SH2B3 Is a Genetic Determinant of Cardiac Inflammation and Fibrosis

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Background: Genome wide association studies (GWAS) are powerful tools for nominating pathogenic variants, but offer little insight as to how candidate genes impact disease outcome. Such is the case for SH2B adaptor protein 3 (SH2B3), which is associated with coronary artery disease (CAD), atherosclerosis, and risk of myocardial infarction (MI), but its role in post-MI response is completely unknown. Methods: Using an experimental model of MI (left anterior descending artery [LAD] occlusion) in wild-type (WT) and Sh2b3 knockout (KO) rats, we assessed the role of Sh2b3 in post-MI fibrosis, leukocyte infiltration, angiogenesis, left ventricle (LV) contractility, and inflammatory gene expression. We also confirmed our findings in LV samples from end-stage heart failure patients with or without the MI-associated SH2B3 risk allele. Results: Compared with WT, Sh2b3 KO rats had significantly increased fibrosis (2.2-fold; P<0.001), which coincided with decreased LV fractional shortening (FS) (-Δ11%; P<0.05) at 7 days post-LAD occlusion. Despite an increased angiogenic potential in Sh2b3 KO rats (1.7-fold; P<0.05), we observed no significant differences in LV capillary density between WT and Sh2b3 KO rats. Of the 903 genes examined, 19 were significantly elevated in the post-LAD occluded hearts of Sh2b3 KO rats relative to WT, of which three (NLRP12, CCR2, and IFNγ) were also significantly elevated in the LV of heart failure (HF) patients carrying the MI-associated rs3184504 [T] SH2B3 risk allele. Conclusions - These data suggest for the first time that SH2B3 is a master risk factor for MI by impacting both MI incidence and post-MI response.