Dr. Gabrielle Fredman

Atherosclerotic cardiovascular disease (CVD) is the leading cause of death in the industrialized world. Studies over the last decade suggest that failed resolution of a chronic inflammatory response is an important driving force in the progression of atherosclerosis. Accordingly, two critical unanswered questions are: (a) what are the endogenous mechanisms underlying dysregulated resolution programs in atherosclerosis and (b) what mechanism-based treatment strategies can be conceived to initiate resolution when it fails. The resolution of inflammation is regulated by specialized pro-resolving mediators (SPMs) that comprise omega-6 derived lipoxins and omega-3 derived resolvins, protectins and maresins. The overall objective of this proposal is to understand the mechanisms of dysregulated resolution in atherosclerosis and to harness SPM signaling pathways towards a novel treatment strategy. A critical enzyme in the biosynthesis of lipoxins and resolvins, 5-lipoxygenase (5-LOX) is expressed in Mφs, which are abundant in atherosclerosis. This proposal is to test the hypothesis that SPM, via 5-LOX in Mφs, limit progression and enhance lesion regression in atherosclerosis. Aim 1 will explore the hypothesis 5-LOX is protective in atherosclerosis. Using chimeric Ldlr-/--5-LOX-/- mice, Sub aim I-A and B will investigate new in vivo mechanisms that underscore how 5-LOX is protective against atherosclerosis progression and regression respectively. Aim 2 will test the hypothesis, and investigate the mechanisms therein, that the 5-LOX-derived SPM resolvin D1 (RvD1) promotes inflammation resolution and plaque stabilization in atherosclerosis. Using Ldlr-/- mice fed on a synthetic diet to induce atherosclerosis, I will investigate whether RvD1 is protective in two clinically relevant models of atherosclerosis; one that simulates aggressive lipid lowering (Sub aim II-A) and one where hyperlipidemia is intact (Sub aim II-B). Aim 3 will explore the hypothesis the RvD1 regulates 5-LOX by controlling the balance between pro-inflammatory (e.g. leukotriene B4) and pro-resolving mediators (e.g. lipoxin A4), a key mechanism of resolution. This research will be accomplished in the setting of a comprehensive career development program designed to provide the candidate with the skills needed to become an independent scientist in cardiovascular research. During the K99/Mentored phase of the award the applicant will continue to gain expertise molecular, cellular and biochemical approaches to study the dysregulated resolution in atherosclerosis from a mechanistic standpoint. An advisory committee of established scientists/mentors in the fields of resolution, CVD and translational science will guide the candidate in her transition to scientific independence over the course of the award period.
