COMPUTATIONAL MULTIVARIATE ANALYSES FOR PHASE-SPECIFIC BIOMARKER IDENTIFICATION IN NOVEL IN VIVO AND IN VITRO VIRAL MYOCARDITIS MODELS INDUCED BY CARDIOVIRUS

Poster Contributions
Hall C
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Background: Viral myocarditis can be initiated by viral replication in the heart (phase I), followed by immune-mediated damage (phase II), and dilated cardiomyopathy (phase III). Ideally, each patient should be treated depending on the phase. However, no clinical or animal model studies have identified the phase-specific biomarkers that distinguish these three phases.

Methods: We have established a novel mouse model for myocarditis induced with cardiovirus, Theiler’s murine encephalomyelitis virus (TMEV). We infected C3H mice with TMEV, and conducted multivariate analyses on days 4 (phase I), 7 (phase II), and 60 (phase III) post infection, using 1) virus titration in the heart, 2) serum cardiac troponin I ELISA, and 3) cardiac gene expression analysis by microarray.

Results: The viral titers in the heart were 10-fold higher in phase I than phase II, while serum troponin levels in phase I were significantly lower than in phase II. The levels of viral titers and troponin were correlated in phase I (P < 0.05), but not in phase II (P = 0.12), suggesting that virus caused direct damage to the heart in phase I. We conducted bioinformatics analyses of microarray data, using principal component analysis (PCA). PCA separated heart samples into three populations corresponding to three phases. In phase I, innate immunity genes, such as Ifit1 and Cxcl10, were upregulated. In phase II, adaptive immunity genes, including a T cell marker and MHC molecules, were upregulated, suggesting that acquired immune cells damaged the heart in phase II. In phase III, genes associated with cardiac remodeling were upregulated. This in vivo model system was complemented by an in vitro model, where we infected the cardiomyocyte cell line HL-1 with TMEV, which mimics phase I in vivo because of no involvement of immune cells. In infected cultures, we detected substantial viral replication, troponin release, and similar upregulation of innate immune molecules that found in phase I in vivo, including Ifit1 and Cxcl10.

Conclusion: Since our novel model systems will allow us to identify phase-specific biomarkers of myocarditis, translational application of our findings will aid in the development of phase-specific therapy for myocarditis.