PGC1β Regulates Anti-Inflammatory Activation in Mouse Macrophages

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Macrophages regulate both the acute and later resolution phases of the inflammatory response to tissue injury. These diverse roles are mediated by distinct subpopulations broadly classified as pro-inflammatory (M1) and anti-inflammatory/wound repair (M2) macrophages, respectively. Proper resolution of tissue injury requires a delicate balance between M1 and M2 activation. Growing evidence suggests chronic inflammation and impaired wound repair may result from dysfunctional M2 activation; thus, it is critical to delineate mechanisms promoting M2 activation. Previous studies have demonstrated that the peroxisome proliferator receptor gamma (PPAR**γ**) signaling pathway promotes M2 phenotype. We hypothesized that PPAR**γ** coactivator 1 beta (PGC1β), a key mediator of PPAR**γ** signaling, is critical in this mechanism. To assess this, we utilized conditional knockout mice in which PGC1β is specifically deleted in CX3CR1+ macrophages (PGC1β KO). Hematopoietic cells were isolated from bone marrow of wild type and PGC1β KO mice, cultured in 20 ng/mL m-CSF for 7 d to promote macrophage differentiation, then stimulated with increasing concentrations of LPS or IL-4 to induce M1 and M2 activation, respectively. Mouse genotypes were confirmed by endpoint PCR and knockdown of PGC1β was confirmed by western blot. Macrophage activation was assessed by analyzing immunophenotype using techniques in flow cytometry and measuring inflammatory mRNA and protein expression by qPCR and western blot, respectively. Flow cytometry data from three independent experiments suggested that PGC1β KO resulted in fewer mature CD11c+ Ly6Clo anti-inflammatory macrophages compared to wild-type after IL-4 induction while no effect was observed on LPS-induced increases in mature CD11c+ Ly6Chi proinflammatory macrophages. Likewise, preliminary qPCR and western blot data suggest reduced expression of the anti-inflammatory marker Arginase-1 (Arg1) in PGC1β KO BMDMs compared to wildtypes after IL-4 exposure. Further studies should investigate whether PGC1β expression is reduced following injury and how to restore it to promote wound repair and limit tissue injury. This work is applicable to a variety of models involving macrophage activation such as ozone inhalation. Supported by R25ES020721, P30ES005022, R01ES004738, and U54AR055073 and the School of Graduate Studies.