Inflammation and Atherosclerosis – New Mechanisms
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Interleukin (IL)-1 participates causally in human atherosclerosis, but will not currently be developed as a therapeutic target. Blockade of IL-1β yielded many benefits, but can cause rare infectious complications. IL-1 powerfully induces IL-6, illustrating a cytokine cascade that likely operates during atherosclerosis with IL-6 downstream of IL-1, potentially less pivotal in host defenses than IL-1β itself. Plasma concentrations of IL-6, a trigger to the acute phase response, predict incident cardiovascular events in humans. IL-6 signaling is complex. *Classical signaling* involves straightforward engagement of the canonical IL-6 surface receptor found primarily on hepatocytes and leukocytes by the soluble ligand IL-6. The IL-6 receptor comprises the ligand binding alpha chain (CD126), which after binding IL-6 associates with gp130 and signals to JAK-STAT components downstream. Cleavage of CD126 by ADAM17 generates a circulating soluble form of CD126 that can bind IL-6 and partner promiscuously with gp130, expressed by many cells, a pathway designated *trans signaling*. Numerous studies have implicated IL-6 in the pathogenesis of atherosclerosis in mice, particularly the trans signaling pathway. Many consider trans IL-6 signaling pro-inflammatory, and classical signaling anti-inflammatory. Yet, strong human genetic data, including our own in individuals with clonal hematopoiesis, indicate that interruption of IL-6 signaling diminishes atherothrombotic events. We recently conducted, RESCUE, a double blind, randomized, placebo-controlled trial, in 264 individuals with chronic kidney disease, and high-sensitivity C-reactive protein (hsCRP) ≥2 mg/L. Participants received placebo or an anti-IL-6 antibody, ziltivekimab. The study showed striking dose-dependent drops in hsCRP after 12 weeks of treatment with ziltivekimab compared with placebo, and markedly reduced other biomarkers of inflammation and thrombosis relevant to atherosclerosis. A follow-on Phase 3 study ZEUS of anti-IL-6 therapy in a similar population powered for cardiovascular outcomes is currently underway.