Role of autoimmunity in dilated cardiomyopathy

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Persistent viral infection of the myocardium and autoimmunity are two of the main pathogenic hypotheses for dilated cardiomyopathy (DCM). A unifying hypothesis also suggests that an initial viral insult may trigger or precipitate autoimmunity. Is it becoming clearer whether DCM is a chronic viral disease, a post-infectious autoimmune process, or genetically determined organ-specific autoimmune disease?

When tolerance to “self” antigens is lost autoimmune disease results. It is characterised by the presence of circulating autoantibodies, which are not necessarily pathogenic but represent markers of continuing tissue damage.¹ In autoimmune disease that is not organ specific there are autoantibodies against ubiquitous autoantigens and tissue damage is generalised. In organ-specific autoimmune disease one organ only is affected and the autoantibodies react with its unique autoantigens.

Heart muscle is the only organ affected in DCM and thus to test the autoimmune hypothesis we need to know whether the criteria of an organ-specific autoimmune disease are fulfilled (table 1). Organ-specific autoimmune diseases occur as a result of genetic pre-

disposition and environmental influences. The genetic predisposition accounts for both the fact that different autoimmune conditions may be associated in patients or in their family members and the common finding that single autoimmune diseases often run in families. The inheritance of susceptibility is usually polygenic. Organ-specific autoimmune diseases are commonly associated with specific HLA class II antigens,¹ but it is not known how the HLA system determines the predisposition to a specific disease.

Most organ-specific autoimmune diseases are chronic and apparently idiopathic. Organ and disease specific antibodies are found in the affected patients. These antibodies are also detected in family members, sometimes years before the disease develops, and they identify symptom free relatives who are at risk.¹

Is organ-specific autoimmunity involved in human acute myocarditis?

There is evidence that acute myocarditis is a continuing autoimmune disease. Many patients have circulating cardiac autoantibodies (table 2)²⁻⁸ and some have several features of classic organ-specific autoimmunity or of insulin dependent diabetes mellitus, which is an atypical but well established organ-specific autoimmune disease in which viruses may be implicated (table 3). Familial aggregation of acute myocarditis has not been systematically investigated, but acute myocarditis and DCM have been reported in different members of the same family.⁹ Little is known about the associations of acute myocarditis with other autoimmune diseases, except that giant cell myocarditis is associated with myasthenia gravis¹⁰ and pernicious

Table 1 Features of organ specific autoimmunity

- Middle aged women most frequently affected
- Familial aggregation
- Organ and disease specific circulating autoantibody in patients and in unaffected family members
- Cell mediated autoimmunity impaired
- Associated autoimmune diseases in the same patient or in family members
- HLA association
- Mononuclear cell infiltration and abnormal HLA molecule expression in the target organ
- Disease induced in animal models after immunisation with relevant autoantigen

HLA, human leucocyte antigen.

Table 2 Circulating autoantibodies in acute myocarditis

Antibody type	Method	% Antibody positive		Healthy controls	Reference
		AM	OCD		
Muscle specific:	IFL				
ASA		47*	NT	25	2 3
AMLA		41*	NT	12	2 3
AFA		28*	NT	6	2 3
IFA		32*	NT	3	2 3
Heart-reactive	IFL	59*	NT	0	4
Anti-laminin	ELISA	73*	NT	6	5
Anti-mitochondrial:					
M7	ELISA	13*	10	0	6
ANT	SPRIA	91*†	0	0	7
Anti-β receptor	Bioassay	96*†	8	0	8

*P < 0.05 v controls; †P < 0.05 v controls with other cardiac disease. AFA, anti-fibrillary antibody; AM, acute myocarditis; AMLA, anti-myolemmal antibody; ANT, adenine nucleotide translocator; ASA, anti-sarcolemmal antibody; ELISA, enzyme linked immunosorbent assay; IFA, anti-interfibrillary; IFL, indirect immunofluorescence; NT, not tested; OCD, other cardiac disease; SPRIA, indirect microsolid-phase radioimmunoassay.

