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"Impact of Excess Lipids on CD4 T Cell Activation and Differentiation"

Previous studies conducted in the LSUHSC Comprehensive Alcohol-HIV/AIDS Research Center, investigated immune responses of rhesus macaques fed a nutritionally balanced diet. However, a diet high in both sugar and fat, also known as a Western diet, is common in people living with HIV (PLWH). To better model the altered nutritional environment prevalent in PLWH enrolled in the New Orleans Alcohol in HIV (NOAH) Study, we designed *in vitro* studies to elucidate the impact of altered nutritional levels produced by consumption of a Western diet. Preclinical *in vivo* rodent models show that high fat diet (HFD) feeding impacts T cell differentiation; however, its impact on human CD4 T cell differentiation and activation is not known. CD4 T cell differentiation and activation are metabolism-dependent. Naive T cells utilize oxidative phosphorylation and shift towards glycolysis after activation. Effector T cells require aerobic glycolysis, and Naïve/Regulatory T cells rely almost entirely on fatty acid oxidation. Considering this, our *in vitro* model system is designed to test the effects of the high fat diet on T cell activation and differentiation. We propose a conceptual model in which high lipid media dysregulates expression of CD4 T cell activation marker CD38 and master transcription factors (*Tbet, GATA3, RORγT, FOXP3*).

Methods: Naïve CD4 T cells isolated from human blood bank samples (N=6) were stimulated on anti-CD3-coated plates in the presence of anti-CD28 and IL-12 and cultured in 1) normal RPMI media, 2) low lipid media (using 250 µM palmitic acid and 100 µM oleic acid), and 3) high lipid media (using 1mM palmitic and oleic acid). After a 3-day incubation period, the cells were immunostained for extracellular and intracellular activation and differentiation markers and flow cytometry was used to assess CD4 T cell activation and differentiation.

Preliminary Results: Preliminary analysis demonstrated CD38 expression, a T cell activation marker, decreased in a dose-dependent manner in the presence of lipids. The lowest expression of CD38 was observed in the high lipid media. This suggests that a high fat diet inhibits naïve T cells from activating. Future experiments include assessing apoptosis, reactive oxygen species, and glycolysis of activated CD4 T cells in the presence of different lipid concentrations.