Nat Med. 2016 Jul;22(7):780-91. doi: 10.1038/nm.4114. Epub 2016 Jun 6.

Loss of the co-repressor GPS2 sensitizes macrophage activation upon metabolic stress induced by obesity and type 2 diabetes

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PMID: 27270589 DOI: 10.1038/nm.4114

Abstract

Humans with obesity differ in their susceptibility to developing insulin resistance and type 2 diabetes (T2D). This variation may relate to the extent of adipose tissue (AT) inflammation that develops as their obesity progresses. The state of macrophage activation has a central role in determining the degree of AT inflammation and thus its dysfunction, and these states are driven by epigenomic alterations linked to gene expression. The underlying mechanisms that regulate these alterations, however, are poorly defined. Here we demonstrate that a co-repressor complex containing G protein pathway suppressor 2 (GPS2) crucially controls the macrophage epigenome during activation by metabolic stress. The study of AT from humans with and without obesity revealed correlations between reduced GPS2 expression in macrophages, elevated systemic and AT inflammation, and diabetic status. The causality of this relationship was confirmed by using macrophage-specific Gps2-knockout (KO) mice, in which inappropriate co-repressor complex function caused enhancer activation, pro-inflammatory gene expression and hypersensitivity toward metabolic-stress signals. By contrast, transplantation of GPS2-overexpressing bone marrow into two mouse models of obesity (ob/ob and diet-induced obesity) reduced inflammation and improved insulin sensitivity. Thus, our data reveal a potentially reversible disease mechanism that links co-repressor-dependent epigenomic alterations in macrophages to AT inflammation and the development of T2D.

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