Our work is focused on the role of the immune system in cardiovascular pathologies, mostly atherosclerosis. In our studies we use both loss and gain of function approaches in mouse models of disease, as well as molecular and cellular approaches to gain insights into mechanisms by which proatherogenic and protective lymphocytes influence atherosclerosis.

Research Brief

Our research is focused on the immune system and cardiovascular disorders, mostly atherosclerosis. Our aims are to (1) understand how different lymphocytes influence development and progression of atherosclerosis (2) interactions between different lymphocytes in influencing atherosclerosis including plaque rupture and (3) translating the findings into novel therapies. Our recent studies on B cells and atherosclerosis have completely changed accepted dogma that B cells are protective against atherosclerosis and have shown that B2 B cells are proatherogenic and dominate development of atherosclerosis whilst B1a B cells are protective, in part by producing natural IgM. In further support of these findings, we have also demonstrated that inhibition of the BAFF receptor using specific monoclonal antibodies deletes only B2 B cells to attenuate atherosclerosis. In other studies we have shown that CD8+ T cells are proatherogenic by secreting cytotoxins such as granzyme B and TNF-alpha and promote development of vulnerable atherosclerotic plaques. In related studies we have found that HMGB1, a nuclear protein that can be secreted by macrophages and is also released by necrotic cells potently stimulates progression of atherosclerosis, in part explaining the cytotoxic-dependent effects of CD8+ T cells on atherosclerosis. In preclinical translational studies we have shown that "therapeutic" expansion of CD4+CD25+ regulatory T cell numbers in vivo using a complex of interleukin-2/anti-interleukin-2 antibody attenuates both development and progression of atherosclerosis by suppressing proatherogenic lymphocytes. We have also reported that regulatory T cells suppress cardiac fibrosis in the hypertensive heart, linking inflammation with cardiac fibrosis.

Methodologies

- Development of unique mouse models of cardiovascular disease
- Large array of Immunological methods, including monoclonal antibody production, generation of mixed chimeras and cell purifications for adoptive transfer studies.
- Histological, immunofluorescence and confocal methodologies
- Molecular biological and biochemical methodologies

Selected Publications

B2 B cells accelerate atherosclerosis in lymphocyte-deficient ApoE/-/- mice

B2 B cell transfer increases atherosclerotic lesions in lymphocyte-deficient ApoE/-/- (TKO) mice. (A), dramatic increase in atherosclerotic lipid content in aortic sinus lesions in TKO mice after spleen B2 B cell transfer (TKO-B2, black bars) compared with PBS transfer (TKO-PBS, white bars) (n=8 in each group). Atherosclerotic lesions stained with Oil Red O, where arrows indicate positively stained areas. (B), exaggerated atherosclerotic lesions in aortic arches. Shown are representative Oil Red O stained aortic arches of TKO-B2 transfer group compared with TKO-PBS transfer group (n=8 in each group). Arrows indicate Oil Red O stained areas. *P<0.05. IA, innominate artery; LCCA, left common carotid artery; LS, left subclavian artery.

CD8 T cells contribute to necrotic cores in atherosclerotic lesions

Pfp- or GZMB-deficient CD8+ T lymphocytes failed to augment apoptosis and necrosis in lymphocyte-deficient ApoE/-/- mice. Cytolytic enzymes-competent CD8+ T lymphocytes increased apoptotic cells as identified by TUNEL assay (A) and necrotic cores as assessed by hematoxylin and eosin stain (B) in adoptive transfer studies. n=6 to 8 in each group. Bars=100 μm, Horizontal bar indicates mean value. *P<0.05 compared to PBS transfer (PBS); # P<0.05 compared with wild-type CD8+ T-cell transfer (WT). ApoE/-/- indicates apolipoprotein E-deficient; GZMB, granzyme B; IFNγ, interferon γ; PBS, phosphate-buffered saline; pfp, perforin; TNFα, tumor necrosis factor α; TUNEL, terminal dUTP nick end-labeling; and WT, wild type.

IL-2/anti-IL-2 therapy increases Tregs and inhibits atherosclerosis progression

IL-2/anti–IL-2 mAb complex treatment suppresses progression of developed atherosclerosis in ApoE/-/- mice. (A), Photomicrographs of aortic sinus atherosclerotic lesions stained with Oil Red O after feeding mice a high-fat diet for 6 weeks before commencing therapy with vehicle (control) or IL-2/anti–IL-2 mAb complex (IL-2/JES6–1) for 6 weeks while continuing the high-fat diet. Bar graphs show means ± SEM for the 3 groups at the end of the study; n=10 to 13. (B), CD4+CD25+Foxp3+ T cells in spleen at the end of the study; n=10 to 13. *P<0.05 from control.