LECTURE

Is cardiomyopathy an autoimmune disease?

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Abstract. Idiopathic dilated cardiomyopathy (DCM) is one of the leading causes of severe heart failure and the most common cause of heart transplantation due to its ventricular dilatations and contractile dysfuntions. Twenty percent of DCM is in the familiar form and the rest is sporadic. The clinical impact of DCM is far greater than its position in epidemiological terms. Despite recent improvements in therapy, both incidence and mortality are still very high. The main problem is its heterogeneous etiology. So far, three factors have been identified to be potentially important: enteroviral infection, immune mechanism and genetic factors. During the last 10 years there have been many investigations showing distinct autoantibodies or other immune factors in heterogeneous subsets of DCM which have contributed supportive and confounding evidence to the hypothesis that multiple autoimmune mechanisms are involved in DCM. Accumulated evidence hitherto demonstrated a variety of circulating autoantibodies in the sera of patients with DCM including antireceptor autoantibodies, myosin and ADP/ATP translocator protein, etc. Data available from both *in-vitro* and *in-vivo* studies of anti-receptor autoantibodies as well as from other autoantibodies and autoreactive lymphocytes demonstrated clearly that a subgroup of DCM is autoimmunity-mediated. This is understandable because DCM is heterogeneous, implying that different subgroups of DCM may have different pathogeneses. It may be practical in the future to separate "autoimmune cardiomyopathy" from other "idiopathic" DCM. (Keio J Med 51 (4): 208–212, December 2002)

Key words: autoimmunity, cardiomyopathy, receptors, antibody

Idiopathic dilated cardiomyopathy (DCM) is one of the leading causes of severe heart failure and the most common cause of heart transplantation due to its ventricular dilatations and contractile dysfuntions. Twenty percent of DCM is in the familiar form and the rest is sporadic. The clinical impact of DCM is far greater than its position in epidemiological terms. Despite recent improvements in therapy, both incidence and mortality are still very high. The main problem is its heterogeneous etiology. So far, three factors have been identified to be potentially important: enteroviral infection, immune mechanism and genetic factors. It is plausible that a subgroup of DCM is a post-infectious autoimmune disease, especially with individuals with genetic susceptibility.

Do We Have Evidence Supporting Cardiomyopathy as An Autoimmune Disease?

Evidence from clinical findings indicating existence of autoimmunity

During last 10 years there have been many investigations showing distinct autoantibodies or other immune factors in heterogeneous subsets of DCM which have contributed supportive and confounding evidence to a hypothesis that multiple autoimmune mechanisms are involved in DCM. In DCM and myocarditis, abnormalities in cell-mediated immunity have been clinically demonstrated by the findings of an altered lymphocyte function, altered relative proportions of lymphocyte subsets, an activated immune cytokine system, the in-

appropriate expression of the major histocompatibility complex on cardiac tissue and expression of adhesion molecules on cardiac myocytes.[1-9] The relative contribution of cellular and humoral immune disturbances to the pathogenesis of myocyte injury in various heart diseases has not been determined.

Accumulated evidence hitherto demonstrated a variety of circulating autoantibodies in the sera of patients with DCM. The list can be long, notably including autoantibodies directed against the myosin,[6,10-14] mitochondrial adenine nucleotide translocator and M7,[15-18] the branched chain alpha-ketoacid dehydrogenase dihydrolipoyl transacylase (BCKD-E2),[19] laminin,[20] β-adrenoceptors,[21-26] M2 muscarinic receptors,[25-27] sarcolemmal Na-K-ATPase[28] and heat shock protein[29] respectively.