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Table 3 A comparison between acute myocarditis and organ-specific autoimmunity

Features	AM	Recent onset IDDM	OS AI
Clinical presentation	Acute	Acute	Chronic
Sex	M > F	M > F	F > M
Age (yr)	20–40	1–19	40
Familial aggregation	Yes?	Yes	Yes
Viral aetiology	?	?	?
Organ specific antibody +ve (%)	40–100	80	80
HLA association	?	DR3–4	DR3–4–5
Abnormal cell mediated immunity	?	Yes	Yes
Association with other AI disease	Yes?	Yes	Yes
Mononuclear cell infiltration	Yes	Yes	Yes
Abnormal HLA expression:			
Target cell	No	Yes	Yes
Endothelium	De novo	Enhanced	Enhanced
Animal models	Yes	Yes	Yes

AM, acute myocarditis; IDDM, insulin dependent diabetes mellitus; OSAI, organ-specific autoimmunity.

anaemia.¹¹ Important autoimmune features, such as the impairment of cell mediated immunity and HLA association have not yet been investigated, but Herskowitz *et al* did not find abnormal expression of HLA on the target cell, the myocyte, in acute myocarditis.¹² This abnormal expression is not an absolute prerequisite for autoimmune conditions: in multiple sclerosis, for example, HLA class II is not expressed on neurons.¹³ Importantly, (see below) animal models of autoimmune myocarditis have been produced.

Evidence for autoimmunity in experimental murine myocarditis

A model for autoimmune myocarditis was found accidentally when workers trying to unravel the mechanisms of myocardial damage in experimental Coxsackie B virus-induced murine myocarditis found that only certain strains of mice (A-J background) were susceptible to acute myocarditis. More chronic sequelae resembling DCM developed in these strains.¹⁴ Early on (7–10 days) in the disease CD8 T cells were cytotoxic for virally infected cells. Later (2–3 weeks) they were able to kill cells that were not infected with viruses, suggesting the generation of autoimmune T cell clones.^{14 15} In the late phase of autoimmune myocarditis no infectious virus was detectable (by conventional virus culture and isolation methods) in the heart of the

Table 4 Autoantibodies in dilated cardiomyopathy

Antibody type	Method	% Antibody positive		Healthy controls	Reference
		AM	OCD		
Muscle specific:	IFL				
ASA		10	NT	25	3
AMLA		9	NT	12	3
AFA		24*	NT	6	3
IFA		41*	NT	3	3
Organ specific cardiac	IFL	26*†	1	3	19
Heart reactive	IFL	20*	NT	0	4
Anti-laminin	ELISA	78*†	NT	6	5
Anti-mitochondrial					
M7	ELISA	31*	10	0	6
ANT	SPRIA	57*†	0	0	7
Anti-β receptor					
Inhibiting	LBI	30*†	8	4	20
Inhibiting	ELISA	31*†	0	12	21
Stimulating	Bioassay	95*†	8	0	8
Anti-α and β MHC	Immunoblot	46*†	8	0	22

*P < 0.05 v controls; †P < 0.05 v OCD. LBI, ligand binding inhibition; MHC, myosin heavy chain. See footnote to table 2 for other abbreviations.

affected mice. Two populations of antibodies developed in these mice: one cross-reacted with skeletal and cardiac myosin and the other was specific for the cardiac isoform.¹⁶

The key experiment to prove the autoimmune nature of the chronic form of myocarditis was then performed: immunisation of A-J normal mice with cardiac myosin alone, without virus, induced histologically and immunologically identical disease.¹⁷ Immunisation with skeletal myosin did not produce myocarditis, showing that myosin-induced myocarditis was a model for an organ-specific autoimmune heart disease. Humoral and cellular transfer experiments in this autoimmune model showed that the myocarditis process was transferable only by T cells and was inhibited by monoclonal antibodies binding to HLA class II molecules which disturbed antigen presentation to the T helper cells.¹⁸

These studies showed that the chronic form of murine myocarditis was an autoimmune disease triggered by a virus in animals with a predisposing genetic background, rather than a persistent viral infection. In addition, the finding that autoimmune myocarditis was produced after stimulation of the immune system with complete Freund's adjuvant and autoantigen (myosin) indicates not only that viral infection but also that other external pro-inflammatory stimuli could trigger autoimmunity in genetically predisposed animals and humans.

