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A critical goal in heart research is to elucidate the mechanisms that promote clinically significant atherosclerosis and then use this knowledge to design novel therapies. The overarching concept that forms the basis of this proposal is that plaque progression represents a pathologic process called defective inflammation resolution. The proposal is based on strong *in vitro* and *in vivo* data supporting a critical role for the macrophage (Mf) MerTK receptor in the resolution response--a response that goes awry in advanced atherosclerosis. MerTK enables Mfs to carry out efferocytosis, a critical resolving process in atherosclerosis, and to promote the synthesis of specialized pro-resolving mediators (SPMs), including lipoxin A4 (LXA4) and resolvin D1 (RvD1). Moreover, in inflammatory settings including in advanced atherosclerotic lesions, MerTK is destroyed by ADAM17-mediated cleavage. We propose that this process compromises both efferocytosis and the synthesis of SPMs, leading to the progression of the type of necrotic, inflammatory plaques that, in humans, are clinically dangerous. In this proposal, Aim 1 will further explore the hypothesis that MerTK signals an inflammation resolution response in Mfs and that MerTK cleavage in atherosclerosis compromises resolution and promotes plaque progression. We will investigate the mechanisms linking MerTK signaling to SPM synthesis and then test the importance of MerTK cleavage in defective efferocytosis, defective mediator synthesis, and plaque progression in atherosclerosis by comparing WD-fed MertkWT Ldlr-/- mice with MertkCR Ldlr-/- mice, which is a unique model in which endogenous Mertk has been replaced by a fully functional cleavage-resistance Mertk. Aim 2 will explore the regulation of MerTK cleavage by athero-relevant factors and SPMs, both in vitro and in atherosclerosis. We will address several hypotheses as to how athero-relevant factors promote ADAM17-mediated MerTK cleavage and, based on new data, how SPMs suppress MerTK cleavage. At the conclusion of this project, we hope to have elucidated new mechanistic links between inflammation resolution and atherosclerosis, which could provide the basis for new drugs that block plaque progress in high-risk humans. Relevance - Atherothrombotic vascular disease is the leading cause of death in the industrialized world, with global spread predicted for the future. Important mechanistic and therapeutic gaps exist in combatting this disease. This proposal will study mechanisms that promote atherosclerosis progression in a manner that has the potential to be highly translatable to human therapy through the use of pro-resolving therapy.