

Using Mass Spectrometry to Identify Pathways Regulated by SH2B3 during Cardiac Remodeling

Mike Flister, Ph.D.

Prolonged cardiac inflammation and remodeling in response to injury has been long been associated with increased risk of heart failure (HF), but the molecular and genetic mechanisms underlying this relationship are poorly understood. One gene variant, the missense single nucleotide polymorphism (SNP) rs318454 located in the pleckstrin homology domain of the adaptor protein SH2B3, is associated with elevated white blood cells, increased inflammatory response, and higher risk of myocardial infarction (MI). Beyond this correlation, no experimental data is available to validate whether R262W substitution caused by rs318454 actually deregulates SH2B3 function and whether SH2B3 is critically involved in cardiac remodeling and inflammation. Since SH2B3 is a negative regulator of inflammation, we hypothesize that disruption of SH2B3 function by the potentially damaging SNP will elevate extent and duration of cardiac inflammation and remodeling following MI, leading to increased risk of HF. The goals of this project are to use mass spectrometry to (1) identify binding partners of the wildtype (WT) SH2B3 protein and then (2) determine whether interaction with these binding partners is disrupted by a R262W substitution in the PHD of SH2B3. The project builds on technologies developed by the Wisconsin CEGS to identify DNA-protein interactions using mass spectrometry.

This project is supported by an Innovation Center Grant for Postdoctoral Fellows at the Medical College of Wisconsin.