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The Role of Exosomal miRNAs in Regulating Lipid Metabolism in Obesity-Associated Hyperlipidemia

Nambi Namusisi H.

School of Natural and Applied Sciences Kampala International University Uganda

ABSTRACT

Obesity-associated hyperlipidemia is a major risk factor for cardiovascular diseases, metabolic syndrome, and other complications. The dysregulation of lipid metabolism in obesity is driven by a complex network of molecular and cellular mechanisms. Among these, exosomal microRNAs (miRNAs) have emerged as key regulators in the communication between adipose tissue, the liver, and other metabolic organs. Exosomes, small vesicles secreted by various cell types, contain miRNAs that can modulate gene expression in recipient cells, thereby influencing lipid metabolism. This review explores the role of exosomal miRNAs in obesity-associated hyperlipidemia, focusing on their mechanisms of action, regulatory functions, and potential therapeutic implications. We highlight specific exosomal miRNAs involved in lipid metabolism pathways, their role in adipogenesis, lipogenesis, and lipid storage, as well as their impact on systemic lipid homeostasis. Additionally, we discuss the potential of targeting exosomal miRNAs as a novel therapeutic approach for managing hyperlipidemia and obesity-related metabolic disorders.

Keywords: exosomal miRNAs, lipid metabolism, obesity, hyperlipidemia, adipogenesis, lipogenesis, therapeutic targeting

INTRODUCTION

Obesity is a global epidemic and a significant contributor to metabolic diseases, including hyperlipidemia, insulin resistance, and cardiovascular disorders[1–3]. Hyperlipidemia, characterized by elevated levels of circulating lipids, is one of the primary metabolic complications of obesity and a major risk factor for atherosclerosis and cardiovascular disease (CVD)[4–7]. The dysregulation of lipid metabolism in obesity involves various molecular and cellular pathways, including hormonal changes, adipokine dysregulation, and inflammation. Recent research has unveiled a novel regulatory mechanism through exosomal microRNAs (miRNAs), which have emerged as critical modulators of lipid metabolism[8, 9].

Exosomes are extracellular vesicles (30-150 nm) released by various cell types, including adipocytes, hepatocytes, and endothelial cells[10, 11]. These vesicles contain diverse cargo, such as proteins, lipids, and miRNAs, and act as mediators of intercellular communication. Exosomal miRNAs can influence gene expression in target cells by binding to messenger RNAs (mRNAs), thereby affecting various biological processes, including lipid metabolism[12]. This review looks into the role of exosomal miRNAs in regulating lipid metabolism in obesity-associated hyperlipidemia, providing insights into their mechanisms of action and potential therapeutic targets.

Exosomal miRNAs: Biogenesis and Function

Exosomes are formed through the endosomal pathway, where multivesicular bodies (MVBs) containing intraluminal vesicles (ILVs) fuse with the plasma membrane to release exosomes into the extracellular space[13, 14]. miRNAs, short non-coding RNA molecules, are selectively packaged into exosomes and are involved in post-transcriptional gene regulation. Upon uptake by recipient cells, exosomal miRNAs can alter gene expression by promoting mRNA degradation or inhibiting translation, thereby influencing cellular functions [15, 16]. The selective packaging of miRNAs into exosomes is not random but is regulated by specific RNA-binding proteins such as heterogeneous nuclear ribonucleoprotein A2B1 (hnRNPA2B1) and the miRNA-sorting motif. This selective sorting enables exosomal miRNAs to play a significant role in intercellular communication, particularly in metabolic regulation. Exosomal miRNAs derived from adipose tissue, liver, and skeletal muscle have been shown to modulate lipid metabolism in various target cells, including hepatocytes and endothelial cells[17].

Exosomal miRNAs and Lipid Metabolism in Obesity-Associated Hyperlipidemia

Adipogenesis and Lipid Storage

Obesity is characterized by excessive lipid accumulation in adipose tissue due to increased adipogenesis and lipid storage. Exosomal miRNAs play a crucial role in regulating these processes. For instance, exosomal miR-27a has been shown to inhibit adipogenesis by targeting peroxisome proliferator-activated receptor gamma (PPARγ), a master regulator of adipocyte differentiation[18]. Conversely, exosomal miR-130b promotes lipid accumulation by targeting PPARγ coactivator 1 alpha (PGC-1α), thereby enhancing lipogenesis. These miRNAs are secreted by adipocytes and can influence lipid storage in neighboring or distant cells, contributing to systemic lipid dysregulation in obesity.

Hepatic Lipid Metabolism

The liver plays a central role in lipid homeostasis, including fatty acid oxidation, lipogenesis, and cholesterol metabolism[19]. In obesity, hepatic lipid metabolism is often dysregulated, leading to conditions such as non-alcoholic fatty liver disease (NAFLD). Exosomal miRNAs, particularly those derived from adipose tissue, can modulate hepatic lipid metabolism. For example, exosomal miR-122, highly expressed in the liver, regulates cholesterol biosynthesis and fatty acid metabolism by targeting genes such as sterol regulatory element-binding protein 1c (SREBP-1c) and fatty acid synthase (FASN). Dysregulation of exosomal miR-122 has been linked to hyperlipidemia and hepatic steatosis in obesity[20, 21].

