1R01HL108735 Systems Biology Analyses for Hemodynamic Regulation of Vascular Homeostasis

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The aim of the multi-PI R01 is to test the hypothesis that, while both athero-protective pulsatile shear stress (PS) and athero-prone oscillatory shear stress (OS) impose mechanical cues in vascular endothelial cells (ECs), the elicited molecular signals will diverge with time due to differential intracellular adaptive responses. Time-dependent mapping of the signal networks will lead to temporal resolution of the gene expression profiles, and hence the differential functional consequences. Our progress is summarized as follows: (1) Time course analyses of the gene expression profile in ECs responding to different flow patterns demonstrate that, over 24 hr, both PS and OS downregulated genes related to EC proliferation, but the degree was much greater for PS than OS. In contrast, OS upregulated the genes related to cell remodeling pathways in ECs to a greater level than PS. Furthermore, the systematic bioinformatics analysis showed that the number of dowregulated cell cycle and mitosis genes are progressively increased in ECs responding to PS. Further tests using deep sequencing to validate the DNA microarray results and to indentify novel genes regulated by different flow patterns are in progress. (2) We have begun to explore the role of AMP-activated protein kinase (AMPK) in regulating chromatin structure of promoter regions of genes involved in mitochondrial biogenesis and functions. Using a systems biology approach, we have identified 40 proteins involved in the epigenetic regulation that putatively contain an AMPK phosphorylation recognition motif. We have constructed a signaling network with AMPK as a central node for epigenetic regulation. This network is separated to identify the key components of chromatin remodeling and DNA modification important for gene transcription. Currently, experiments are conducted to validate the biological functions of AMPK regulation of mitochondrial biogenesis. The uniqueness of the project stems from the systems approach using information-rich assays as a function of time with the objective of deciphering mechanisms and reconstructing networks involved in hemodynamic regulation of endothelial homeostasis.