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## Role of microRNA-206 and microRNA-133b in facilitating insulin signaling and inhibiting lipogenesis

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**Background:** The US obesity epidemic is driving a surge in the incidence of two highly-associated diseases: Non-alcoholic fatty liver disease (NAFLD) and type 2 diabetes (T2D). Insulin resistance is widely considered to be central to the pathogenesis of T2D and NAFLD. However, the phenomenon of selective hepatic insulin resistance, in which hepatic glucose metabolism becomes unresponsive to insulin but hepatic lipogenesis continues unabated, is a long-standing paradox.

**Methods:** A mini-circle vector was used to deliver microRNA-206/133b into livers of dietary obese mice to evaluate their effects on hyperglycemia and NAFLD, and a CRISPR/Cas9 approach were used to study the interaction between microRNA-206/133b and their targets.

**Results:** microRNA-206 and microRNA-133b (miR-206/133b), two miRNAs from the same primary transcript, are two of the most reduced miRNAs in livers of dietary obese mice and NAFLD individuals, and delivery of miR-206/133b into livers of dietary obese mice produced strong therapeutic effects on NAFLD and hyperglycemia. Mechanistically, we identified *Ptpn1* (Protein tyrosine phosphatase non-receptor type 1), *Sp1*, and *Yy1* (Yin Yang 1) as direct targets of miR-206/133b. Of note, *Sp1* is a transcription activator of Srebp1c; *Ptpn1* impairs insulin signaling by de-phosphorylating *Insr* (insulin receptor) but induces *Srepb1c* expression by increasing activity of *Sp1* via PP2A (protein phosphatase 2A)-mediated dephosphorylating of *Sp1*; and *Yy1* is a transcription repressor with elevated expression in insulin-resistant livers. Indeed, liver-specific expression of miR-206/133b facilitated insulin signaling by modulating *Ptpn1*-Inrs/Irs1 axis and reduced Srebp1c-mediated lipogenesis through *Ptpn1*-PP2A-*Sp1*-Srebp1c and *Sp1*-Srebp1c pathways. We further identified *Yy1* as a transcription repressor of miR-206/133b primary transcript. *Yy1* overexpression impaired miR-206/133b biogenesis both *in vivo* and *in vitro*. Through deleting the *Yy1* binding site within the miR-206/133b promoter, we simulated the function of miR-206/133b in facilitating insulin signaling and inhibiting lipogenesis. Together, a negative feedback loop consisting of *Yy1*, miR-206/133b, *Ptpn1*, and *Sp1* controls the pathogenesis of NAFLD and hyperglycemia, once this circuit is activated, it maintains the suppression of miR-206/133b and the activation of *Yy1*, *Ptpn1* and *Sp1*, which subsequently impairs insulin signaling and induces lipogenesis.

**Conclusion:** Our findings will fill the gap in knowledge about the mechanisms of selective hepatic insulin resistance in the pathogenesis of NAFLD and hyperglycemia, which may lead to rational therapeutic strategies for both disorders.

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