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Leukocytosis is associated with CVD risk in humans. WTD-fed Apoe-/- mice develop leukocytosis in association with increased proliferation of HSPCs with increased expression of the common B subunit (CBS) for IL-3/GM-CSF receptors. ApoE in a cell autonomous fashion controls HSPC proliferation, leukocytosis and accumulation of monocytes in lesions. rHDL or LXR activators reduces HSPC proliferation and monocytosis in Apoe-/- mice by decreasing the expression of the CBS.
Specific Aims:
1) Mechanisms of increased expression of the CBS. Expression of the CBS appears to be modulated by cellular cholesterol. We will systematically explore all the processes involved to determine how the CBS is increased.
2) Assessment of the role of increased CBS in HSPCs and monocytes in promoting leukocytosis and accelerated atherosclerosis in Apoe-/- mice. The role of the CBS will be studied in Ldlr-/- mice using BM transplantation studies. We hypothesize that deletion of the Cbs will result in decreased HSPC proliferation and monocytosis compared to Apoe-/-Cbs+/+ mice and therefore will decrease atherosclerotic lesions. As Ldlr-/- mice do not have increased levels of the CBS on their HSPCs and do not develop monocytosis, deletion of the Cbs should have no effect. We will measure leukocytes in the blood and the percentage and proliferation of HSPCs in the BM. We will also perform an in-depth characterization of the lesions. We expect to see a dramatic reduction in lesion size in the Apoe-/- mice transplanted with Apoe-/-Cbs-/- BM due to less circulating monocytes.
3) To determine if the anti-proliferative effects of rHDL and LXR activators are mediated through down-regulation of the CBS. rHDL and LXR treatments suppressed the expression of the CBS in Apoe-/- HSPCs, we will examine if this is a key mechanism for these agents in inhibiting monocytosis. To test this Ldlr-/- mice transplanted with Apoe-/- or Apoe-/-Cbs-/- BM will be treated with saline, rHDL or LXR activators. HSPC proliferation and monocyte levels will be quantified. If the down-regulation of the CBS is a key mechanism in rHDL and/or LXR attenuating HSPC proliferation, rHDL and/or LXR activators should have no effect in the Apoe-/-Cbs-/- mice. We expect this to be the case as both rHDL and LXR activators appear to reduce HSPC proliferation and monocytosis via a common mechanism, reduction of the CBS on HSPCs.