Humoral autoimmune phenomena in dilated cardiomyopathy

Clinical and experimental observations indicate that myocarditis is a likely candidate for autoimmune pathogenesis. But are organ and disease specific circulating cardiac antibodies detectable in patients with DCM?

Several groups have consistently found cardiac antibodies in DCM (table 4),^{3–8 19–22} but the organ and disease specificities of these antibody types have not been always evaluated. For instance, using indirect immunofluorescence (IFL) earlier studies identified antibodies to sarcolemmal and myofibrillar antigens, but these were not strictly cardiac specific because they cross reacted with skeletal muscle.³ In addition, it was not clear whether these muscle specific antibodies were associated with DCM, because controls with other cardiac disease and with heart failure not caused by DCM were not evaluated.

When the frequency of cardiac antibodies was recently reassessed using IFL on human hearts, organ and disease specific antibodies of the IgG class were found in 26% of DCM patients from England.¹⁹ These antibodies did not stain human skeletal muscle and their specificity to the heart was confirmed by relevant absorption studies.¹⁹ Interestingly, another group reported that 20% of DCM patients from the United States had antibodies that gave a diffuse cytoplasmic staining pattern on rat heart.⁴ The cardiac specificity of these antibodies was not investigated by

testing on skeletal muscle and by absorption studies, but their IFL pattern on rat heart was indistinguishable from that given on human heart by the organ-specific cardiac antibodies. This suggests that the antibodies detected by IFL on human and on rat heart recognise the same organ-specific cardiac autoantigen(s). Two of the autoantigens recognised by these antibodies have already been identified as the α and β heavy chains of myosin; additional and as yet unknown antigens are also present.²² The β chain is expressed in skeletal and cardiac myosin and is therefore not specific to the heart. The α isoform is expressed solely within the myocardium. Antibodies to this molecule are truly organ-specific cardiac autoantibodies.²²

The identification of α and β heavy chains of myosin as relevant autoantigens in DCM patients parallels what is seen in the experimental model of autoimmune myocarditis DCM.^{16–18} But what is the pathogenic relevance of these findings? Until recently it was thought unlikely that any intracellular autoantigen would be of primary importance in pathogenesis, but it is now clear that endogenous peptides derived from the intracellular processing of self cytoplasmic proteins are normally present in the cleft of surface HLA molecules.²³ Thus intracellular autoantigens can be seen by the immune system and under normal conditions tolerance is maintained. In the presence of appropriate triggers (for example, viral infection or other inflammatory stimuli) and of genetic predisposition, tolerance could break down and autoimmunity to these self intracellular autoantigens might ensue. Recent work with T cell hybridomas showed that residential antigen presenting cells (APC) in the normal mouse heart process and express myosin/MHC complexes (MHC is the mouse equivalent of the HLA system). Expression of these myosin complexes was increased by the induction of autoimmune myocarditis.²⁴ Clearly there is local turnover of myosin molecules by the local APCs in the absence of cardiac damage. This strongly accords with myosin being an important cardiac autoantigen. The release or exposure of antigen may be a vital step in the disease process but only in those individuals that are susceptible to the disease. It may be that part of this susceptibility to autoimmune myocarditis is conferred both by MHC and non-MHC genes.¹⁴

