IL-17 Family Members Coordinate Immunometabolic and Structural Networks

Brenneth Stevens

Abstract

The interleukin-17 (IL-17) cytokine family has an established role in orchestrating barrier defense, leukocyte recruitment, and inflammatory disease. Recently, the two principal members of this family, IL-17A and IL-17F, have been shown to regulate cellular and systemic metabolism. The molecular mechanisms underpinning this immunometabolic axis are not well defined, however. Here, we used genetic, dietary, and pharmacological methods to elucidate the metabolic actions of IL-17A and IL-17F in liver and adipose tissue. IL-17A had a significant impact on carbohydrate utilization and fatty acid synthesis, effects that were most prominent during the postprandial state and following high-carbohydrate feeding. Unexpectedly, we found that biological sex was a critical determinant of IL-17's impact on thermoregulation, substrate utilization, and lipid synthesis in brown adipose tissue and liver. At the whole-body level, male *Il17a/f*$^{-/-}$ mice resisted sucrose-induced weight gain, whereas female *Il17a/f*$^{-/-}$ mice did not show protection and instead exhibited increased susceptibility in our model. Our findings highlight IL-17 as an important player in directing metabolic and immune homeostasis and raise questions regarding sex differences in these pathways.

To gain further insight on the non-canonical roles of IL-17 family members, we constructed a spatially-resolved protein interactome for the receptor subunit IL-17RC. This map, generated via high-resolution proximity proteomics, revealed an extensive network of intracellular partners with significant enrichment for proteins associated with the centrosome and mitochondrial protein complexes. The composition of this interactome pointed towards an unexplored IL-17A/F-independent role for IL-17RC in cellular organization. This suggests that, in addition to its canonical function in cytokine signaling, IL-17RC may physically associate with the core machinery governing cytoskeletal and metabolic homeostasis, providing a new mechanistic framework for the immunometabolic functions of the IL-17 pathway.