Since Venter et al. reported autoantibodes against β2-adrenoceptors in allergic rhinitis and asthma in 1980,[30] there is a great amount of evidence available describing autoantibodies against β1-adrenoceptors in patients with DCM. Wallukat and Wollenberger found in 1987 that the IgG fraction of patients with DCM was able to display positive chronotropic effect on cultured neonatal rat myocytes.[22] By using the ligand bindings of DCM sera on rat cardiac membranes, Limas et al. demonstrated autoantibodies against β-adrenergic receptors in 40% of patients with DCM.[31] Magnusson et al., by using synthetic peptides corresponding to the second extracellular loops of human β1- and β2-adrenergic receptors as coated antigens in an enzyme-linked immunosorbent assay (ELISA), found autoantibodies against β1-adrenergic receptor peptide in 31% of patients with DCM but no autoantibodies against β2-adrenergic receptor peptide.[24] We have demonstrated for the first time that the sera from patients with DCM recognized the M2 muscarinic receptor peptide (36–37%).[25-27] Further study demonstrated that anti-M2 muscarinic receptor and β1-adrenoceptor autoantibodies have an almost identical spectrum of frequencies of occurrence in patients with DCM despite different geographical origins from Japan, China and Sweden.[25-27,32] Moreover, anti-β1-adrenoceptor autoantibodies are mainly present in DCM but not in hypertension[25] and valvular heart disease.[33] On the contrary, autoantibodies against the α1-adrenoceptors and AT1 receptors were demonstrated mainly in hypertension (64% and 44% of cases, respectively).[34,35]

Although it has been shown that anti-muscarinic receptors and β1-adrenoceptor autoantibodies are more common in DCM compared with other antireceptor autoantibodies, it does not mean that these antireceptor autoantibodies are only specific for DCM since there are only limited data available from antibody screenings from other cardiovascular diseases and/or by use of other autoantigens. Recently we have shown that, in aortic banding- and adriamycin-treated rats, the frequencies and titers of autoantibodies to the muscarinic receptor and β1-adrenoceptor were increased when myocardial remodeling occurred, suggesting that cardiac remodeling itself, in two disparate models of cardiomyopathy, was able to trigger the genesis of anti-receptor autoantibodies.[36] Therefore anti-muscarinic receptor and β1-adrenoceptor autoantibodies are possibly triggered by myocardial remodeling in patients with DCM. This may explain why there are also anti-muscarinic receptor and β1-autoantibodies adrenoceptor in about 40% of patients with chronic Chagas' infection.[37] But this does not rule out that anti-muscarinic receptor and β1-adrenoceptor autoantibodies can be pathogenic and play an important role in the progression, instead of initiation, of cardiomyopathy and heart failure, and as long as they are functionally active in-vivo and persist over a certain period they may contribute to the pathophysiology of the disease. For example, viral infection can induce myocardial damage which in turn triggers antibody production which can escalate to aggravate myocardial damage. It is worthwhile to point out that antibody production may be triggered due to myocardial injury secondary to ischemia because of alteration of self-antigens that are normally sequestered from the immune system. Therefore, whether autoantibodies play an important role in the development of disease depends on the availability of sustained antigen exposure, properties of autoantibodies in immunological, biochemical and kinetic aspects and other genetic factors as well as subclasses in serum of autoantibodies. Recently, Jahns et al. showed that anti β1-adrenoceptor antibodies from six of eight patients with DCM act as receptor-sensitizing agents whereas two of eight acts as partial agonists,[38] and Warraich et al. showed that IgG3 is probably more important than other subclasses in mediating DCM.[39]

Evidence from in-vitro studies

Low titers of autoantibodies, which can be part of the normal immunologic repertoire, are not necessarily pathogenic.[32] Functional characterization of an antibody is the first step toward defining the role of the antibody in the development of disease. Wallukat et al. demonstrated that the IgG fractions of patients with DCM were able to increase the beating rate of myocytes.[22,40] Limas et al. found that positive sera from DCM were able to immunoprecipitate β-adrenergic receptors and to inhibit adenylyl cyclase activity.[31] Magnusson et al. demonstrated that purified autoantibodies can not only decrease the the binding sites but also recognize the target receptors by both immunobloting and immunocytochemistry.[24,41] Krause et al. demonstrated that autoantibodies against β1-adrenergic

receptors from DCM were able to increase the activity of cAMP-dependent protein kinase (PKA).[42] Likewise, we have demonstrated specific localization of muscarinic receptors in the human myocardium from DCM using anti-M2 muscarinic receptor autoantibodies, thus suggesting that autoantibodies can interact with their target receptors in failing heart tissue. In addition, anti β1 adrenergic receptor and M2 muscarinic receptor autoantibodies from DCM patients displayed positive and negative chronotropic effects respectively, which were resistent to desensitization, being different from the classical β-adrenergic receptor agonist isoprenaline and the muscarinic receptor agonist carbachol which can induce desensitization after the short a period of time.[41,43,44]

