Dr. Alan Tall

Leukocytosis and thrombocytosis are associated with increased atherothrombotic risk in the general population. LNK is a scaffolding protein that in mice inhibits thrombopoietin signaling in hematopoietic stem cells (HSCs) and megakaryocyte progenitors. A LNK variant (R262W) has been associated with leukocyte, platelet counts and CHD in human GWAS. Using human cord blood we discovered an association of the TT risk SNP (R262W) of *LNK* with expansion of HSCs, increased TPO signaling and enhanced megakaryopoiesis, indicating reduced *LNK* function and increased MPL signaling. To assess the role of reduced LNK function in atherothrombosis, we transplanted WT or *Lnk*$^{-/-}$ bone marrow (BM) into irradiated WT or *Ldlr*$^{-/-}$ mice and fed recipient mice chow or Western diets (WD), respectively. While the *Lnk*$^{-/-}$ BM recipients showed similarly increased platelet counts with both diets, platelet activation, leukocyte counts, formation of platelet/leukocyte aggregates (PLA), atherosclerosis and thrombosis were markedly increased by hematopoietic *Lnk* deficiency combined with hypercholesterolemia. Thus we hypothesize that in the setting of hypercholesterolemia, genetic variants that cause activation of TPO signaling predispose to atherothrombosis via leukocytosis and platelet activation. Aim 1 will determine the mechanisms of platelet activation and leukocytosis in mice with hematopoietic *Lnk* deficiency and hypercholesterolemia. Aim 2 will assess mechanisms of accelerated atherosclerosis and thrombosis in these mice and the relative contributions of increased leukocytes, activated platelets, platelet-leukocyte aggregates and neutrophil-derived NETs to these processes. Therapeutic interventions with JAK2 or ERK inhibitors or rHDL infusions will be assessed. Aim 3 will employ human cord blood stem cells in a humanized mouse models to assess the impact of the TT risk SNP on hematopoietic functions in human cells.