On the role of non-coding RNAs in the epigenomic control of insulin resistance and type 2 diabetes

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Background:
Our research investigates epigenomic mechanisms that underlie the development of obesity-associated insulin resistance and type 2 diabetes. Metaflammation describes the state of metabolically driven low-grade inflammation that is typically associated with these diseases (Gregor and Hotamisligil, 2011). In addition to metabolic stress signals, alterations of the epigenome play fundamental roles in metaflammation, because they shape the chromatin landscape and determine gene expression patterns, cellular identity and signal responses (Glass and Natoli 2016). In search for epigenomic modifiers we have identified a key role of a transcriptional corepressor complex containing GPS2 (G protein pathway suppressor 2) as core subunit (Toubal et al. 2013; Fan et al. 2016). In particular, our data suggest that the anti-inflammatory function of the entire complex is compromised by loss of the GPS2 subunit in adipocytes and in macrophages of obese humans and mice. Most recent preliminary data suggest that distinct non-coding (nc) RNAs regulate GPS2 pathways by acting at different levels 'upstream' or 'downstream' of the chromatin-bound complex. Because the expression of many ncRNAs is altered in obesity and type 2 diabetes (Kornfeld and Bruning, 2014; Arner et al. 2015), we suspect that such alterations contribute to the documented inappropriate GPS2 complex function in humans as well as to the corresponding phenotypes of GPS2-deficient mice.

Objectives:
The objective is to investigate the role of diverse ncRNAs (e.g. miRNAs, lncRNAs, eRNAs) in epigenomic pathways controlled by the GPS2 corepressor complex, a key regulator of obesity-associated inflammation and insulin resistance in macrophages and adipocytes. Within three specific aims the project will identify candidate ncRNAs that act either as effectors/downstream targets (Aim 1) or regulators/upstream targets of GPS2 pathways (Aim 2), and then develop proof-of-concept models for therapeutic intervention (Aim 3). We expect that the project will contribute to a better understanding of epigenetic mechanisms underlying the development of insulin resistance and type 2 diabetes, and we hope that specific ncRNAs can be further employed as targets for epigenome-based therapeutic developments.

Methodology:
The postdoc will apply state-of-the art genomic and biochemical approaches to identify and characterize ncRNA from adipocytes and macrophages. Differentially expressed ncRNAs will be identified using RNA-seq. Following bioinformatics analysis and annotation differentially expressed ncRNAs will be validated. Human/mouse cell lines, primary cultures (obtained from clinical collaborators), conditional KO mice that selectively inactivate the complex have
already been generated, allowing an immediate screening start of screenings. Functional analysis will involve the specific silencing or deletion of these ncRNAs, followed by (epi)genomic analysis using RNA/ChIP-seq. In a final step, silencing of top-ranked ncRNAs, which are conserved in humans/mice, will be established in mice to generate in vivo models.

**Work plan:**

*The postdoc may focus on either aim 1 or aim 2, depending on preferences and status of the preliminary data by project start.*

(Aim 1) Identify ncRNAs that are regulated by the GPS2 corepressor complex. As they may contribute to the loss-of-GPS2 phenotypes in mice and humans, we propose to screen for such ncRNAs and then test which of the GPS2-regulated ncRNAs are also altered in obesity and type 2 diabetes. Focus will be on ncRNA circuits which are conserved between humans and mice (Arner et al. 2015; Fan et al. 2016).

(Aim 2) Identify ncRNAs that regulate the expression and function of the GPS2 complex. The question of how GPS2, along with its complex, is regulated is key to understand how disease alterations develop, for example from obesity to type 2 diabetes. We will address these aspects by developing screenings for (i) ncRNAs that regulate the mRNA expression of complex subunits or (ii) ncRNAs that modulate the complex function at chromatin (Tsai et al. 2010).

(Aim 3) Develop proof-of-concept models for the therapeutic intervention by targeting specific ncRNAs. ncRNA-based therapeutics (Kornfeld and Bruning, 2014) provides a unique opportunity to modulate the expression and chromatin-modifying activities of GPS2 complexes in a cell-type selective manner, thereby overcoming difficulties in drug-targeting this multi-protein complex directly. In addition to serving as intervention models to combat metaflammation in the context of type 2 diabetes, the application of ncRNA inhibitors will further facilitate the discovery of targets and pathways that are regulated by these ncRNAs.

**References:**

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