Evidence from in vivo studies

According to the definition of autoimmune disease as suggested by Rose and Bona (1993),[45] it is not enough to define DCM as an autoimmune disease although our and others' previous data have shown functional activities of autoantibodies *in vitro*. Direct evidence is still needed *in vivo* to make sure that cardiomyopathy can be reproduced in animals by autoimmunity, either by passive transfering of immune components from patients with DCM to SCID (Severely Combined Immunodeficieny) mice or by chronic active immunization of animals with autoantigens. Schwimmbeck *et al.* successfully transfered peripheral blood leukocytes of patients with chronic myocarditis into SCID mice that developed human cellular infiltrates of the myocardium and an impairment of the left ventricular function.[46] Another study from our laboratory showed that transfer of lymphocytes from patients with DCM to SCID mice demonstrated induced unfavourable remodeling and increased myocardial fibrosis.[47]

By use of active immunization with receptor peptide(s) during 1 year, it was shown that both groups of rabbits immunized with either the β1-adrenoceptor peptide or the M2 muscarinic receptor peptide displayed significantly enlarged ventricles and thinner walls, as compared with the control group. When immunization was performed using combined β1 and M2 receptor peptides, cardiac hypertrophy was seen. Moreover, microscopic examinations of the rabbit hearts from both immunized groups demonstrated mainly degenerative changes.[48–50] Recently, Iwata *et al.* used a similar protocol but in only 6 months demonstrated myocardial hypertroph, β1-adrenoceptor receptor desensitization, increased Gi protein and G-protein-coupled receptor kinase-5 expression in association with myocyte disorganization and interstitial fibrosis.[51,52]

Evidence from therapeutical approaches

Theoretically, autoimmune therapy should be aimed at modulating the immune system to inhibit antibody production and at blocking the active autoantibodies of pathogenic importance. In order to restore normal immune function, it necessitates elucidation of mechanisms for initiation, development and regulation of autoimmunity including genetic factors, cytokines, heat shock proteins etc. Unfortunately this mechanism has not been fully understood yet. Therefore current autoimmune therapy is focused more upon inhibiting antibody activity and elimination of antibodies. For example, Matsui *et al.* has shown that the β1-receptor blocker bisoprolol was able to prevent autoimmune injury by β1-receptor antibody.[52]

Immunoadsorption has been and still is a heated topic. Several studies have demonstrated that immunoadsorption can improve cardiac functions.[53–56] The underlying mechanisms for favourable effects on cardiac function remain unsolved. It has been postulated that antireceptor autoantibodies play an important role.[52,53,57,58] Our data from antibody analyses of immunoadsorption, however, demonstrated that elimination of antireceptor autoantibodies may be important but not the only explanation. A recent study by Felix *et al.* showed that removal of circulating negative inotropic autoantibodies may contribute to the early beneficial hemodynamic effect of immunoadsorption.[59] However, the specific antigen(s) to these negative inotropic autoantibodies have not been clarified. Another study by Staudt *et al.* demonstrated that immunoadsorption can ameliorate myocardial inflammation.[56]

The above therapeutic approaches add further weight to the hypothesis that cardiomyopathy is autoimmunity-mediated.

A Subgroup of Cardiomyopathy Is Autoimmune Disease Related

To summarize the data available from both *in-vitro* and *in-vivo* studies of antireceptor autoantibodies as well as from other autoantibodies and autoreactive lymphocytes, it is evident that a subgroup of DCM is autoimmunity-mediated. This is understandable because DCM is heterogeneous, implying that different subgroups of DCM may have different pathogeneses. It may be practical in the future to separate "autoimmune cardiomyopathy" from other "idiopathic" DCM.

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