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Name of Scholar: RUKSHAR KHAN

Name of Supervisor: Dr. Amit Kumar Verma

Name of Co-Supervisor: Dr. Malabika Datta

Name of Department: Department of Biosciences, JMI

Topic of Research: "Identifying the roles of altered circulatory microRNAs in the deregulated liver physiology during diabetes"

Key Findings

Diabetes mellitus is a chronic metabolic disorder characterized by a complex interplay between reduced insulin production and insulin resistance in various body tissues. The liver act as a central hub to maintain body's metabolism along with the pancreas, skeletal muscles, and adipose tissue, and maintaining overall physiological balance. However, any disruptions in this balance such as insulin resistance as seen in diabetes, obesity, lead to conditions like non-alcoholic fatty liver disease (NAFLD). Recently, microRNAs have emerged as influential regulators of gene expression, impacting various biological processes. Also, circulating miRNAs in the bloodstream have gained attention because they can be transported without degradation, mediating communication between organs and influencing cellular functions. Altered levels of these circulating miRNAs are associated with several diseases like diabetes making them potential therapeutic and diagnostic tools.

One such miRNA, miR-98-5p, has been discovered to be significantly involved in diabetes. Notably, miR-98-5p levels exhibit a downregulation in the circulation during diabetes, hinting its involvement in the disease pathogenesis. We unveil that miR-98-5p exerts its influence by targeting PPP1R15B, a critical protein phosphatase involved in eIF2α dephosphorylation. This interaction promotes an accumulation of phosphorylated eIF2α (p-eIF2α), a pivotal regulator governing selective mRNA translation and global translation repression in response to cellular stress. Given the established role of eIF2α phosphorylation in metabolic control, this miRNA-mediated modulation emerges as a key player in hepatic metabolism. We investigated two chief hepatic hallmarks of diabetes: hepatic lipid accumulation and glucose output. miR-98-5p overexpression in HepG2 cells orchestrated a reduction in the transcript levels of genes associated

with gluconeogenesis and lipogenesis. These changes translated into a substantial decrease in hepatic glucose production and fat deposition in the liver.

Moreover, we investigated for transcriptional control for such reduction in the crucial genes of metabolic pathways. CREB, a transcription factor was found in regulating genes linked to gluconeogenesis and lipogenesis, emerging as a significant regulator using PASTAA tool. While miR-98-5p overexpression didn't cause a significant change in CREB transcript levels, but there was a significant change in its protein levels, suggesting the complexity of miR-98-5p's influence on key regulators of hepatic metabolism. In the presence of miR-98-5p inhibitor alone, the effects were abrogated causing an increase in gluconeogenic and lipogenic genes underscoring the bidirectional control that miRNAs can exert in shaping hepatic processes. Therefore, the miR-98-5p/PPP1R15B axis offers potential therapeutic strategies to address such metabolic disturbances during diabetes and paves the way for new approaches to restore metabolic balance in diabetes. Altogether, our research unveils the exquisite role of miR-98-5p, which acts as a key player in orchestrating the harmony of hepatic metabolism.