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Commentary

LncRNAs in Adipose Tissue from Obese and Insulin-Resistant Subjects: New Targets for Therapy?

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The mammalian transcriptome predominantly comprises non-coding RNAs, being the long non-coding RNAs (lncRNAs) the most abundant. This heterogeneous newly discovered class is formed by tissue-specific RNAs able to regulate gene expression by transcriptional or post-transcriptional regulation and epigenetic targeting, in accordance with their binding and localization. The amount of non-protein coding sequences tends to increase with organismal complexity (Giroud and Scheideler, 2017). As transcriptional regulators, lncRNAs constitute emerging targets to consider when studying adipocyte development and hyperplasic/hypertrophic adipose tissue present in obese patients. Although considerable advance has been achieved in understanding adipose tissue biology, there have been little success in the prevention or treatment of obese patients. In this context, an important goal of clinical and basic research is to identify new targets to combat this epidemic disease.

In *EBioMedicine*, Gao and collaborators (Gao et al., 2018) analysed the expression of lncRNAs in human subcutaneous white adipose tissue in association with obesity and insulin resistance. The study included two cohorts formed by 108 women recruited from a general adult population from Sweden. RNA sequencing data from lean/obese patients and gene microarray analyses from individuals with/without insulin resistance led to the identification of a set of potentially relevant lncRNAs that could play a role in these phenotypes. The potential candidates were subjected to further scrutiny based on cell-type specificity in the different cell fractions isolated from subcutaneous adipose tissue, and also evaluating the expression pattern during adipogenesis. In order to investigate the potential functional roles of lncRNAs, correlation analysis with adipose functions narrowed down the lncRNAs of interest, being one lncRNA correlated with lipogenesis and the other with lipolysis. Moreover, weighted gene co-expression network analyses shed light on the involved regulatory pathways for these lncRNAs, contributing to lipid metabolism and inflammation pathways, respectively. These lncRNAs were thus named adipocyte-specific metabolic related lncRNAs (ASMERs). The narrow down procedure was held on the consistent finding that both ASMER-1 and ASMER-2 were enriched in fat cells and differentially regulated in the context of obesity and insulin resistance.

To gain insights into functional roles, loss-of-function studies were performed using two antisense oligonucleotides for each gene in *in vitro* differentiated human adipose-derived stromal cells, in order to analyse mature adipocyte function and adipogenesis. The silencing of the genes led to similar results, inhibiting both lipolysis and adiponectin release, but most likely through different mechanisms, as evidenced by their gene expression effects and transcriptome analysis.

Being the primary goal the identification of adipocyte-specific lncRNAs linked to obesity and insulin resistance, the authors succeeded in finding a potential functional role in controlling lipolysis and adipokine release. Over the last decades, research on lncRNAs has allowed an increasing understanding of novel actors involved in the regulation of adipogenesis (Wei et al., 2016). In this sense, Gao and collaborators have expanded the knowledge beyond SRA (Xu et al., 2010), HOTAIR (Divoux et al., 2014) or ADINR (Xiao et al., 2015), as previous examples of lncRNAs involved in fat accumulation. lncRNAs are known to affect chromatin remodelling, influencing both transcription and post-transcriptional processing. It has also been demonstrated that approximately 40% of lncRNAs are translated into peptides. Although most of them are non-functional, a minority of lncRNAs encodes functional peptides conferring potential specific biological functions (Ji et al., 2015). All these characteristics convert these molecules in a current interesting topic in life sciences and give them potential diagnostic and therapeutic implications.

lncRNAs have been exponentially recognized as viable biomarkers for a wide number of diseases (Qiu et al., 2017). In addition to its potential role as biomarkers, lncRNAs could be used in the design of lncRNA-based therapies for obese patients through the development of pharmacological compounds able to regulate lncRNAs, and consequently, their ability to regulate adipocyte differentiation. In 2015, Howe and colleagues described a synthetic small molecule selectively targeting the specific non-coding RNA structure, so non-coding RNA structural elements could be more broadly targeted than expected (Howe et al., 2015).

There are still pending questions to answer and further comprehensive investigation is warranted to develop better approaches to finally unveil their utility as diagnostic and therapeutic strategies in human disease (Wu et al., 2016). Specifically, in metabolic disorders, and given their effects in lipolysis and adipocyte differentiation, the identification of lncRNAs such as ASMERs by Gao and co-workers are on the road to open new therapeutic avenues.

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Disclosure

The authors declared no conflicts of interest.

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