Hepatic lipid metabolism is a complex process that regulates the synthesis, breakdown, and storage of lipids in the liver. It plays a crucial role in maintaining whole-body lipid homeostasis and energy balance, as lipids serve as a major energy source.[22] Key aspects of hepatic lipid metabolism include lipid uptake, denovo lipogenesis (DNL), beta-oxidation, triglyceride synthesis, VLDL secretion, cholesterol metabolism, and regulation of lipid metabolism. Lipid uptake involves the liver taking up circulating lipids, primarily free fatty acids (FFAs), from the blood, which are either derived from the diet or released from adipose tissue during lipolysis. Denovo lipogenesis (DNL) is the liver's ability to synthesize fatty acids from non-lipid precursors like glucose, regulated by enzymes like acetyl-CoA carboxylase (ACC) and fatty acid synthase (FAS). DNL is stimulated by insulin and is often upregulated in conditions like hyperinsulinemia and obesity[22].

Fatty acid oxidation is the breakdown of fatty acids in hepatocyte mitochondria through beta-oxidation, generating ATP and ketone bodies[23]. This process is tightly regulated by hormonal signals, with glucagon and catecholamines stimulating oxidation during fasting and insulin inhibiting it during the fed state. Triglyceride synthesis involves esterifying fatty acids with glycerol to form triglycerides, which can be stored in the liver or packaged into very low-density lipoproteins (VLDL) for export. Dysregulation in VLDL secretion can contribute to hyperlipidemia and atherosclerosis. Cholesterol metabolism is regulated by the mevalonate pathway, which can be used for bile acid production or incorporated into lipoproteins for export. Imbalances in hepatic lipid metabolism are linked to various metabolic disorders, including NAFLD, metabolic syndrome, obesity, type 2 diabetes, and cardiovascular disease. Understanding the intricate balance of hepatic lipid metabolism is essential for developing therapies to treat metabolic diseases associated with dysregulated lipid metabolism.

Lipolysis and Fatty Acid Oxidation

Lipolysis and fatty acid oxidation are crucial metabolic processes involved in energy production from stored fat. Lipolysis is the breakdown of triglycerides into free fatty acids (FFAs) and glycerol, primarily in adipose tissue[24]. Hormonal signals, particularly catecholamines, activate lipases such as hormone-sensitive lipase (HSL) and adipose triglyceride lipase (ATGL), which are then transported to various tissues for energy production. Lipolysis involves hormone activation, which stimulates cyclic AMP production, which activates protein kinase A (PKA). Lipases like HSL and ATGL are then activated, and triglycerides are broken down into FFAs and glycerol. FFAs are then released into the bloodstream and transported by albumin to tissues like the liver and muscle for energy use[25]. Fatty acid oxidation, or beta-oxidation, occurs primarily in the mitochondria of cells and involves the breakdown of FFAs to generate energy in the form of ATP[25]. This process produces acetyl-CoA, which enters the citric acid cycle for further energy production. Regulation of lipolysis and fatty acid oxidation is crucial for maintaining energy homeostasis, particularly during periods of low carbohydrate availability or increased energy demand. Insulin inhibits lipolysis, while catecholamines and glucagon promote it. Fatty acid oxidation is upregulated during fasting, exercise, and low carbohydrate intake, where the body requires alternative energy sources.

Therapeutic Potential of Targeting Exosomal miRNAs

Given their role in regulating lipid metabolism, exosomal miRNAs represent promising therapeutic targets for managing obesity-associated hyperlipidemia. Strategies to modulate exosomal miRNA levels include the use of miRNA mimics, antagomirs (miRNA inhibitors), and exosome-based delivery systems. For instance, targeting exosomal miR-122 with antagomirs has shown potential in reducing hepatic lipid accumulation and improving lipid profiles in obese individuals.[26] Similarly, miR-27a inhibitors could enhance adipogenesis and improve lipid storage capacity, alleviating systemic hyperlipidemia. Exosome-based therapies also offer the advantage of targeted delivery, as exosomes can be engineered to carry specific miRNAs to desired tissues. This precision in targeting could minimize off-target effects and improve the therapeutic efficacy of miRNA-based treatments.

CONCLUSION

Exosomal miRNAs play a pivotal role in regulating lipid metabolism in obesity-associated hyperlipidemia. By modulating adipogenesis, lipogenesis, and lipid storage, these miRNAs contribute to the dysregulation of lipid homeostasis in obesity. Understanding the mechanisms by which exosomal miRNAs influence lipid metabolism offers new insights into the pathophysiology of hyperlipidemia and opens up novel avenues for therapeutic intervention. Future research should focus on elucidating the full spectrum of exosomal miRNAs involved in lipid metabolism and developing targeted miRNA-based therapies for the management of obesity-related metabolic disorders.

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