoparticles coupled with hepatocyte-specific antibodies was used to identify hepatocyte-derived exosomes[50]. Furthermore, microarray analysis of exosomal miRNAs isolated from the serum of 41 patients with NAFLD (diagnosed using liver biopsy) suggested that serum exosomal miRNAs could be used to assess the severity of NAFLD and identify potential targets for NAFLD treatment[33]. One of the determinants of liver degeneration in the progression of NAFLD is Wnt/frizzled (FZD) signalling; for example, FZD7 delivered by plasma-derived exosomes is a good candidate for a novel and effective biomarker for the diagnosis and prognosis of NAFLD[51].

CONCLUSION

The incidence of NAFLD is rapidly increasing with changes in lifestyle and dietary habits[1]. Exosomes not only mediate communication between cells but can also be engineered to deliver specific substances. Engineered exosomes have shown some effects on NAFLD in animal experiments. Owing to their low immunogenicity and liver targeting[52,53], engineered exosomes have great potential to treat NAFLD.

FOOTNOTES

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