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New Findings on Regulation of Lipid Metabolism by HuR

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Abstract

Lipid metabolism is a vital physiological process that includes the biosynthesis, absorption, transport, and elimination of lipids, playing an essential role in maintaining health and preventing obesity-related diseases. Recent findings highlighted the significance of Human antigen R (HuR), an RNA-binding protein, in regulating intestinal fat absorption and lipid homeostasis. The absence of HuR could lead to decreased expression of these enzymes, resulting in impaired dietary fat absorption and reduced risk of high-fat diet-induced Non-Alcoholic Fatty Liver Disease (NAFLD) and obesity. Additionally, HuR influenced the expression of other lipid metabolism-related genes, suggesting its broader role in lipid regulation. In this review, we discussed the mechanisms by which HuR modulates the expression of key enzymes involved in Triacylglycerol (TAG) synthesis, specifically *MGAT2* and *DGAT2*, in the intestinal epithelium, and emphasized the potential of HuR as a therapeutic target for obesity and related metabolic disorders, as well as its dual role in atherosclerosis progression.

Keywords: HuR; Lipid metabolism; Obesity; NAFLD; Triacylglycerol synthesis

Introduction

Lipid metabolism is a complex physiological and biochemical process that encompasses lipid biosynthesis, absorption, transport, and elimination, proper lipid metabolism is essential for maintaining overall health and well-being. Among these processes, intestinal lipid absorption plays an important role in maintaining lipid homeostasis [1]. The regulation of intestinal lipid absorption and its subsequent redistribution to peripheral tissues is a key defense mechanism against obesity and related pathologies [2]. The absorption process of Triacylglycerols (TAGs), the major dietary lipids, involves hydrolysis to fatty acids and Monoacylglycerols (MAGs) in the intestinal lumen, lipid uptake by intestinal cells, and re-synthesis of TAGs. In the intestine, MAG is the preferred receptor for FFAs, and TAG resynthesis occurs mainly through the MAG pathway [3]. In the MAG pathway, the high intestinal expression of *MGAT2* and *DGAT2* isoforms, which correspond to Monoacylglycerol Acyltransferases (MGATs) and Diacylglycerol Acyltransferases (DGATs), is important for regulating dietary fat absorption and related processes. Alterations in the expression or regulation of these TAG synthases can disrupt dietary fat absorption and increase susceptibility to lipid metabolism-related diseases [4,5]. Previous studies on *MGAT2* and *DGAT2* have focused on the transcriptional level, with key transcription factors including Sterol Regulatory Element Binding Protein 1C (SREBP-1c) and Peroxisome Proliferator-Activated Receptor-g (PPARg) [3]. Integration of transcriptional and post-transcriptional data indicates that many essential genes are highly regulated at the post-transcriptional level. However, the post-transcriptional regulation of TAG synthases remains largely unexplored. RNA-Binding Proteins (RBPs), a key class of post-transcriptional gene regulators, primarily function by binding to and modulating target transcripts, forming what are known as 'regulatory' functional units [6]. 'Human antigen R' (HuR), also known as Embryonic Lethal Anomalous Visual-Like 1 (ELAVL1), is a key member of the Hu/ELAV RNA-Binding Protein (RBP) family. It binds to Adenosine-Uridine (AU)-rich regions of target RNAs and regulates various aspects of RNA metabolism, including nuclear mRNA export, mRNA stabilization, and translation. Through these mechanisms, HuR influences critical cellular functions such as proliferation, survival, apoptosis, and senescence. Notably, HuR has been implicated in the regulation of lipid metabolic processes such as hepatic lipid homeostasis and adipose triglyceride storage. However, its role in intestinal fat absorption and the underlying mechanisms remain to be fully elucidated. Recent findings from this study suggest that HuR influences intestinal fat absorption and lipid homeostasis by modulating key enzymes involved in intestinal TAG synthesis, specifically *MGAT2* and *DGAT2*, in mice. In this review, we will provide an overview of HuR's role in the regulation of lipid metabolism.

Literature Review

This study investigated the role of HuR in intestinal fat absorption by creating intestinal epithelium-specific HuR Knockout mice (cKO). It was found that HuR interacts with intron 1 of mouse *MGAT2* pre-mRNA and the 3' UTR of *DGAT2* mRNA, regulating *MGAT2* pre-mRNA processing and *DGAT2* mRNA conversion. Knockdown of

