#3: Ron receptor tyrosine kinase plays a protective role in diet induced obesity and associated steatohepatitis

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Obesity is one of the leading causes of preventable death in the U.S and a well-established risk factor for several pathological conditions including steatohepatitis. The activation of inflammatory tissue resident macrophages has proven to play a key role in the progression of the metabolic syndrome. Consequently, mechanisms that manipulate macrophage phenotype has become of great interest for developing therapeutic strategies for combating obesity and its associated diseases. Our lab has shown that Ron tyrosine kinase, a receptor expressed on tissue resident macrophages, limits an inflammatory response while promoting tissue repair. In this study, we first investigate the impact of Ron signaling on metabolic features preceding steatohepatitis using high fat diet (HFD) fed wild type (WT) and Ron deficient (Ron KO) mice. Ron KO mice demonstrated more severe events associated with obesity such as increased adiposity, exacerbated hyperglycemia and trend toward increased liver weights when compared to WT animals. Altered Ron signaling resulted in a shift in the plasma lipoprotein distribution from primarily VLDL and LDL to predominantly HDL in the WT control mice. To then establish the role of Ron signaling in steatohepatitis, high cholesterol diet (HCD) fed ApoE KO and Ron KO ApoE KO mice (DKO) were evaluated. We showed that DKO mice experience more severe steatohepatitis which is attributed to an increased prevalence of activated inflammatory Kupffer cells. In vitro studies ascertain that Ron manipulation of macrophage phenotype is in part, a result of downstream AMPK activation. These data indicate the role of Ron in attenuating obesity and its associated diseases and identify a novel downstream pathway involved in this process.