CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP110405

Project Title:
Lumen formation during blood vessel angiogenesis

Award Mechanism:
Individual Investigator

Principal Investigator:
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Entity:
The University of Texas Southwestern Medical Center

Lay Summary:

“Angiogenesis”, or the growth of new blood vessels, is critically required for tumor growth and metastasis. All tumors must recruit ingrowing vessels by angiogenesis, to provide their rapidly dividing cells with proper nutrition and gas exchange. Without functional vessels to carry in blood, cells within tumors die of asphyxiation and starvation. We found that Ras interacting protein 1 (Rasip1) is essential to developing blood vessels. In the absence of Rasip1 function, blood vessel progenitor cells (endothelial cells, ECs) never undergo the transition from solid ‘cords’ to patent blood-carrying vessels. Rasip1 mutant embryos die early during embryonic development, as a result of global failure of lumen formation and blood circulation. Rasip1 is thus essential to both vasculogenesis (initial vessel formation) and angiogenesis. Vascular lumenogenesis is an area of recent intense interest, but where little is known. Here, we will characterize the role of Rasip1 during vessel formation, focusing vascular lumen morphogenesis. Using both in vitro (cultured ECs) and in vivo models (mouse embryos and adults), we will analyze: 1. the cellular basis of failed lumens, including cytoskeletal, polarity and adhesive properties of ECs, either in the presence or absence of Rasip1, and 2. the molecular basis for Rasip1 function, by assessing its influence on Rho family small GTPases and its binding partners. Importantly, building upon our collected observations, we will test the requirement for Rasip1 during tumor angiogenesis, using conditional inactivation of Rasip1 in tumor bearing adults. This proposed work will broaden our understanding of molecular mechanisms underlying EC biology, cardiovascular development and tumor angiogenesis. Understanding the molecules involved in angiogenesis will lay the foundation for developing novel targets for alternative anti-angiogenic approaches, via the screening for drugs that block these newly discovered pathways.