We have previously demonstrated that the combination of chronic hyperandrogenemia (elevated circulating testosterone; T) and an obesogenic Western-style diet (WSD) exerts synergistic effects on the metabolic and reproductive axis, leading to the development of insulin resistance, visceral obesity, and ovarian dysfunction in female rhesus macaques. The underlying cellular connection between T+WSD treatment and abnormal metabolic and reproductive function is not well understood. Tissue resident-memory T-cells (Trm) have emerged as potent regulators of local inflammation. Thus, we hypothesized that T+WSD treatment drives proinflammatory phenotypic changes in Trm cells. To address this hypothesis, we studied a cohort of adult female rhesus macaque exposed to a low-fat diet and no exogenous T (controls) versus those treated with T+WSD for one year. T+WSD animals became insulin resistant and had higher visceral adiposity than control animals. During the mid-luteal phase, all animals were necropsied and immune cells residing in visceral omental white adipose tissue (OM-WAT), the corpus luteum (CL), the contralateral ovary not containing the CL (OV), endometrium (ENDO), lymph nodes (LN), bone marrow (BM), and peripheral blood mononuclear cells (PBMC) were characterized by flow cytometry. Non-activated CD4+ and CD8+ naïve/central memory cells expressing CD28 were detected in all tissue examined. However, the tissue retention receptor CD69 was expressed only on CD4+ and CD8+ cells residing in OM-WAT, CL, OV, and ENDO. These Trm subsets expressed high levels of the C-C Motif Chemokine Receptor 5 (CCR5), whose role in inflammation has been previously reported. Combined T+WSD treatment resulted in a significant increase in CD8+ Trm cell populations in OM-WAT. Notably, the frequencies of Trm in OM-WAT were positively correlated with HOMA-IR, the indicator of insulin resistance. Collectively, our data indicate that combined hyperandrogenemia and WSD can lead to selective recruitment or local differentiation of Trm cells in visceral fat. Trm activation in fat may drive the development of a proinflammatory environment that negatively affects adipose metabolic function, leading to altered systemic metabolic parameters (i. e., hyperinsulinemia) that influence ovarian and uterine processes. Future studies are warranted to define how Trm cell-adipocyte interactions affect adipose metabolic processes.

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Effects Of Hyperandrogenemia And Western-style Diet On Rhesus Macaque Tissue-resident Memory T-cells And Their Potential Role In Controlling Local Inflammation And Insulin Sensitivity

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