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TLR4 exacerbates a novel model of myocarditis induced with a picornavirus

◯Fumitaka Sato[1)], Seiichi Omura[1)], Eiichiro Kawai[2)], Nicholas E. Martinez[3)], Madan M. Acharya[3)], Pratap C. Reddy[3)], J. Steven Alexander[3)], Ikuo Tsunoda[1)]

Microbiology, Kindai University Faculty of Medicine, Osaka, Japan[1)], Pediatrics, Tohoku Medical and Pharmaceutical University, Miyagi, Japan[2)], Microbiology & Immunology, Louisiana State University Health Sciences Center-Shreveport, Louisiana, USA[3)]

Although Toll-like receptor (TLR) 4 is a pattern recognition receptor that plays a key role in both innate and acquired immunities against microbes, TLR4 has been shown to contribute to the pathogenesis of some picornavirus infections: viral entry/replication and tissue damage. Picornavirus infections are known as a leading cause of viral myocarditis in humans. We have recently established a novel model of myocarditis induced with Theiler's murine encephalomyelitis virus (TMEV), which belongs to the picornavirus family, in C3H mice. In this study, we aimed to characterize the pathomechanism of TMEV-induced myocarditis using wild-type C3H/HeNtac and TLR4-deficient C3H/HeJ mice. TEMV-induced myocarditis can be divided into three phases in the two C3H mouse strains. In phase I, 4 days post infection (p. i.), the levels of viral genome correlated with the levels of serum cardiac troponin I, an indicator of cardiomyocyte damage. In phase II, 1-2 weeks p. i. , $CD3^+$ T cell infiltration in the heart was associated with abnormalities in echocardiograms. In phase III, 2 months p. i. , mice developed progressive fibrosis in the hearts, which was visualized by Masson's trichrome staining (collagen) or picrosirius red staining (collagen I and III). In TLR4-deficient mice, we found a lower incidence of myocarditis with decreased amounts of proinflammatory cytokines [interleukin (IL)-6 and IL-17] than those of wild-type mice. Principal component analysis showed that TLR4, IL-6, IL-17, and anti-viral immunity were associated with the myocarditis susceptibility. Thus, TLR4 may play a detrimental role in viral myocarditis by enhancing pro-inflammatory cytokine production.