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Reply from the next generation: "myocarditis"

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Predecessors provided us with a large inheritance. Now, we face an aging society that rapidly increases disease prevalence and socioeconomic load. Accumulation of evidence helps us to overcome the diseases of the aging society. Myocarditis, a fatal cardiac disease frequently occurs in healthy young people who mainly support socioeconomic status. Thus, we have to adequately consider such disease background. Predecessors showed us basic understanding of myocarditis. The next generation has a responsibility for identifying diagnostic and prognostic biomarkers and therapy specific for diseases.

Introduction

Our predecessors have left us a great inheritance, much knowledge and the courage to fight against diseases, and concomitantly they have given the next generation several important issues. Furthermore, the next generation has met their expectations with new technologies. Although nobody knows what human beings can get at the end of this continuous trip of a pursuit between generations, this chain of knowledge has definitely saved lives and improved disease outcomes. However, this, too ironically, has resulted in an aging society which has increased not only the prevalence rate of disease but also the various related socioeconomic problems. Considering our predecessors' achievements, we now have to undertake any and all possible measures for this society.

Background

Maintenance of a healthy young generation is indispensable for an aging society from a socioeconomic aspect. Generally, myocarditis unexpectedly occurs in healthy young people and often leads to fatal clinical courses. We need more detailed understanding of myocarditis. Its pathogenicity widely spreads from acute myocarditis to chronic myocarditis and dilated cardiomyopathy. This pathogenic variability affects its outcome and therapeutic strategy. Acute myocarditis has been classified into fulminant and non-fulminant myocarditis on a basis of clinicopathological criteria. Patients with fulminant myocarditis usually die without mechanical circulatory support (MCS), given its unexpected involvement with congestive heart failure and further cardiogenic shock. In other words, we are able to save their lives with the early provision of MCS and subsequently promise a favorable long-term outcome. On the other hand, those with non-fulminant myocarditis usually develop chronic heart failure derived from chronic myocarditis or dilated cardiomyopathy, which leads to a poor long-term outcome. They require a standard heart failure pharmacotherapy and further may be considered for biventricular pacing or even heart implantation. Immune processes following viral infection have been implicated in clinical course of myocarditis. Viral infection is a major causative factor of myocarditis, including Coxsackievirus, parvovirus, and hepatitis C virus. Although cytokine storm mediated by innate immunity against pathogenic viruses is the first line against viral infection, its excessive expression leads to an acute exacerbation of hemodynamics. On the other hand, insufficient viral clearance is thought to result in chronic myocarditis or dilated cardiomyopathy via chronic viral infection and subsequent autoimmunity. Interestingly, it has been demonstrated that Coxsackievirus that invaded into myocardium through coxsackie-adenovirus receptor cleaves the cytoskeleton via their protease enzyme. Additionally, Toll-like receptors (TLRs) and RIG-I-like receptors that emerged as important pathogenic sensors against viruses have been reported to regulate the linkage of innate, adaptive, and autoimmune responses. These observations have inserted many pieces into the puzzle of myocarditis.

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Remaining issues

We have to resolve the remaining issues of diagnostic and prognostic biomarkers and therapies specific for pathomechanisms. Clinical resemblance of acute myocarditis to more common causes of cardiovascular disease such as atherosclerotic and valvular heart disease has made the diagnosis difficult. Endomyocardial biopsy is still a useful diagnostic tool. Against this background, additionally, histological findings are important determinants for therapeutic strategy. Generally, giant cell myocarditis derived from autoimmunity requires immunosuppressive therapy, and lymphocytic myocarditis from viral infection requires an antiviral agent. However, some problems should be argued, although endomyocardial biopsy is clearly important to diagnose cardiovascular disease. First, its diagnostic accuracy may be relatively low, because this includes pseudo-negative samples. Secondly, its traumas are often critical, including cardiac rupture, cardiac tamponade, and fatal arrhythmias. Third, immunological consequence from innate to autoimmunity makes the distinction of predominant pathomechanism difficult. Therefore identifying simple pathological biomarkers specific for myocarditis would contribute to the establishment of therapeutic strategies and further dramatically improve outcomes.

Future directions

Key proteins regulating the immune sequence from innate immunity to autoimmunity should be comprehensively examined from many directions including immunology, molecular biology, virology, and genomics. Especially, definitive mechanisms of immune tolerance and chronic viral infection remain uncertain. Animal models (experimental murine viral myocarditis and experimental rat autoimmune myocarditis) that predecessors provided us are available for identification of biomarkers and specific therapies, given their close resemblance to human disease. We should extend an understanding of animal models to human myocarditis.