A miR-29a-driven negative feedback loop regulates peripheral glucocorticoid receptor signalling

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Abstract

The glucocorticoid receptor (GR) represents the crucial molecular mediator of key endocrine, glucocorticoid hormone-dependent regulatory circuits, including control of glucose, protein and lipid homeostasis. Consequently, aberrant glucocorticoid signalling is linked to severe metabolic disorders, including insulin resistance, obesity, and hyperglycemia, all of which also appear upon chronic glucocorticoid therapy for the treatment of inflammatory conditions. Of note, long-term glucocorticoid exposure under these therapeutic conditions typically induces glucocorticoid resistance, requiring higher doses and consequently triggering more severe metabolic phenotypes. However, the molecular basis of acquired glucocorticoid resistance remains unknown.

In a screen of differential miRNA expression during glucocorticoid-dependent adipogenic differentiation of human Multipotent Adipose Stem (hMADS) cells, we identified miR-29a as one of the most downregulated transcripts. Overexpression of miR-29a impaired adipogenesis. We found that miR-29a represses GR in human adipogenesis by directly targeting its mRNA, and downstream analyses revealed that GR mediates most of miR-29a's anti-adipogenic effects. Conversely, miR-29a expression depends on GR activation, creating a novel miR-29-driven feedback loop. miR-29a and GR expression were inversely correlated both in murine adipose tissue and in adipose tissue samples obtained from human patients. In the latter, miR-29a levels were additionally strongly negatively correlated with BMI and adipocyte size. Importantly, inhibition of miR-29 in mice partially rescued the downregulation of GR during dexamethasone treatment.

In addition to modulating GR function under physiological conditions, we discovered that pharmacological glucocorticoid application in inflammatory disease also induced miR-29a expression, correlating with reduced GR levels. This effect was abolished in mice with impaired GR function.

In summary, we uncovered a novel GR-miR-29a negative feedback loop conserved between mice and humans, in health and disease. For the first time, we elucidate a microRNA-related mechanism that might contribute to GR dysregulation and/or resistance in peripheral tissues.

Keywords: adipogenesis; adipose tissue; miRNA; glucocorticoids; glucocorticoid receptor; arthritis