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MicroRNAs and Lipid Metabolism

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Abstract: Lipid metabolism is closely related to the occurrence and development of various diseases, and microRNAs, as important post-transcriptional regulatory factors, are involved in various biological processes of adipocyte differentiation and lipid metabolism to regulate lipid metabolism. In this paper, the effects of miRNAs on adipocyte differentiation, lipid synthesis, decomposition and transport reported in recent years are reviewed, with the hope of promoting the mechanism of microRNA in lipid metabolism disorders.

Key words: Lipid, Metabolism, MiRNAs

Introduction

Lipid metabolism is one of the three major metabolisms of the body, which is of great significance for the maintenance of energy, physiological function and regulation of the body. The regulatory process of lipid metabolism is mainly related to the formation and differentiation of adipocytes, lipid synthesis, decomposition and transport. MicroRNAs (miRNAs for short) are endogenous, highly conserved single-stranded non-coding RNAs with a size of about 18-25 nucleotides. Since the discovery of miRNAs[1], their relationship with diseases has attracted increasing attention. Up to now, miRNAs have been proved to be involved in many complex physiological processes in organisms, such as lipid metabolism. Oxidative stress. Current studies have found that miRNAs are closely related to various processes of lipid metabolism.

1.MiRNA and adipocyte differentiation

At present, it is generally believed that adipocytes are gradually differentiated from mesenchymalstem cells (MSC) from the mesoderm, through APC, preadipocytes, immature adipocytes, and finally mature adipocytes.Many studies have shown that adipocyte differentiation regulates lipid metabolism,and microRNAs[2] seem to play an important role in adipocyte differentiation.

Asha [3] reported the role of miR-26 family (miR-26a-1, miR-26a-2 and miR-26b) in regulating the differentiation of adipocytes into new adipocytes and adipose tissue quality. In vivo experiments, mice were deletions of all miR-26 coding sites in vivo, resulting in significant dilation of adipose tissue in adult animals fed a normal diet. In contrast, overexpression of miR-26a in mice protected the mice from high-fat diet-induced obesity.

Xu[4] found that miRNA-16-5p was significantly up-regulated during the differentiation of 3T3-L1 preadipocytes to mature adipocytes, and the overexpression of miRNA-16-5p led to the promotion of mature adipocyte-specific gene expression and fat droplet accumulation in vitro and in vivo.EPT1 was also identified as the target gene of miRNA-16-5p.Martinelli[5] showed that miR-519d specifically and in a dose-dependent manner inhibited the translation of PPARA protein and increased lipid accumulation during preadipocyte differentiation. The 30-UTR of PPARA contains a putative miRNA binding site that has been shown to bind specifically to miR-519d.

Zhang [5] pointed out that miRNA-200a plays an important role in promoting adipocyte differentiation in yaks in their study on the relationship between miRNAs and adipocyte differentiation in domesticated yaks, and miRNA-200a

can also lead to lipid accumulation in transfection adipocytes. The results also showed that miR-200a increased the expression of adipocyte-specific genes such as PPARγ, ELVOL and C/EBPα.

2. MiRNAs and lipid synthesis

Lipid mainly includes fats, sterols and lipids, while fats refer to triglycerides, which are synthesized by a molecule of glycerol and three molecules of fatty acids. Triglycerides account for the vast majority of human lipids. Triglyceride molecules represent the main form of storage and transport of fatty acids in cells and plasma. Liver [6] is the central organ of fatty acid synthesis. Fatty acids accumulate in the liver through uptake by liver cells from plasma and de novo biosynthesis.

MiR-122 is not only the first known miRNA to regulate lipid metabolism, but also a tissue-specific miRNA. Systemic or liver miR-122 deletion showed significant reductions in serum total cholesterol and triglyceride levels. Anti-miR-122 therapy resulted in a significant reduction in K-circulating cholesterol levels (25%-30%), suggesting that miR-122 may directly regulate cholesterol synthesis [7]. Chofit Chai [8] analyzed the activity of miR122 promoter, and verified its target mRNA by using luciferase reporter gene, and verified human AGPAT1 and DGAT1 mRNAs involved in triglyceride synthesis as miR-122 targets. Interestingly, miR-370 also affects lipid synthesis and has similar effects to miR-122. However, unlike miR-122, which directly regulates cholesterol synthesis, miR-370 plays a role mainly by modifying the expression of miR-122.In addition, miR-33a has also been proved to regulate cholesterol synthesis through targeting relationships [9].

