

Etiologies of cardiomyopathy and heart failure

Evidence for a final common pathway for disorders of the myocardium (pages 246 and 320–330).

THIS ISSUE OF *Nature Medicine* presents three papers that provide new data on the pathogenesis of heart muscle disease and heart failure. Two of these elegant studies characterize the pathogenic mechanisms underlying hypertrophic cardiomyopathy (HCM) and associated heart failure^{1,2}; the third provides important new information on the development of dilated cardiomyopathy³ (DCM). Although both disorders cause heart muscle abnormalities, they differ in that HCM is a disease in which the ventricular walls and interventricular septum are thick (hypertrophic), whereas DCM is a disease in which the ventricle (mainly the left ventricle) is dilated, thin-walled and contracts poorly.

HCM is a genetic disorder⁴ that presents with left ventricular and interventricular septal hypertrophy (Fig. 1), hypercontractile ventricular function and, sometimes, ventricular outflow tract obstruction. Histopathologic evaluation identifies myocyte hypertrophy, myocyte disarray and fibrosis leading to diastolic dysfunction (that is, abnormalities of ventricular relaxation). Mutations in genes encoding sarcomeric proteins⁴, which include β -myosin heavy chain, α -tropomyosin, cardiac troponin T and troponin I, myosin binding protein C, and regulatory and essential myosin light chain, have been shown to cause familial HCM.

Specific mutations have been found that result in severe, life-threatening HCM, whereas others seem to be benign⁵. Georgakopoulos *et al.*¹ present physiologic data obtained from mice with one of the more severe genetic mutations, the Arg403Gln β -MHC mutation. The authors identify alterations in contraction kinetics, with delayed pressure relaxation and chamber filling but accelerated pressure development in very young mice, similar to the diastolic dysfunction of the human disorder. Older mice also develop systolic abnormalities including reduced cardiac output and increased chamber stiffness. Increased calcium sensitivity was suggested to be underlying the diastolic dysfunction. Related to this conclusion, Lim and Molkenin² describe in this issue the apparent interaction of calcium handling,

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cardiac hypertrophy and heart failure. Intracellular calcium is known to regulate contractile function and relaxation of the myocardium by coordinated release and sequestration of calcium from the sarcolemma and sarcoplasmic reticulum. At the onset of cardiac hypertrophy, intracellular calcium release increases, but as hypertrophy progresses to heart failure, the amplitude of this release decreases, resulting in substantial increase in dias-

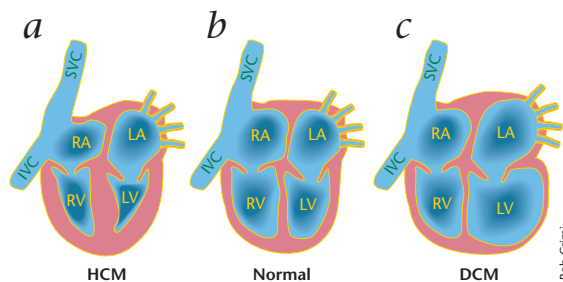


Fig. 1 Normal and cardiomyopathic hearts. **a**, Hypertrophic cardiomyopathy (HCM), with thick walls and small ventricular chambers. **b**, Normal cardiac anatomy. **c**, Dilated cardiomyopathy (DCM), with a large left ventricular (LV) cavity and thin LV wall. RA, right atrium; LA, left atrium; RV, right ventricle; LV, left ventricle; IVC, inferior vena cava; SVC, superior vena cava.

tolic calcium, manifested as diastolic dysfunction. Calcineurin, a calcium-regulated phosphatase, mediates cardiac hypertrophy in transgenic mouse hearts when overexpressed⁶ and regulates the hypertrophic response through action on the transcription factor NF-AT3. In addition, cyclosporine and FK506, calcineurin inhibitors, can prevent cardiac hypertrophy and DCM as well as cause a hypertrophic dilated myopathy when mutated⁷. In this report, Lim and Molkenin² show that calcineurin is activated in heart failure, suggesting that calcineurin plays an essential part in the progressive nature of human heart failure as well. Thus, a concept emerges for cardiac hypertrophy and its resultant pathophysiology whereby a variety of signaling factors and active molecules act on a cascade of events, ultimately affecting the sarcomeric protein, and the sarcomeric function, the final common pathway of HCM development⁸

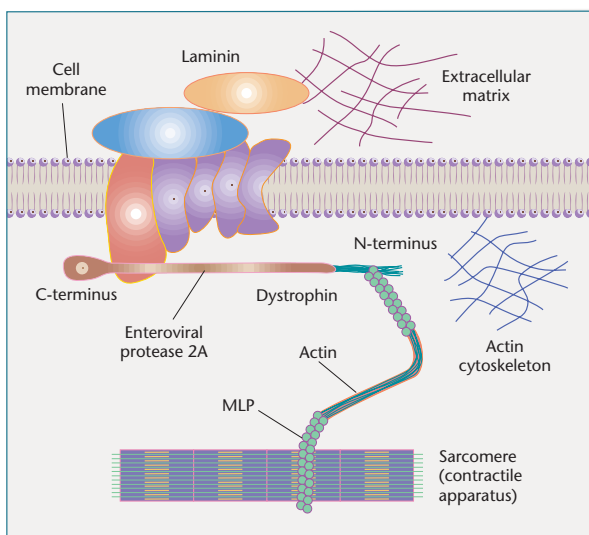
(Fig. 2).

