Dr. Ali

Abstract
Receptor tyrosine kinases (RTK) are important regulators of cellular signal transduction pathways that play crucial roles in regulating cellular proliferation, differentiation, migration and death; processes integral to the development of atherosclerosis and the response to vascular injury. To identify novel aspects of biology and new therapies we used a systems biology approach performing comprehensive gene network analysis of human atherosclerosis and in-stent stenosis (ISS). This method provides the distinct advantage of identifying hubs, which are highly connected and critical for organism survival; and nodes, which are less connected but more perturbable and thus more relevant to dysfunction and disease. In this context nodes are often identified as non-obvious mediators of disease. Via the hub gene network glutathione peroxidase-1 (GPX1), which ranked as the most differentially regulated among 40000 networks, we identified the most highly connected node as the orphan proto-oncogene RTK Ros1. Evidence for the importance for Ros1 in cardiovascular disease is suggested by studies linking specific Ros1 alleles and heart disease. Allelic variation in ROS1 has been implicated in myocardial infarction, ischemic stroke, ISS and hypertension. The causative genes and molecular pathways responsible for the relationship between this genetic variation and the observed cardiovascular risks remain unknown. In this proposal, the investigators seek to elucidate the relationship between the orphan RTK Ros1 and vascular disease including its connection to Gpx1. Proposed experiments will build on preliminary work implicating a role for RTKs in the response to vascular injury and specifically a role for Ros1 in cell-cycle regulation. Specific aims to be investigated in this proposal will include: (1) determining the role of Ros1 in relevant vascular smooth muscle cell processes, in vitro and (2) characterizing the *in vivo* effects of Ros1 on atherosclerosis and the response to vascular injury in models with specific relevance to revascularization in humans with flow limiting atherosclerosis. These studies are intended to build on those performed during the mentored (K99) phase of the award and form the foundation of a lifelong career in vascular biology.