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High-fat diet-induced obesity displays altered adipocyte differentiation in the absence of Interleukin-1 Receptor I (IL-1RI)

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High-fat diet (HFD)-induced obesity is associated with chronic low grade inflammation within adipose tissue where proinflammatory interleukin 1 β (IL1 β) expression is present⁽¹⁾. Absence of IL-1 Receptor (*IL-1RI*^{-/-}) protects against high-fat diet (HFD)-induced insulin resistance after 3 months HFD⁽²⁾, but this protection was lost after 6 months HFD⁽³⁾. Wildtype (WT) mice were more glucose tolerant and insulin sensitive than *IL-1RI*^{-/-} mice following 6 months HFD. Also, *IL-1RI*^{-/-} mice showed a loss in adipose functionality, increased adipocyte hypertrophy and reduction in TNF α and IL-6 secretion from stromal vascular fraction (SVF). It was unknown if/how lack of *IL-1RI* disrupted pre-adipocyte differentiation. Additionally, it has been suggested that microbiome transfer can affect weight gain and phenotype in mice with inflammation-induced disease. The purpose of this study was to determine how lack of *IL-1RI* altered adipogenic potential and adipokine secretion in adipose tissue.

WT and *IL-1RI*^{-/-} mice were fed a HFD for 6 months (45 % kcal). A subset of cages cohoused WT and *IL-1RI*^{-/-} mice to determine whether microbiome transfer can affect phenotype. Glucose tolerance (1.5 g/kg) and insulin tolerance (0.5 U/kg) were tested. We investigated PPAR- γ and FASN gene expression in preadipocytes and differentiated adipocytes, lipogenesis in preadipocytes and differentiated adipocytes and IL-6 secretion in adipose tissue organ culture in wildtype versus *IL-1RI*^{-/-}. Pre-adipocytes were isolated and differentiated from adipose tissue. Adipogenic marker expression was measured by real time PCR. Oil Red O absorbance measured triacylglycerol (TAG) accumulation. IL-6 secretion from adipose tissue (AT) explants following IL-1 β /TNF α stimulation was measured by ELISA. Statistical significance was determined through one – and two-way ANOVA for PCR and GTT/ITT respectively and unpaired t-test for TAG accumulation.

IL-1RI^{-/-} mice had increased body weight ($P \leq 0.05$) and AT weight compared to WT but both groups had similar glucose tolerance. *IL-1RI*^{-/-} had higher insulin resistance but this was not statistically significant. Higher glucose tolerance was seen in both *IL-1RI*^{-/-} and WT mice when they were cohoused together. Analysis of adipogenesis showed *Fasn* expression was 11- fold higher in differentiated adipocytes from *IL-1RI*^{-/-} mice compared to WT mice. Conversely, *Ppar- γ* expression was 37- fold higher in differentiated adipocytes from WT mice compared to *IL-1RI*^{-/-} mice. TAG accumulation was 50 % lower in differentiated adipocytes from *IL-1RI*^{-/-} compared to WT. Adipose tissue explants had higher IL-6 secretion from WT than *IL-1RI*^{-/-}. The microbiomes impact was determined and will be presented. *IL-1RI*^{-/-} mice may have an increase in AT weight but adipocyte differentiation is impaired and IL-6 secretion is lower. The number of mature adipocytes and their affiliated inflammation is decreased. *IL-1RI*^{-/-} may protect from HFD induced inflammation through disruption of adipogenesis. Co-housed mice total weight gain indicates a microbiome transfer which could provide a mechanism linking the beneficial alteration to adipogenesis and reduction of inflammation with a decrease in amount of adipose tissue.

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