Basic Science & Translational Research Category
Young Scientist Award

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Adipocyte Long Noncoding RNA Transcriptome Analysis of Obese Mice Identified Lnc-leptin which Regulates Leptin

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Aims: Obesity is a global epidemic. Central to obesity is adipocytes, which play a dual role of storing excess energy and secreting adipokines. Obesity induces profound transcriptome changes in adipocytes. While most studies have focused on changes in protein-coding genes, little is known about long non-coding RNAs (lncRNAs). In this study, we systemically profiled lncRNAs dysregulated in adipocytes upon obesity and functionally characterised a few selected lncRNAs.

Methodology: C57/BL6 male mice were put on a high-fat diet for 16 weeks. RNA was extracted from adipocytes isolated from interscapular brown, inguinal and epididymal white adipose tissues in both diet-induced obese and normal chow-fed mice. RNA-Sequencing was performed, yielding over 200 million reads that were aligned to an adipose-specific lncRNA catalogue. By various loss-of-function approaches, one particular lncRNA, Lnc-leptin, was characterised in detail.

Result: Our analysis revealed a set of obesity-dysregulated lncRNAs, many of which exhibit dynamic changes in fed vs. fasted state and ob/ob vs. wildtype mice, potentially serving as novel molecular markers reflecting adipose energy status. Among the most prominent ones is Lnc-leptin, an lncRNA transcribed from an enhancer region upstream of leptin. Expression of Lnc-leptin is sensitive to insulin and closely correlates to expression of leptin across diverse pathophysiological conditions. Functionally, induction of Lnc-leptin is essential for adipogenesis, and its presence in mature adipocytes is required to maintain leptin expression in vitro and in vivo. Interestingly, the orthologous genomic region of Lnc-leptin in human is an enhancer, and a single nucleotide polymorphism (SNP: rs791595) in this region has been associated with Type2 diabetes mellitus in East Asian populations.

Conclusion: Our study has delineated transcriptional changes in adipocytes during obesity and established Lnc-leptin as a new regulator of leptin. The orthologous region of Lnc-leptin in human is an enhancer which may regulate energy homeostasis and has functional consequences on metabolic disease susceptibility.