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Project Title: " Cellular Mechanisms of ROS-Induced Increases in Microvessel Permeability In Vivo".

Project Summary:

ROS-induced tissue damage is thought to contribute to various pathological conditions such as inflammation, ischemic reperfusion, and atherosclerosis. Our previous studies demonstrated that ROS production under either fMLP-stimulated neutrophils or leukocyte/platelet aggregate situations induced either transient or prolonged increase in microvessel permeability. To test whether the different patterns of increase in microvessel permeability is due to the different type of ROS, our recent studies using enzymatically generated superoxide and exogenously applied H2O2, demonstrated that superoxide induced immediate and transient increases in microvessel permeability whereas H2O2 caused delayed and progressive permeability increase. The pattern of superoxide-induced permeability increase is similar to other inflammatory mediators-induced response, suggesting superoxide acts like an inflammatory mediator to cause vascular barrier dysfunction while H2O2 induces vascular leakage through a different cellular mechanism. This proposal aims to define the underlying mechanisms of H2O2-induced increase in microvessel permeability with sequential investigations of the roles of NO, peroxynitrite-induced protein nitration, Ca2+ overload and vascular cell apoptosis in H2O2-induced vascular barrier dysfunction and further test whether this mechanism applies to the adhered leukocyte-platelet aggregate-induced prolonged vascular leakage. Cellular and molecular mechanisms will be explored on H2O2-perfused intact mesenteric venules by combining permeability measurements with quantitative fluorescent imaging and confocal structural studies under the same experimental condition. Acute inflammatory situation with leukocyte/platelet aggregate adhesion to vascular wall will be established and causal relationship between H2O2 and leukocyte/platelet aggregate-induced prolonged increase in microvessel permeability will be examined.