cKO mice significantly decreases intestinal fat absorption. Additionally, these regulatory processes may influence the impact of Caloric Restriction Diets (CRD) on lipid metabolism. Specifically, CRD reduces the protein levels of HuR, *DGAT2*, and *MGAT2* in the proximal jejunum, which may further contribute to improvements in lipid metabolism. Additionally, RNA-seq analysis revealed that HuR knockdown also decreased the mRNA levels of *APOA4*, *AGPAT2*, *APOA1*, *ABCG5*, *ABCG8*, *DGAT1*, and *NPC1L1* genes encoding factors involved in fat digestion and absorption. For instance, *APOA4* is an apolipoprotein secreted by the small intestine during lipid absorption and chylomicron formation. It plays a role in regulating chylomicron composition and metabolism and is closely associated with obesity in both mice and humans [7,8]. ABCG5/G8 transporter proteins, located in the apical membrane of enterocytes, are essential for the intestinal absorption of phytosterols and cholesterol [9]. Additionally, selective inhibition of the intestinal cholesterol transporter NPC1-L1 reduces the production of cholesteryl esters in the intestine and their release into the lymphatic system [10]. Since HuR targets a range of lipid metabolism-related RNAs, it is important to explore whether HuR can also regulate fat absorption by modulating genes beyond *DGAT2* and *MGAT2*.

Discussion

Several studies have found the importance of RNA-Binding Protein (RBP) in regulating the expression of genes related to lipid metabolism at the post-transcriptional level. Research from various groups has demonstrated that HuR is pivotal in controlling lipid metabolic processes beyond fat absorption, including fat formation, lipid transport, and cholesterol homeostasis. For instance, Diana et al., discovered that HuR enhances RNA stability by binding to Insulin-induced gene 1 (*INSIG1*), an insulin-inducible gene that negatively regulates adipogenesis, thereby impairing adipogenesis [11]. HuR promotes the expression of Ndufb6, Uqcrb and Apob by binding to Ndufb6 and Uqcrb mrna as well as Apob precursor mRNAs, thereby regulating hepatic lipid transport and ATP synthesis [12]. Additionally, HuR plays a significant role in managing macrophage lipid homeostasis *in vivo* by directly binding to and modulating the expression of *ABCA1* mRNA, a key regulator of cellular cholesterol efflux and plasma HDL biosynthesis [13]. HuR also plays a role in regulating lipid metabolism in skeletal muscle. Deficiency of HuR in skeletal muscle results in reduced metabolic flexibility and decreased lipid oxidation [14]. Interestingly, lipids themselves can interact with HuR to influence lipid metabolism. For instance, butyric acid can inhibit AMPK activation during chronic intermittent hypoxia, leading to increased cytoplasmic accumulation of HuR. This interaction regulates the expression of downstream genes, promoting apoptosis, inhibiting adipocyte production, and contributing to anti-inflammatory effects [15].

Understanding the regulatory role of HuR in different lipid metabolism is important for studying pathological changes associated with abnormal lipid metabolism. Multiple studies have found that in Non-Alcoholic Fatty Liver Disease (NAFLD), characterized primarily by hepatic steatosis (excessive fat accumulation), HuR can prevent the onset of NAFLD by influencing hepatic lipid metabolism through the regulation of various RNA targets, including the adenylate-uridylate-rich elements of Phosphatase and tensin homolog deleted on chromosome 10 (PTEN) [16,17]. Multi-omics studies, including lipidomics, transcriptomics, and RNA immunoprecipitation sequencing, suggest that HuR orchestrates a protective network for maintaining hepatic metabolic and lipid homeostasis. Consistent with this, HuR-deficient livers exhibit triglyceride accumulation at steady state similar to the triglyceride profile observed in NAFLD livers [18]. Obesity is characterized by Excessive Triglyceride (TG) storage in adipose tissue. HuR regulates adipogenesis and lipid accumulation by modulating RNA stability. Adipose-specific HuR deficiency exacerbates high-fat diet-induced obesity, impairs adipose function, and worsens glucose intolerance and insulin resistance. Consequently, HuR may serve as a promising therapeutic target for alleviating obesity and related metabolic disorders [19]. Dyslipidemia resulting from abnormal lipid metabolism can contribute to the development of Atherosclerosis (AS). Evidence suggests that HuR plays a dual role in AS. On one hand, HuR accelerates AS progression by promoting endothelial activation, smooth muscle proliferation, and inflammation. On the other hand, it has protective effects by reducing macrophage apoptosis, modulating lipid efflux, and enhancing autophagy [20]. Additionally, both HuR and abnormal lipid metabolism are closely linked to aging and cancer, with HuR-mediated regulation of lipid metabolism potentially influencing the processes of aging and carcinogenesis.

Conclusion

HuR plays an essential role in various lipid metabolic processes by mediating the post-transcriptional regulation of lipid metabolism-related target mRNAs. A key finding of this study is that HuR affects intestinal fat absorption and lipid homeostasis by regulating the stability of *DGAT2* mRNA and the splicing of *MGAT2* mRNA, providing new insights into HuR's role in lipid metabolism regulation. This discovery also provides insights for future research on the regulatory role of HuR in *DGAT2* and *MGAT2* outside the intestine and their related functions.

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