PADPIN: Protein-Protein Interaction Networks of Angiogenesis, Arteriogenesis, and Inflammation in Peripheral Arterial Disease

Liang-Hui Chu¹*, Brian H. Annex², Joel S. Bader¹,³, Aleksander S. Popel¹,
¹Department of Biomedical Engineering, School of Medicine, Johns Hopkins University, Baltimore, MD 21218, United States
²Cardiovascular Medicine, Department of Medicine, University of Virginia School of Medicine, Charlottesville, VA 22901, United States
³High-Throughput Biology Center, Johns Hopkins University, Baltimore, MD 21218, United States

Introduction: Peripheral arterial disease (PAD) results from an obstruction of blood flow in arteries other than the heart, most commonly the arteries that supply the legs. The complexity of the known signaling pathways involved in PAD, including various growth factor pathways and their crosstalks, suggests that high-throughput experimental data could lead to a new level of understanding of the disease as well as novel and heretofore unanticipated potential targets. All PAD clinical trials using approaches to promote angiogenesis conducted in the last decade have failed, including stimulating vascular growth and remodeling with vascular endothelial growth factor (VEGF). Such bioinformatic analyses have not been systematically performed for PAD.

Materials and Methods: We used a recently developed machine-learning algorithm GeneHits to construct the global protein-protein interaction network of angiogenesis (angiome) comprising 1,233 proteins and 5,726 interactions. Using a similar approach, we constructed the global PIN of immune response (immunome) and arteriogenesis (arteriome). We identified differentially expressed genes from the four microarray datasets by GenePattern 3.6.1. These samples include ischemic gastrocnemius muscle from C57BL/6 and BALB/c mice.

Results: The immunome comprises 3,490 proteins and 21,164 interactions. The arteriome comprises 289 proteins and 803 interactions. The high overlap of genes between angiome and immunome might reflect the regulation by endothelial of various biological processes, including both vascular and immune response.

We compare the differentially expressed genes between ischemic versus nonischemic C57BL/6 and BALB/c mice with the three microarray datasets in PAD patients. We predict that the inhibition of THBS1 is a potential therapeutic angiogenesis target to PAD patients. Nitric oxide (NO) modulates blood flow and tissue perfusion by relaxing and dilating the arteries. Thrombospondin 1, through its cell surface receptor CD47, limits the ability of NO and thus decreases tissue blood flow and perfusion. Thus, we propose that THBS1 and its receptors CD47 or CD36 are novel targets for PAD.