Stearyl coenzyme A desaturase 1 (SCD-1) is A delta-9 fatty acid desaturase that catalyzed the synthesis of monounsaturated fatty acids [10].Cheng[11] verified the targeting of SCD-1 and miR-125b by bioinformatics analysis and dual luciferase method, and demonstrated the relationship between the targeting relationship of the two and lipid metabolism in vivo and in vitro. Overexpression of miR-125b decreased lipid droplets and triglyceride concentration accumulation, and inhibited SCD-1 protein expression and MUFA composition. The miR-125b inhibitor had the opposite effect. Small interfering RNAs tested in adipocytes further demonstrated a direct correlation between miR-125b and SCD-1.Himanshi Bhatia[12] showed that miR-107 inhibits fatty acid synthase FASN level by binding to its 3'UTR, and this interaction promoted ER stress induction and lipid accumulation in HepG2 cells and primary liver cells.

LXR activates and induces the expression of adipogenic genes, thereby promoting hepatic steatosis and steatohepatitis. After RNA-seq, mass spectrometry and bioinformatics analysis, Lei Fan[13] explored the relationship between miR-552-3p and lipid metabolism through in vivo experiments, and the results showed that miR-552-3p in the nucleus could regulate the transcriptional activity of LXRα and regulate lipid metabolism by binding to the complementary sequence of AGGTCA. Zhong[14] also found that miR-1/miR-206 has a similar regulatory relationship with LXRα

3. MiRNA and lipid decomposition

Lipid decomposition refers to the oxidative decomposition of fatty acids, cholesterol and triglycerides in the body [15].Catabolism of triglycerides, also known as fat mobilization, refers to the breakdown of triglycerides into fatty acids and glycerol under the action of hormone-sensitive triglyceride lipases in adipocytes and their release into the blood for oxidation by other tissues. Oxidative decomposition of fatty acids [16] refers to the β-oxidation of various fatty acids in mitochondria directly or after oxidation. In addition, fatty acids can be eliminated by secreting them into plasma via very low-density lipoprotein (LDL), which is rich in triglycerides. The main metabolic way of cholesterol in the body is to produce bile acid through oxidation in the liver [17], which is excreted with bile, and the daily excretion accounts for about 40%-50% of cholesterol synthesis.

MiR-378/378* is highly expressed during adipogenesis. Zhang[18] found that miR-378 significantly increased in fatty liver of diet-obese mice and human hepatocellular carcinoma HepG2 cells with accumulated lipids. Further studies identified NRF1 (nuclear receptor factor 1) as a key regulator of fatty acid oxidation (FAO) and as a direct target of

miR-378.and its ASO (antisense oligonucleotide) knockdown of miR-378 improved FAO and reduced intracellular lipid content in HEPA1-6 cells.

Mattis [19] found that after injecting miR-29a antisense oligonucleotide in mice, triglyceride accumulation in liver increased, and after being treated with LPL antisense oligonucleotide, triglyceride accumulation decreased, suggesting that miR-29a may reduce triglyceride accumulation by inhibiting LPL. After miR-29a was inhibited, the expression levels of LPLmRNA and protein were significantly increased, and the accumulation of triglyceride and cholesterol were significantly increased, suggesting the relationship between the binding of miR-29a and LPLmRNA and lipid decomposition in fatty liver mice. It is worth mentioning that Yang[20] found that miR-29b homologous to miR-29a also has a similar effect in binding to LPL targeting.

MiR-122 is not only involved in the synthesis of cholesterol in liver, but also closely related to the oxidative decomposition of fatty acids. Inhibition of miR-122 expression could enhance the activity of PMVK, increase the β-oxidation of fatty acids and promote the decomposition of fatty acids. Gatfield [21] indicated that miR-122 can directly act on peroxisomal proliferator-activated receptor genes, which can be activated by fatty acids and exogenous peroxisomal proliferators to regulate the expression of enzymes involved in fatty acid decomposition and participate in fatty acid metabolism. After knockout of miR-122, PPARβ protein level was significantly increased and fatty acid content was decreased. Similarly, miR-30b [22] has also been proved to be involved in lipid decomposition and also acts on peroxisome proliferator-activated receptor genes.

