4-18-2018

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Interference of the Inflammasome Via Interferonβ
Honors Thesis
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Background and Significance
Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder that has become increasingly common in the United States and around the world. Metabolic disorders such as T2DM and obesity are known to have a chronic low grade inflammatory tissue environment as well as an increase in excess lipids. Current research suggests that a tightly regulated oligoprotein complex known as the NLRP3 inflammasome is highly activated in T2DM and obesity. However, it is not well understood the interplay between excess lipids and inflammation. A key transcription factor that is known to have both an inflammatory effect as well as an effect on lipid metabolism is PPARγ. For this reason, we attempted to determine if PPARγ had an effect on the degree of pro-inflammatory cytokine release such as IL-1β in the presence of excess lipids.

The NLRP3 Inflammasome Activation

Figure 1. Schematic of lipotoxic inflammasome activation with and without PPARγ.

Hypothesis
We hypothesized loss of PPARγ would be protective by altering lipid metabolism in macrophages.

Figure 2. mPPARγ KO mouse model.

Methods
In an attempt to determine the interplay between lipid metabolism and inflammation, we created a myeloid specific PPARγ KO mouse model. WT or indicated KO peritoneal macrophages (pMACs) were isolated from mice and adhered to indicated plates. To activate the inflammasome a lipid cocktail, namely palmitate, and LPS were given to activate the inflammasome complex in pMACs.

Figure 3. mPPARγKO pMACs selective depletes IL-1 levels. Loss of PPARγ from activated macrophages led to a selective reduction in IL-1 mRNA and protein (A-C).

Discussion
Myeloid specific loss of PPARγ leads to selective reduction of IL-1β due to an effect on signal 1 of the inflammasome and increased IFNβ. Further research should investigate how loss of PPARγ leads to increased IFNβ. Also it is advantageous to study how increased IFNβ leads to selective depletion of IL-1 levels.

Figure 4. Heightened production and release of IFNβ signaling in mPPARγ KO cells. RNA sequencing and qPCR revealed an increase IFN-regulated genes (A-B), as well as IFNβ levels (C-D).

Figure 5. Neutralization of IFNβ signaling normalized IL-1 Levels. Blockade of IFNβ signaling with the IFNAR1 antibody restored IL-1β levels to WT levels.

Figure 6. rIFNβ sufficient to reproduce PPARγ KO phenotype. rIFNβ given to WT cells phenocopied mPPARγKO cells. IFNβ levels caused a dose dependent decrease in IL-1β and had no effect on TNFα.

Figure 7. Schematic of inflammasome with IFNβ response.