Multimodal Analysis of Adipose-Gut Crosstalk Identifies Adipocyte FFAR2 Signaling as a Distal Guardian of Intestinal Homeostasis and Epithelial Integrity

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The gut and adipose tissue work in concert to modulate metabolic health and the immune system by producing short-chain fatty acids (SCFAs). FFAR2 signaling plays a vital role in regulating metabolism and immune function. SCFAs activate FFAR2, but its role in this crosstalk remains unclear. It is hypothesized that FFAR2 is a novel contributor to adipose-gut crosstalk, regulating inflammation, epithelial integrity, and dysplasia, via its metabolic signaling. To investigate, paired adipose and colon tissue bulk RNA-seq data from the GTEx portal were obtained. A multivariable linear regression was performed to establish the link. Differential expression analysis was performed on jejunal and mature adipocyte RNA samples extracted from adipose-specific FFAR2KO mice. Jejunal samples also underwent histopathological analysis. The regression shows a negative correlation between adipose FFAR2 expression and epithelial-mesenchymal transition-defined dysplasia in the gut. Transcriptomic analysis reveals that the downregulation of FFAR2 in adipose tissue promotes the upregulation of inflammatory, oxidative stress, and immune-activating genes, as well as metabolic dysfunction. The primary upregulated genes are Nf-?B activators. In jejunal samples, FFAR2KO is associated with downregulation of epithelial barrier-protective genes and Nf-?B regulators. This pattern is also observed in 3T3-L1 cells with FFAR2KD.

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