Jonathan R. Brestoff, MD, PhD, MPH

Outstanding Paper of the Year

Jonathan R. Brestoff, MD, PhD, MPH, Assistant Professor of Pathology & Immunology in the Division of Laboratory and Genomic Medicine, is honored for his outstanding paper of the year: *Intercellular Mitochondria Transfer to Macrophages Regulates White Adipose Tissue Homeostasis and Is Impaired in Obesity* published in *Cell Metabolism*.

Although obesity is driven by chronic positive energy balance, recent studies indicate the immune system modulates neuroendocrine pathways that govern food intake and energy expenditure. Over the past 10 years, it has become clear that some cell types have the ability to obtain mitochondria from their environment or neighboring cells and then use these "foreign" mitochondria for their own metabolic benefit. However, it remains unknown whether this process of intercellular mitochondria transfer occurs in adipose tissue to regulate weight gain and obesity pathogenesis. Brestoff and colleagues generated adipocyte-specific mitochondria reporter mice and found that the majority of macrophages in fat tissue contain mitochondria that originated in adipocytes and that these macrophages are transcriptionally distinct. To determine how this process occurs, the team performed a genome-wide CRISPR-Cas9 knockout screen, which revealed that mitochondria capture by macrophages is dependent on heparan sulfates (HS). Adipose-resident macrophages downregulate their production of HS in the setting high fat diet (HFD)-induced obesity, and this leads to reduced mitochondria transfer from adipocytes to macrophages in vivo. Genetically deleting the rate-limiting enzyme of HS synthesis, *Ext1*, from myeloid cells reduced mitochondria transfer from adipocytes to macrophages, increased fat mass, lowered energy expenditure, and exacerbated diet-induced obesity in mice. Collectively, this study suggests that adipocytes transfer their mitochondria to macrophages as a homeostatic process that supports normal metabolism and that is impaired in metabolic diseases such as obesity.