Role of autoimmunity in dilated cardiomyopathy

Ziya Kaya · Hugo A. Katus

Published online: 14 October 2009
© Springer-Verlag 2009

Heart failure has become an increasingly prevalent disorder with considerable morbidity and mortality. While many causal mechanisms such as abnormal heart valves, inherited cardiomyopathies, severe coronary artery or hypertensive heart disease are easily identified in clinical practice, the precise mechanisms that determine the progression of heart failure and ventricular remodelling are largely unknown. In recent years, there is growing evidence that autoimmunity and inflammatory mechanisms may contribute to disease progression in heart failure [3, 5, 8, 15].

Viral infections are widely believed to serve as a trigger for initiating autoimmune disease in humans. Sometimes these virus-triggered immune responses progress to a pathogenic autoimmunity state transforming into an autoimmune disease. The pathogenetic process leading from infection to inflammatory dilated cardiomyopathy (DCM) reflects known different stages of an organ-specific autoimmune disease. The first stage is dominated by viral infection itself, the second stage by the onset of multiple autoimmune reactions, and the third stage by the progression to cardiac dilatation and dysfunction [10]. Thus, myocardial inflammation, increased expression of pro-inflammatory cytokines and circulating autoantibodies are frequently observed in patients with myocarditis and DCM. In animal models an acute myocarditis leading to DCM can be induced both by viral infection or immunization with heart-specific autoantigens such as cardiac myosin or cardiac troponin I [4, 6, 9, 11].

In clinical practice the diagnosis of autoimmune myocarditis requires myocardial biopsy using established

histological (Dallas criteria), immunological, and immunohistological criteria or detection of cardiac-reactive autoantibodies in blood. Until now different autoantibodies directed against multiple cardiac antigens have been identified [12]. Circulating autoantibodies may even predict DCM development among relatives of DCM patients years before onset of symptoms [1]. Some antibodies have negative effects not only on myocytes in vitro and in animal models but also in some patients with DCM. In line with these observations is the interesting clinical observation on clinical improvement following extracorporeal immunoadsorption of these antibodies [2, 7, 13].

In this issue of *Basic Research in Cardiology*, Voigt and colleagues report on an enhanced autoimmune response to cardiac proteasomes in DCM patients [14]. They found that proteasome antibody (PA) levels are particularly increased in patients with advanced heart failure. Furthermore, the authors suggested a link between the detection of cardiotropic viruses in endomyocardial biopsies and detection of PA. Likewise, PA levels are enhanced in a murine model of chronic enterovirus myocarditis. Finally they demonstrated that PA exerts negative inotropic effects on cardiomyocytes.

The ubiquitin–proteasome system is known to play an important role in regulation of many cellular processes such as expression of transcription factors, regulation of gene transcription, cell proliferation, inflammation, cell death, and the removal of altered or misfolded proteins. Lately, activation or impairment of the ubiquitin–proteasome system has been shown to play a central role in a variety of cardiac diseases [16]. Furthermore there is compelling evidence that degradation-prone substrates accumulate in the myocardium of DCM patients [16]. In this context, the findings of Voigt and colleagues may be important for further understanding of the aetiology of inflammatory cardiovascular diseases and may open new approaches to treatment.

Z. Kaya · H. A. Katus (✉)
Department of Cardiology, University of Heidelberg,
69120 Heidelberg, Germany
e-mail: sekretariat_katus@med.uni-heidelberg.de

Even though the role of autoimmunity and autoantibodies in heart failure is still unclear, this and other studies provide compelling evidence that autoantibodies do exist in some patients with DCM and may contribute to disease progression in these patients. Therefore, the clinical significance of autoimmune responses and autoantibodies in patients with DCM should further be studied in large multicenter trials.

