Abstract

Type 2 diabetes is a complex multifactorial disease triggered by the combination of β-cell dysfunction and insulin resistance of target tissues. Although a huge variety of processes involved in the development of insulin resistance have already been described, the underlying exact molecular mechanisms remain to be elucidated. The novel concept of posttranscriptional gene silencing (PTGS) further extends the complex picture of gene regulation and microRNAs, the key players in PTGS, regulate many important metabolic signaling cascades. Since hepatic insulin resistance is a hallmark feature of type 2 diabetes, this study aimed to elucidate whether dysregulation of hepatic miRNA expression can contribute to the pathogenesis of insulin resistance and thereby lead to the development of type 2 diabetes.

In this study, microRNA miR-143 was identified to be upregulated in livers of obese insulin-resistant mice. To elucidate a possible contribution of miR-143 to the pathogenesis of insulin resistance, a novel mouse model was generated that allows for inducible overexpression of miR-143 predominantly in the liver (miR-143^{DOX} mice). These animals exhibit impaired glucose homeostasis possibly arising from reduced hepatic insulin action through miR-143 mediated inhibition of insulin-stimulated AKT activation. This finding was further approved in a loss-of-function approach, where glucose metabolism of diet–induced obese miR-143-deficient mice was markedly improved. In addition to impaired glucose metabolism, miR-143^{DOX} mice show alteration in hepatic cholesterol and lipid content.

Taken together, the current study identifies miR-143 as a crucial player in hepatic insulin action and cholesterol/lipid metabolism. Further analysis of the metabolic function of miR-143 will contribute to the understanding of the molecular mechanisms underlying obesity and type 2 diabetes and potentially define a novel route for therapeutic intervention.