**Abstract**

**Objectives** Myocarditis is an inflammatory disease of the heart. The discovery of myocarditis in 1 to 9% of autopsies showed that myocarditis is an underdiagnosed cause of sudden death. Interaction with leukocytes, particularly macrophages, is a major cause of myocarditis. Viral myocarditis has been proposed to be divided into three phases, acute, chronic, and chronic fibrous. Although each phase requires specific treatment, single biomarker that can distinguish the three phases does not exist. We aimed to identify 1) phase-specific heart biomarkers and 2) blood surrogate markers that reflect changes in the heart, using a novel mouse model of myocarditis.

**Methods** We infected mice with Thelrer’s murine encephalomyelitis virus (TMEV), which belongs to the genus Cardiovirus, family Picornaviridae, to induce myocarditis. We conducted bioinformatics analyses, using microarray transcriptomic data of the heart and blood samples from TMEV-infected mice at days 4, 7, 14, 21, and 60 (chronic phase). Microarray analysis was conducted, using GeneChip Mouse Gene 1.0ST Arrays (Affymetrix). Data were normalized by Robust Multi-array Average.

**Results** Principal component analysis (PCA) of heart transcriptome data from days 4, 7, 14, and 60, showed the separation clearly between the three phases. Innate and acquired immunity-related genes, such as ifitm1, Xbp1, and Igk, were upregulated on day 60. Heat map shows similar patterns between days 4 and 7 as well as day 60. The set of molecules, but not a single molecule, was positive and negative correlation with the heart PC1 value (-log10) between the heart PC1 values and blood microarray data on day 4. Conventional markers of viral myocarditis (IgM, IgG, and MHC class II) were not correlated with the heart PC1 values. K-means clustering shows the distinct expression patterns among the genes.

**Conclusions** The set of molecules, but not a single molecule, was useful as phase-specific biomarkers of myocarditis. Microarray analysis, using heart PC1 values and blood microarray data, identified the blood surrogate markers which reflect the changes in the heart. Future translational application of this approach will lead to discovery of not only phase-specific markers in the heart, but also the biomarkers in the periphery (surrogate markers), which will be useful to diagnose myocarditis without having to biopsy the heart.

**Materials and Methods**

Conventional markers for viral myocarditis

Cardiovascular remodeling and immunoglobulin

**References**

2. Sato F et al. (2014). Distinct kinetics of viral replication, T cell expansion, and MHC class I expression in the cardiac microarray data of the heart.

**Conflict of Interest (COI)**

We have no conflict of interest.