Using this 'final common pathway' hypothesis, the work of Bardorff *et al.*³ can be interpreted in a broad context that defines the development of myocarditis and its sequelae, DCM. Myocarditis is an inflammatory disorder of the heart, commonly caused by viruses (particularly adenoviruses and enteroviruses), which results in contractile dysfunction and ventricular dilation, as seen in other forms of DCM (Fig. 1). In about 33% of patients, this acute disorder resolves; in the remainder, it develops into chronic DCM. Although most myocarditis is acquired, a small percentage is inherited, probably because of an abnormality of host function. DCM, on the other hand, seems to be inherited in >30% of patients. The only genetic abnormalities identified as causes of familial DCM and well-characterized in humans so far include dystrophin mutations in X-linked dilated cardiomyopathy⁹ and, more recently, mutations in cardiac actin¹⁰. Interestingly, actin, an important component of the thin filament of the sarcomere (Fig. 2), is the only main sarcomeric protein not associated with HCM development. However, this protein links up with the dystrophin protein, which in turn hooks up with the dystrophin-associated glycoproteins

(the sarcoglycans and dystroglycans) and ultimately the basal lamina (Fig. 2). Many animal models have been produced that develop DCM (ref. 10) because of mutations in the sarcoglycans, dystroglycans, and other proteins that interact with these proteins (vinculin, metavinculin), as well as proteins interacting with actin (MLP) and dystrophin (Fig. 2). In this issue of *Nature Medicine*, Bardorff *et al.*³ demonstrate that enteroviral protease 2A cleaves dystrophin directly, resulting in the development of post-myocarditis DCM. This intriguing report further supports previous speculations that cytoskeletal disruption is ultimately responsible for the development of DCM because of interruption of the final common pathway.

These studies further our understanding of the heart in health and disease, particularly in the development of abnormalities of cardiac contraction and relaxation. Once this is fully described and under-

Fig. 2 Sarcomere and cytoskeleton. In hypertrophic cardiomyopathy (HCM), direct sarcomeric gene mutations or a flaw in the cascade of events involved in sarcomeric function results in this cardiac phenotype. In dilated cardiomyopathy (DCM), abnormalities of the cytoskeleton or molecules interacting with the cytoskeleton result in the dilated, dysfunctional ventricular phenotype. MLP, muscle LIM Protein.



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stood, new and improved therapeutic strategies will be developed to combat these diseases which are responsible for nearly five million cases of heart failure in our country at a cost of over \$12 billion². Focusing research efforts on the cascade of events involved in development of a cardiomyopathic disorder or its final com-

mon pathway should ultimately lead to a longer and healthier life for all.

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Fas counter-attack—the best form of tumor defense?

New *in vivo* evidence confirms that tumor-expressed Fas ligand impairs immune responses to cancer by inducing apoptosis of anti-tumor immune effector cells.

FAS LIGAND (FasL) induces cell death in apoptosis-sensitive cells expressing its receptor, Fas (CD95/APO-1). FasL-mediated apoptosis of activated immunocytes regulates immune responses and contributes to immune privilege in the eye and reproductive organs. Tumors also express FasL, and the ability of tumor cells to induce Fas-mediated apoptosis of co-cultured lymphoid cells *in vitro* has indicated that FasL expression enables cancers to mount a 'Fas counterattack' against anti-tumor immune effector cells¹. Since this first suggestion of an orchestrated defense against immune attack, considerable evidence has accumulated to support the hypothesis. It is now clear that intratumoral lymphocytes are susceptible to counterattack; that the mechanism is active *in vivo* in human cancer and is effective against natural killer (NK) cells (one of the main anti-tumor effector cells); and that FasL mediates immune privilege rather than neutrophil recruitment in human tumors.

FasL expression has been demonstrated *in vivo* in several types of cancer, and recent evidence suggests that tumor-infiltrating lymphocytes (TILs) are suscep-

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tible to Fas-mediated counterattack. TILs have been shown to express substantially upregulated Fas relative to peripheral blood lymphocytes (PBLs), suggesting activation in response to tumor antigens and consequent sensitization to FasL-mediated counterattack². Lack of expression of the co-stimulatory molecule B7 by tumor cells enhances the Fas sensitivity of co-cultured T cells *in vitro*³. As many tumors downregulate expression of B7 *in vivo*, T cells may be particularly susceptible to FasL-mediated counterattack within the tumor microenvironment (see Fig.).

Apoptosis has been demonstrated *in situ* in TILs within FasL-expressing melanomas⁴, hepatocellular carcinomas and gastric adenocarcinomas. In esophageal cancer, the extent of apoptosis of TILs was found to vary regionally within the tumors in relation to the local status of FasL expression. There was a statistically significant, mean

fivefold reduction of TILs concomitant with a mean twofold increase in TIL apoptosis within FasL-positive compared with FasL-negative tumor nests⁵. Hence, in the esophageal cancers, local expression of FasL by nests of tumor cells was associated with apoptotic depletion of TILs. This finding provided compelling evidence that the Fas counterattack was operative in human esophageal cancers *in vivo*.

A recent report demonstrated that murine AK-5 tumor cells transiently upregulated FasL when grown in the peritoneal cavity of syngeneic mice, and that this FasL upregulation coincided with depletion of the intraperitoneal NK cell population⁶. Depletion of NK cells was local to the tumor microenvironment, as splenic and peripheral NK cells were unaffected. The same AK-5 tumor cells did not express FasL when injected subcutaneously. FasL-negative, subcutaneous AK-5 tumors showed about 70% regression, mediated largely by NK cells, whereas FasL-expressing intraperitoneal tumors grew successfully, always resulting in death of the host. These findings suggest that FasL-mediated counterattack against