Although myosin is probably an important autoantigen, the work on the animal model of DCM suggests that it is unlikely that the cardiac myosin antibody is directly responsible for cardiac damage. Passive transfer of highly concentrated autoantibody in the mouse does not induce myocarditis in genetically susceptible recipients, and the disease is clearly T cell mediated.²⁵ T cells are also more likely to be the effector arm of the suggested autoimmune pathogenesis in patients. This does not undermine the possible importance of the antibody to cardiac myosin as a disease marker or even or predictive marker, like the islet cell autoantibodies in IDDM.¹

Antibodies against two distinct mitochondrial antigens, the M7 antigen⁶ and the adenine nucleotide translocator (ANT),⁷ have also been detected in DCM sera. Mitochondrial antigens have generally been classified as non-organ specific,¹ thus their suggested involvement in a supposedly organ-specific autoimmune disease seemed novel. None the less, the heart-specificity of the M7 antibodies was shown by absorption studies; ANT antibodies were not tested. Studies should be performed to rule out a potential cross reactivity with skeletal muscle because it is not known whether there are two distinct translocator isoforms for cardiac and skeletal muscle.

Schultheiss *et al* found that experimentally induced affinity-purified anti-translocator antibodies cross reacted with calcium channel complex proteins of rat cardiac myocytes, enhanced transmembrane calcium current, and produced calcium dependent cell lysis in the absence of complement.²⁶ They suggested that these effects may impair the function of the carrier protein, imbalance energy delivery and demand within the cell, and lead to cell death. They also speculate that this may be an important pathogenic mechanism of autoimmune myocardial damage in DCM and in myocarditis. The presence of this novel mechanism of antibody dependent cell lysis has not, however, been shown using the antibodies present in patients' sera. Specific confirmation of binding to and a deleterious effect on the calcium channel is now required.

Several groups have demonstrated antibodies against the β_1 adrenoceptor.^{8, 20, 21} Limas and Limas detected these antibodies in 30–40% of DCM patients by a binding inhibition assay.²⁰ Antibody positive DCM sera induced sequestration and endocytosis of β_1 receptors that were predominantly dependent on β receptor kinase and selectively inhibited isoproterenol-sensitive adenylate cyclase activity.²⁰

Wallukat *et al* studied another functional index of the β_1 receptor antibody. Antibody positive DCM sera accelerated the beating of neonatal rat heart myocytes in vitro.⁸ The effect was inhibited by propranolol, bisoprolol, and metoprolol. It is well known that some patients with DCM benefit from treatment with β blockade. Wallukat *et al* suggested that this permanent humoral stimulation of the β_1 receptor could account for the accelerated decline in function of the failing heart in some patients with DCM. This hypothesis offers a rationale for the use of β_1 antagonists in these patients.

There is a question mark over the organ specificity of the anti- β_1 receptor antibodies. β Receptors are situated in several different tissues and even the supposedly cardiac specific β_1 receptors are found in low concentration in the liver and the kidney. There does not appear to be a cardiac specific isoform for the β receptor as there is for the α myosin heavy chain. In addition cross reactivity was reported between anti- β_1 receptor antibodies and anti-HLA antibodies.²⁷ If this is con-

firmed the incidence of the anti- β_1 receptor antibodies in DCM will be considerably lower and their projected importance much less.

In other organ-specific autoimmune diseases antibodies in most cases are not cytotoxic; so attempts passively to transfer DCM from human to genetically susceptible mice with one or more antibody would provide conclusive evidence for antibody mediated pathogenesis.

The argument that ANT, the M7 antigen, and β_1 receptor are important cardiac autoantigens would also be strengthened if they can be shown to induce myocarditis in the animal model in the same way as myosin does.

Is organ-specific autoimmunity involved in dilated cardiomyopathy?

