

# Relationship of Circulating miRNAs with Insulin Sensitivity and Associated Metabolic Risk Factors (e.g., dyslipidemia and elevated blood pressure) in Humans

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The role of microRNA (miRNA) in the pathophysiology of diabetes and cardiovascular disease has been of emerging interest in recent years. miRNAs are short, noncoding RNA strands (about 22 nucleotides long) that base-pair with mRNA to post-transcriptionally modify gene expression. They are found in all tissues, but recent studies have suggested that they can also be secreted from cells and enter the bloodstream. To better elucidate the relationship between circulating miRNAs and insulin sensitivity, we first used a screening approach to identify candidate miRNAs in nondiabetic, human plasma samples, then individually evaluated each of the miRNAs for association with insulin sensitivity, as measured by clamp. The goal of this study was to identify miRNAs that may be related to human insulin sensitivity and associated Metabolic Syndrome risk factors such as dyslipidemia and elevated blood pressure.

Our study implicated a cluster of miRNA species as having a potential role in human insulin resistance. Plasma levels of miR-16, -107, -150, -33, and -222 were found to be significantly associated with insulin sensitivity. These miRNAs could serve as biomarkers in humans, or more importantly, act as pathophysiological mediators in diseases characterized by insulin resistance. In addition, miR-16 and miR-33 were also associated with Metabolic Syndrome traits. Specifically, miR-16 was found to be related to triglyceride levels, HDL cholesterol, and waist circumference. miR-33 was related to systolic blood pressure.

In conclusion, circulating miR-16, -107, -150, -33, and -222 may have the ability to alter gene expression in target organs to produce systemic insulin resistance. Further, traits that cluster with insulin resistance vary from individual to individual. The relationship between miR-160 and lipids suggest that this microRNA may produce dyslipidemia in the context of insulin resistance and those with elevated miR-33 may be more predisposed to hypertension. Thus, miRNAs may be involved with the interaction between insulin resistance and development of additional traits that characterize cardiometabolic disease.

Given that miRNAs can be transported in blood and delivered to specific tissues where they can impact biological functions, the miRNAs we have identified, or others, may have potential as pharmacological agents that could be introduced into the bloodstream for targeted delivery to metabolically relevant tissues. miRNAs could therefore constitute a novel therapeutic approach for the treatment and prevention of cardiometabolic disease.