LncRNA GAS5 Directed Therapeutic Increases Insulin Receptor Expression in Adipocytes

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JOURNAL ARTICLE

OR01-6 LncRNA GAS5 Directed Therapeutic Increases Insulin Receptor Expression in Adipocytes

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Abstract

Obesity continues to escalate as a significant public health problem and as the leading preventable cause of death. Obesity is a major risk factor for cardiovascular disease and type 2 diabetes. Obese patients with high morbidities are directed towards bariatric surgeries such as Roux-En-Y gastric bypass (RYGB). These procedures not only result in successful weight loss, but also reduce insulin resistance and lead to resolution of type 2 diabetes mellitus independently of BMI reduction. Type 2 Diabetes Mellitus (T2DM) is polygenic in nature and is frequently associated with insulin resistance and impaired insulin signal transduction. Using the oral glucose tolerance tests (IVGTT), the glycosylated hemoglobin (HbA1c) and the homeostasis model assessment of insulin resistance (HOMA-IR), large cohort studies revealed diabetes resolution in 74–83% of patients who underwent Roux-en-Y procedure. While the underlying genetics of T2DM has been extensively studied, the emphasis has been on genes encoding transcripts that are translated to proteins. However, it is becoming increasingly clear that regulatory noncoding transcripts play an important role in disease manifestation. Long noncoding RNAs (lncRNA) are regulatory RNAs >200nt. We previously showed that lncRNA GAS5 decreased significantly in serum of type 2 diabetes mellitus (T2DM) patients. The data here shows that GAS5 levels are low in obese and diabetic patients and are increased post-RYGB in adipose tissue. Adipose tissue is an important endocrine
regulator of energy homeostasis and glucose metabolism. Hence, we sought to decipher the molecular mechanisms underlying the role of GAS5 in T2DM in adipose tissue (AT). We used an unbiased diabetes array to determine the genes affected by knockdown of GAS5 in human AT. Our results show a sharp reduction of insulin receptors A and B with depletion of GAS5. Using CHIP–RIP, we demonstrate that GAS5 binds to promoter of insulin receptor to regulate its expression, and its depletion inhibits glucose uptake and insulin signaling. Towards stabilizing GAS5 levels in adipocytes, a small molecule was identified using OBTC screening strategy. NP–C86 binds to GAS5 with high affinity, increases GAS5 levels and glucose uptake in diabetic patient adipocytes. These results demonstrate that GAS5 plays a pivotal role in resolution of T2DM post RYGB.

**Issue Section:** Adipose Tissue Signaling and Obesity