About 30–40% of patients with DCM have organ and disease specific autoantibodies. In these patients the disease may be claimed to be autoimmune. But what about the antibody negative patients? There are several concomitant or alternative explanations. Firstly, DCM may be an aetiologically heterogeneous condition; the absence of cardiac antibodies could indicate that cell-mediated autoimmune mechanisms are predominant, or that autoimmunity is not involved in the antibody negative patients, or both.

Secondly, because cardiac antibodies are early markers of disease that become undetectable as the disease progresses, as seen in IDDM, they may not be found in some DCM patients.²⁸ There is a report that cardiac antibodies are more common in patients with better exercise tolerance, as measured by oxygen consumption during maximal symptom-limited treadmill exercise testing.²⁹ In another preliminary report, cardiac antibodies were detected in asymptomatic DCM relatives with early cardiac dysfunction.³⁰ These data support the possibility that the absence of cardiac antibodies, at least in some DCM patients, is related to disease progression. Clinical and serological follow up studies of the antibody positive patients, and relatives with cardiac antibodies are needed. Finally, different DCM patients can have antibodies with different antigen specificities. Collaborative work with exchange of sera by different laboratories

and assessment of more than one antibody specificity in standard positive and negative samples is likely to clarify this.

In addition to the presence of the antibody markers, how many of the criteria for an autoimmune disease are fulfilled in DCM? As with myocarditis most features are present (table 5). Myocarditis resembles recently diagnosed IDDM, whereas DCM resembles long-standing IDDM. These common features include: male predominance, HLA-DR4 association,³¹ familial aggregation of cases (20–25% of DCM cases)³², and a relative lack of mononuclear cell infiltrates in the target organ. Indeed most patients with DCM come to their physician with overt heart failure and a history going back several weeks, months, or even years. It is highly likely that such patients are presenting at a late stage in the natural history of the disease, when the autoimmune damage has already occurred and fibrosis is all that is seen on the cardiac biopsy specimen.

Cell-mediated immunity seems to have been less extensively investigated than humoral immunity in patients with myocarditis or DCM and the results are controversial.^{33–36} Examination of T cell subsets has revealed isolated abnormalities of T helper/suppressor cell ratios³³ and of suppressor cell function.³⁴ Natural killer (NK) cell activity has been shown to be reduced in DCM,³⁵ but this finding is not cardiac specific. Leucocyte migration inhibition and lymphocyte transformation assays did not show significant differences between DCM patients and controls, but some DCM patients did show leucocyte migration inhibition with cardiac antigens, suggesting that autoimmunity might be involved in this subgroup.³⁶

Most of this work was completed before animal studies and human humoral work established that the myosin heavy chain,²² the β_1 receptor,^{8 20 21} and the ANT⁷ were potentially important autoantigens. None of this previous cellular work has involved antigen specific targeting or T cell proliferation studies. None studied patients with early disease, in whom antigen-specific cellular activation is more likely to be detected. Thus the central role of cell-mediated immunity in experimental DCM is now very clear whereas the potential role of the T lymphocyte in human DCM warrants further investigation. Autoimmunity is involved in causing myocardial damage in about a third of patients with dilated cardiomyopathy.

Table 5 A comparison between dilated cardiomyopathy and organ specific autoimmunity

Features	DCM	Longstanding IDDM	OSAI
Clinical presentation	Chronic	Chronic	Chronic
Sex	M > F	M > F	F > M
Age	20–40	20–40	40
Familial aggregation	Yes	Yes	Yes
Viral aetiology	?	?	?
Organ specific antibody +ve (%)	30	30	80
HLA association	DR4–5	DR3–4	DR3–4–5
Abnormal cell-mediated immunity?	?	Yes	Yes
Association with other AI disease	No?	Yes	Yes
Mononuclear cell infiltration	No	No	Yes
Abnormal HLA expression:			
Target cell	No	Yes	Yes
Endothelium	De novo	Enhanced	Enhanced
Animal models	Yes	Yes	Yes

DCM, dilated cardiomyopathy. See footnote to table 1 for other abbreviations.

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