4. MiRNAs and lipid transfer

Microsomal triglyceride transfer protein (MTP) was first identified as an endoplasmic reticulum (ER) resident protein that helps transfer neutral lipids to neonatal apolipoprotein B(ApoB)[34-36].ApoB-containing lipoproteins are macromolecular lipids and protein micelles that can be used as specialized transport vehicles for hydrophobic lipids.The secretion of lipoprotein into circulation is conducive to reducing lipid accumulation in tissues or organs [23].

Zhang [24] observed that the overexpression of miR-130b in HepG2 cells significantly enhanced the secretion of very low-density lipoprotein (VLDL) particles, enhanced glycerol metabolism-labeled triglyceride (TG), respectively. The over- expression of miR-130b significantly increased the mRNA and protein expression levels of microsomal triglyceride transfer protein (MTP). These results suggest that miR-130b has a potential role in promoting hepatic VLDL assembly and secretion by significantly stimulating MTP expression and TG mobilization.

Ma[25] verified the targeting relationship between microRNA-101-2-5p and ApoB by database target prediction and dual luciferase reporter gene, and analyzed the effect of miRNA on the expression of ApoB in 17β-estradiol-stimulated chicken embryo hepatocytes. Bioinformatics algorithm showed that there were two potential binding sites of miR-548p on human ApoB mRNA, and Zhou[26] cotransfected with miR-548p,After a series of verifications such as site-directed mutagenesis, it was also confirmed that miR-548p interacted with the 3' -untranslated region of human ApoB mRNA to enhance transcription. James Soh[27.28] demonstrated that miR-30c regulates the assembly and secretion of ApoB lipoproteins by regulating MTP activity, and this regulation requires interactions between miR-30c and MTP genes, including seed and complementary sequences [29].However, it is worth mentioning that other members of the miR-30 family are not targeted at MTP because they do not form the same complementary interactions.

Adenosine triphosphate binding box transporter A1(ABCA1) is a key transporter for cholesterol reversal. Bioinformatics analysis of the target ABCA1-3'UTR was conducted to search for conserved miRNAs, and it was found that miR-106b [30] could target ABCA1 binding. Moreover, in neural cell lines, miR-106b can reduce cholesterol flow to apoAI under both physiological and LXR stimulation. In addition, Zhisheng Wang et al. [31] detected 9 candidate differential miRNAs in plasma exosomes of 42 patients with coronary atherosclerosis, and found higher expression of miR-30e and miR-92a in the patients. After bioinformatics analysis and confirmation, It was proved that ATP binding box (ABC)A1 was the direct target of miR-30e and miR-92a, and miR-30e was negatively correlated with ABCA1 or cholesterol content.

5. Summary

In general, the regulation of lipid metabolism by miRNAs is a complex network regulation process, with overlapping targeting sites among different miRNAs, and related mechanisms of action involve the synthesis, metabolism and transformation of lipids such as cholesterol, triglyceride and fatty acids. The regulation of miRNAs on lipid metabolism is no single, but multi-directional. A miRNA has several target genes, and a gene may be regulated by multiple miRNAs simultaneously. MiRNAs constitute an extremely complex regulatory network in vivo, and these phenomena can reduce the importance of specific miRNAs in normal cell homeostasis. From the perspective of evolution, miRNA plays a role in regulating gene mutation during evolution, and its main role may be to "fine-tune" gene expression. However, even though miRNA has limited effect on many target mRNAs, the superposition of regulatory factors of the same biological process can result in enhanced expression of a phenotype. The complexity of miRNAs not only adds another layer of complexity to the molecular causes of modern human disease, but also opens up the possibility of miRNA-based treatment of disease.

There is no doubt about the role of miRNA in lipid metabolism. With the in-depth study of miRNAs, their regulation of lipid metabolism has been gradually revealed. At the same time, more and more miRNAs involved in the regulation of lipid metabolism pathway will be discovered. It provides a new idea for the treatment and prevention of many diseases.

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