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MicroRNA-378 in metabolic inflammatory stress and hepatic insulin resistance

Xiao Cheng, Yongyan Song, Neetu Sud and Qiaozhu Su
University of Nebraska-Lincoln, USA

Statement of the Problem: MicroRNAs (miRNAs) are non-coding RNAs with a length of 19 to 25 nt that are involved in posttranscriptional gene regulation by binding to the 3'-untranslated regions (3'-UTR) of targeted mRNA and impacting diverse cellular processes, including cell differentiation, energy metabolism and chronic inflammation. MicroRNA-378a (miR-378a) has been reported to regulate adipose tissue browning and cancer development. However, its role in cellular stress signaling and hepatic insulin resistance has not yet been investigated. Findings: Here we reported that expression of hepatic miR-378a was upregulated by metabolic inflammatory inducers, such as high fructose feeding, bacterial lipopolysaccharide (LPS) and inflammatory cytokine TNFα. The elevated miR-378a subsequently targeted the 3'-UTR of PPARα which compromised mitochondrial fatty acid β-oxidation and induced mitochondrial and ER stress. miR-378a was further found to directly interact with the dsRNA binding motifs within the dsRNA activated protein kinase PKR and activated the kinase to sustain the inflammatory stress and blunt the insulin signaling in the liver. Genetic depletion of miR-378a rescued hepatocytes from mitochondrial and ER stress, systemic inflammation and insulin resistance induced by fructose and LPS. Conclusion & Significance: This study, for the first time, demonstrates that miR-378a is a mediator in metabolic inflammatory stress and contributes to the onset of insulin resistance. It further unveils that certain miRNA is capable of directly interacting with and activating protein kinase PKR to sustain the stress signaling between mitochondria and ER. This discovery greatly broadens the physiological function of miRNAs by demonstrating that, in addition to target genes on the mRNA level, miRNAs are able to interact with RNA binding protein(s) and directly exert its regulatory effect on the protein levels. Results from this study may provide rationale for using miR-378a as a pharmaceutical target in the prevention and treatment of insulin resistance and related metabolic syndrome.

e: qsu2@unl.edu

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