Dr. Ira Tabas

A key event in atherothrombotic vascular disease is the conversion of subclinical lesions to disrupted plaques that trigger acute lumenal thrombosis. The PI's laboratory is focused on cellular and molecular processes involved in a critical feature of dangerous plaques, the necrotic core, which contributes to inflammation, plaque disruption, and thrombosis. Necrotic cores arise from the apoptosis of advanced lesional macrophages coupled with defective phagocytic clearance, or "efferocytosis," of the apoptotic macrophages. The objective of this proposal is to elucidate mechanisms and consequences of defective efferocytosis in the two major populations of monocyte-derived cells in advanced atherosclerosis, macrophages and dendritic-like cells (DCs). Aim 1 will explore the hypothesis that ADAM17-mediated cleavage of the efferocytosis receptor MerTK in advanced lesional macrophages contributes to defective efferocytosis and plaque necrosis. Subaim 1A will explore in vitro and in vivo a new mechanism that leads to MerTK cleavage involving athero-relevant activators of a CD36/Toll-like receptor 2/NADPH oxidase/PKCδ pathway. One such activator is apolipoprotein(a), which associates with apoB to form lipoprotein(a) [Lp(a)] and is genetically associated with human CAD. Subaim 1B will first investigate the temporal and quantitative relationships between lesional sol-Mer and plaque stage in murine and human atheromata and then will test causation by using a mouse with non-cleavable MerTK, which we predict will be protected from defective efferocytosis and plaque necrosis during lesion progression. Aim 2 will explore the hypothesis that enrichment of atheromata with mature DCs (mDCs), which lose efferocytic capacity, contributes to defective efferocytosis and plaque necrosis. We have shown that areas of advanced plaques enriched in mDCs, like those enriched in macrophages, are located near areas of plaque necrosis and have even worse efferocytosis than macrophage-rich regions. Subaim 2A will test the hypothesis that MerTK cleavage in DCs leads to defective efferocytosis by promoting DC maturation through inflammatory signaling. Subaim 2B will first study the relationships among lesional DCs, efferocytosis, and plaque necrosis in human carotid atheromata and in plaques of fat-fed Ldlr-/- and Apoe-/- mice and will then test causation by assessing the effect of two genetic manipulations that suppress DC development or maturation—GM-CSF deficiency and DC MyD88 deficiency. Achieving the stated objective will provide critical information for understanding how necrotic cores form and may help in the design of new therapeutic strategies to prevent the clinical progression of atherosclerotic lesions.