References

1. Caforio AL, Mahon NG, Baig MK, Tona F, Murphy RT, Elliott PM, McKenna WJ (2007) Prospective familial assessment in dilated cardiomyopathy: cardiac autoantibodies predict disease development in asymptomatic relatives. *Circulation* 115:76–83
2. Dorffle WV, Wallukat G, Dorffle Y, Felix SB, Baumann G (2004) Immunoadsorption in idiopathic dilated cardiomyopathy, a 3-year follow-up. *Int J Cardiol* 97:529–534
3. Ebermann L, Piper C, Kuhl U, Klingel K, Schlattner U, Sielarzik N, Zeichhardt H, Schultheiss HP, Dörner A (2009) Impact of myocardial inflammation on cytosolic and mitochondrial creatine kinase activity and expression. *Basic Res Cardiol* 104:247–257
4. Goser S, Andrassy M, Buss SJ, Leuschner F, Volz CH, Ottl R, Zittrich S, Blaudeck N, Hardt SE, Pfitzer G, Rose NR, Katus HA, Kaya Z (2006) Cardiac troponin I but not cardiac troponin T induces severe autoimmune inflammation in the myocardium. *Circulation* 114:1693–1702
5. Huang CH, Vallejo JG, Kollias G, Mann DL (2009) Role of the innate immune system in acute viral myocarditis. *Basic Res Cardiol* 104:228–237
6. Huber SA, Gauntt CJ, Sakkinen P (1998) Enteroviruses and myocarditis: viral pathogenesis through replication, cytokine induction, and immunopathogenicity. *Adv Virus Res* 51:35–80
7. Jahns R, Boivin V, Hein L, Triebel S, Angermann CE, Ertl G, Lohse MJ (2004) Direct evidence for a beta 1-adrenergic receptor-directed autoimmune attack as a cause of idiopathic dilated cardiomyopathy. *J Clin Invest* 113:1419–1429
8. Kawai C (1999) From myocarditis to cardiomyopathy: mechanisms of inflammation and cell death: learning from the past for the future. *Circulation* 99:1091–1100
9. Kaya Z, Goser S, Buss SJ, Leuschner F, Ottl R, Li J, Volkers M, Zittrich S, Pfitzer G, Rose NR, Katus HA (2008) Identification of cardiac troponin I sequence motifs leading to heart failure by induction of myocardial inflammation and fibrosis. *Circulation* 118:2063–2072
10. Mason JW (2003) Myocarditis and dilated cardiomyopathy: an inflammatory link. *Cardiovasc Res* 60:5–10
11. Neu N, Rose NR, Beisel KW, Herskowitz A, Gurri-Glass G, Craig SW (1987) Cardiac myosin induces myocarditis in genetically predisposed mice. *J Immunol* 139:3630–3636
12. Schulz-Menger J, Maisch B, Abdel-Aty H, Pankowitz S (2007) Integrated biomarkers in cardiomyopathies: cardiovascular magnetic resonance imaging combined with molecular and immunologic markers—a stepwise approach for diagnosis and treatment. *Herz* 32:458–472
13. Staudt A, Böhm M, Knebel F, Grosse Y, Bischoff C, Hummel A, Dahm JB, Borges A, Jochmann N, Wernecke KD, Wallukat G, Baumann G, Felix SB (2002) Potential role of autoantibodies belonging to the immunoglobulin G-3 subclass in cardiac dysfunction among patients with dilated cardiomyopathy. *Circulation* 106:2448–2453
14. Voigt A, Bartel K, Egerer K, Trimpert C, Feist E, Gericke C, Kandolf R, Klingel K, Kuckelkorn U, Stangl K, Felix SB, Baumann G, Klotzel PM, Staudt A (2009) Humoral anti-proteasomal autoimmunity in dilated cardiomyopathy. *Basic Res Cardiol*
15. Zimmermann O, Bienek-Ziolkowski M, Wolf B, Vetter M, Baur R, Mailander V, Hombach V, Torzewski J (2009) Myocardial inflammation and non-ischaemic heart failure: is there a role for C-reactive protein? *Basic Res Cardiol* 104:591–599
16. Zolk O, Schenke C, Sarikas A (2006) The ubiquitin–proteasome system: focus on the heart. *Cardiovasc Res* 70:410–421