HDAC6 mediates inflammatory macrophage phenotype through regulation of NFkB nuclear localization

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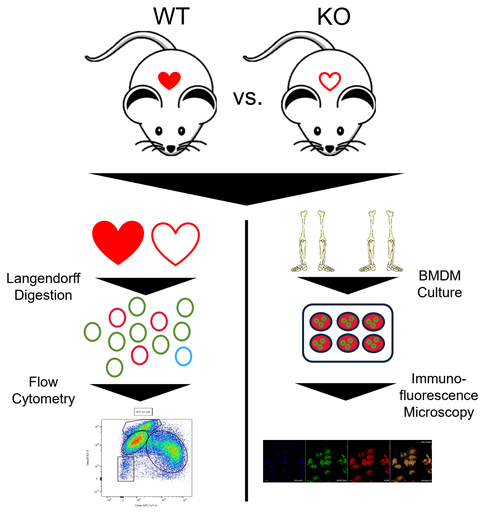
Background

- Macrophages perform vital functions in cardiac healing and remodeling.
- Histone deacetylase 6 (HDAC6) performs a number of functions outside of canonical chromatin remodeling
- The role of HDAC6 in mediating inflammation in macrophages has yet to be defined
- HDAC6/Macrophage interactions have implications for cardiovascular would healing and disease

Methods



Results

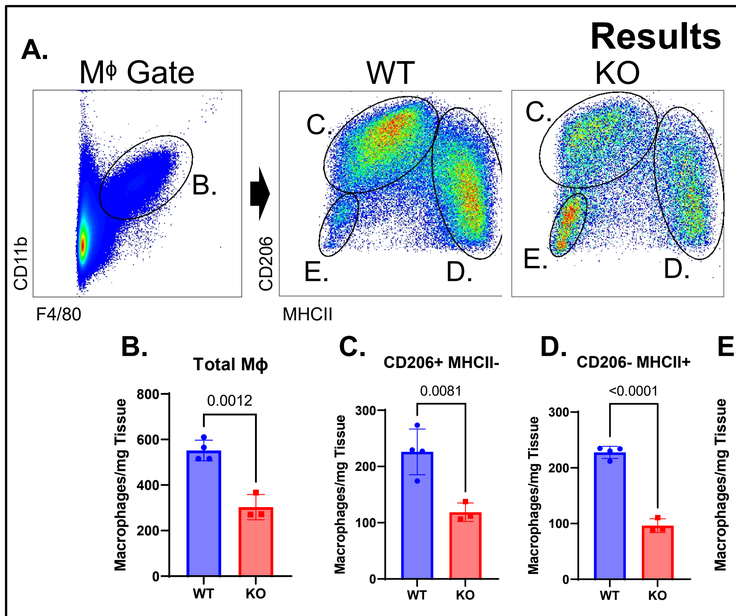


Figure 1. HDAC6 knockout mice have altered cardiac macrophage populations during homeostasis. **(A.)** Representative flow cytometric gating plots for the analysis of macrophage populations in the heart. **(B.-E.)** Quantification of total macrophages and macrophage sub-populations normalized to tissue weight based on the surface expression of CD206 and MHC-II. **(F.)** Analysis of inflammatory gene expression in bone marrow-derived macrophages *in vitro* in the presence of Lipopolysaccharide (LPS). All statistical comparisons made using unpaired t-test for B.-E. Gene expression data normalized to 18s RNA before comparison to untreated samples.

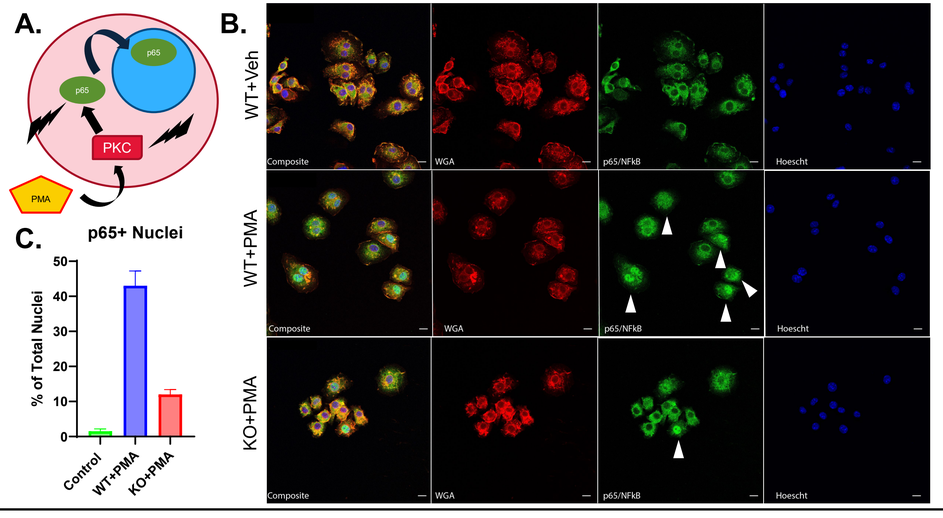


Figure 2. HDAC6 KO macrophages show impaired p65 nuclear translocation. **(A.-B.)** Bone marrow-derived macrophages from WT and KO mice were cultured and stimulated with 100nM phorbol myristate acetate (PMA), an NFkB agonist, and stained for WGA, p65, and Hoescht nuclear stain. White arrows indicate p65+ nuclei. Scale bars = 10um. **(C.)** Quantification of the number of p65+ nuclei as a percentage of total nuclei counted. 5 images taken per slide and Hoescht/p65 co-localization analyzed using ImageJ.

Conclusions

- HDAC6 KO cardiac macrophage populations differ in number and type.
- HDAC6 KO macrophages have blunted responses to inflammatory LPS.
- HDAC6 inhibits the nuclear localization of the pro-inflammatory transcription factor NFkB outside of the canonical LPS/TLR4/MyD88 signaling cascade.

Implications

- HDAC6 may regulate upstream targets of inflammatory gene expression in macrophages.
- The regulation of macrophage phenotype and response to inflammatory stimuli may change their function in the wounded or diseased heart.
- HDAC6 may prove to be a efficacious anti-inflammatory target.

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