What we learned from pandemic H1N1 influenza A

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Online publish-ahead-of-print 22 December 2010

This editorial refers to ‘Up-regulation of ectopic trypsins in the myocardium by influenza A virus infection triggers acute myocarditis’ by H.-Y. Pan et al., pp. 595–603, this issue.

Myocarditis is defined as inflammation of the heart muscle, and it frequently associates with impaired cardiac function. Although many kinds of viruses have been implicated as causes of myocarditis, these most commonly include enteroviruses, such as coxsackieviruses. Beside enteroviruses, adenovirus, hepatitis virus, parvovirus, and influenza virus have been reported to cause myocarditis. Of the viruses that cause myocarditis, the cellular and molecular mechanisms of myocarditis induced by coxsackievirus infection have been most thoroughly investigated with murine models. In 1999, the importance of enteroviral protease 2A was reported as a cause of acquired cardiomyopathy associated with coxsackievirus B3 (CVB3) myocarditis. However, the molecular mechanisms of myocarditis induced by influenza virus have not been fully clarified.

The study reported by Pan et al. is a continuation of their previous study demonstrating that influenza A virus (IAV) infection increased the ectopic trypsin expression in the brain. They further examined the molecular mechanism of IAV-induced myocarditis and revealed the importance of trypsin induction in the pathogenesis of acute myocarditis. Expression of ectopic trypsins, especially trypsin 2 (T2), was increased in myocardium after IAV infection, and subsequently increased matrix metalloproteinase (MMP)-9, MMP-2, and cytokines such as interleukin (IL)-6, IL-1β, and tumour necrosis factor (TNF)-α. Pan et al. nicely showed that the inhibition of trypsin suppressed viral replication, upregulation of MMPs and cytokines, and significantly improved the cardiac function after IAV infection.

Viral myocarditis and dilated cardiomyopathy can be caused by common viral pathogens, such as enteroviruses and adenoviruses, that can have a direct cardiac myocyteopathic effect. Viral infection induces myocardial necrosis and triggers a series of immune responses to eliminate the viral agents. Although several studies have indicated the crucial role of cytokines and the induction of apoptosis in the heart, the precise pathogenic role of a cytokine-mediated signalling system remains unclear. Production of proinflammatory cytokines and stimulation of apoptosis may contribute to myocardial cells loss, which results in compensatory myocardial hypertrophy, fibrosis, scarring, and ventricular dilatation.

Previously, we determined the pathological role of cardiotoxphins-1 (CT-1) in a murine model of CVB3-induced acute myocarditis. CVB3 infection resulted in a distinct expression of CT-1 in the heart that preceded TNF-α and IL-1 expression, and subsequently myocardial degeneration and inflammatory cellular infiltration occurred. TNF-α and IL-1 released from virus-infected cardiomyocytes induce infiltration of inflammatory cells, including natural killer cells and helper T cells, resulting in myocardial degeneration. Treatment with anti-gp130 functional antibody significantly decreased the survival of CVB3-infected mice. These results indicated that activation of gp130 might exert a protective signal by modulating cytokine production and preventing cardiac myocyte apoptosis in CBV3-infected murine heart. Recently, Yajima et al. reported that CVB3 infection associates with activation of JAK-STAT signalling in the heart. In accordance with these observations, an obligatory role of the JAK-STAT pathway for the prevention of viral myocarditis has lately gained considerable support. It is well known that CVB presents a high affinity for cardiac myocytes. It has been reported that the pathological findings of IAV myocarditis are milder than those of patients with CVB myocarditis. However, the clinical symptoms of patients with IAV myocarditis are relatively severe in some cases. There is a distinct difference in the pathological findings between IAV- and CVB-induced myocarditis; e.g. inflammatory changes are milder and are localized in IAV-induced myocarditis. Electron microscopic findings of the heart from a murine model of IAV-induced myocarditis show many infiltrating lymphocytes directly attached to the cardiomyocytes. Therefore, aside from the direct effect of viral infection, cytokines are presumed to contribute significantly in the pathogenesis of severe clinical symptoms including impaired cardiac function in IAV myocarditis.

The prevalence of myocardial involvement in influenza infection ranges from 0 to 11% depending on the diagnostic criteria. In the 2009 pandemic of H1N1 IAV, a higher rate of cardiac complications was reported than the seasonal IAV infection. Fulminant myocarditis due to viral infection is an uncommon form of acute myocarditis. In addition, IAV-associated fulminant myocarditis is exceedingly rare, with only a few cases reported in the literature. However, there are some reported cases of fulminant myocarditis in association with pandemic H1N1 IAV infection, especially in juvenile patients. A novel H1N1 IAV might more commonly associate with a severe form of myocarditis than previously encountered influenza strains. The Japanese Ministry of Health, Labour and Welfare reported that...
of the 100 deaths due to the 2009 H1N1 IAV pandemic in Japan, a direct cause of six deaths was myocarditis.

In summary, Pan et al. clearly described close interaction among IAV, proteases, and cytokines in the pathogenesis of severe influenza infection. The trypsin inhibitor aprotinin and selective trypsin knockdown intercept this cycle and interrelationships among members of this signalling pathway. Until recently, there were no effective therapies for IAV-induced myocarditis apart from anti-viral drugs and symptomatic treatment. It is proposed that selective trypsin inhibition might be a novel therapeutic strategy for the treatment of IAV myocarditis.

Conflict of interest: none declared.

Funding
This study was supported by a grant from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

References