LEPTIN REPROGRAMS THE MACROPHAGE RESPONSE TO INFLAMMATORY MEDIATORS: LINK BETWEEN METABOLISM AND IMMUNITY IN OBESITY

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Background Obesity is a major risk factor for the incidence and severity of multiple cancer types. Growing evidence indicate that obesity is associated with dysregulation of metabolism and immunity. Leptin, a hormone regulating hunger and food intake, plays a key role in the development of obesity and systemic metabolic dysregulation. Leptin has been identified as an inducer of chronic inflammation promoting tumor growth, but its function in inducing immunosuppressive TME is poorly understood.

Methods We used the TCGA data, tumor samples, and fresh blood samples to analyze the association between BMI, leptin, and tryptophan metabolism. We used human monocyte-derived macrophages as an in vitro model, and applied RNA sequencing, metabolomics, ImageStream to determine the effects of leptin in regulation of metabolism and the underlying mechanisms. Using macrophage/T cell coculture, we tested the role of leptin in T cell activation and differentiation.

Results Leptin expression was associated with dysregulation of tryptophan catabolism in the TME of patients with colon and stomach adenocarcinoma. Leptin upregulated IDO1 in macrophages through activation of STAT3 and NF-κB pathways. Leptin-treated macrophages show activated tryptophan catabolism and elevated secretion of tryptophan metabolites including kynurenine, suppressing CD8+ T cell- and Th1-type CD4+ T cell responses.

Conclusions Leptin reprograms the metabolic response to type-1 immune mediators, promoting the development of immunosuppressive TME through induction of IDO1 and biased tryptophan metabolism. This novel role of leptin helps to understand the mechanism of obesity-associated immune dysfunction, and develop new therapeutic modalities.

Ethics Approval Roswell Park Institutional Review Board approved the study from 7/19/2023 to 3/10/2026. IRB ID: MOD00013543/BDR 097118

http://dx.doi.org/10.1136/jitc-2023-SITC2023.1040-A