

Summary: Atherosclerotic vascular disease is the leading cause of death in most populations. Only a minority of atherosclerotic lesions actually cause clinical disease, and a key, distinguishing feature of those that do is plaque necrosis. The overall objective of this proposal is to gain in-depth understanding of the signaling pathways involved in plaque necrosis, with the ultimate goal of developing novel therapeutic measures for high-risk individuals. Our and others' previous work has provided evidence that plaque necrosis and inflammation are promoted by leukocyte/macrophage (Mf) apoptosis in advanced lesions, a major cause of which is exposure to endoplasmic reticulum (ER) stress and reactive oxygen/nitrogen species. However, there are critical gaps in our understanding of the mechanisms that trigger these stress pathways and how they lead to apoptosis. Based on new data in the PI's lab, the proposal will address these gaps by focusing on new upstream and downstream signaling pathways involved in Mf apoptosis. We hypothesize that oxidative stress originating from the mitochondria, referred to as "mitoOS," plays a key upstream role and that a novel Bax/Bak-caspase 8 (casp8) pathway plays a major downstream role in advanced lesional Mf apoptosis and plaque necrosis. In Aim 1, we will elucidate how mitoOS induces the ERstress apoptosis effector CHOP; evaluate whether mitoOS pathways in addition to CHOP promote Mf apoptosis; and explore the role of 2 inducers of mitoOS, Drp1 and mitochondrial Ca²⁺ uptake. Most importantly, we will study fat-fed Ldlr^{-/-} mice in which (a) Mfs express mitochondria-targeted catalase, which suppresses mitoOS and apoptosis; and (b) Drp1 is absent in Mfs, which blocks mitochondrial fission, mitoOS, and apoptosis. In Aim 2, we will explore the mechanism of the new Bax/Bak-casp8 apoptosis pathway and investigate links to the mitoOS-CHOP pathway in Aim 1. We will then test causation in advanced atherosclerosis, following the same overall strategy as in Aim 1, using two unique models: mice whose Mfs lack Bax/Bak and mice expressing a form of casp8 that specifically blocks its role in apoptosis. We will also explore the presence of act-casp8 in advanced human atheromata. These combined studies will add significantly to our knowledge of how clinically dangerous atherosclerotic plaques form and how the process may be therapeutically suppressed. Summary of Relevance: Coronary artery disease is the leading killer in most populations. Current therapies are focused on risk factor reduction. A complementary approach directly targeting lesion progression could be extremely valuable in decreasing heart disease. This proposal is focused on specific processes that are known to promote atherosclerosis progression and which, with knowledge gained herein, could be excellent drug targets.
