Calcineurin Inhibition as Therapy for Cardiac Hypertrophy and Heart Failure

Requiescat in Pace?

Richard A. Walsh

Congestive heart failure is a major public health problem that is increasing, despite a reduced incidence and prevalence of other forms of cardiovascular disease. Initially, the heart responds to diverse pathological stimuli by an increase in mass achieved principally by enlargement of terminally differentiated cardiomyocytes. The resulting augmented chamber mass provides temporary maintenance of wall stress and organ function. If the pathological stimulus is sufficiently intense or prolonged, decompensated hypertrophy characterized by diminished cardiomyocyte and organ function occurs, and the syndrome of congestive heart failure ensues.1

Over the past decade, the application of molecular and cellular biological techniques to this process has begun to provide mechanistic insights into the subcellular processes responsible for impaired cardiac function in hypertrophy and failure.2 Evidence has accumulated to implicate both cell death (necrosis and apoptosis) and chamber remodeling due to alterations in the extracellular matrix in the pathogenesis of heart failure. In addition, multiple laboratories have focused on biochemical alterations intrinsic to the cardiomyocyte, such as abnormalities of calcium homoeostasis, altered myofilament activation, and altered abundance or activity of sarcolemmal ion pumps and channels. In particular, a number of laboratories using a variety of in vitro and in vivo approaches have implicated changes in signal transduction pathways in the development of this pathological process. In this context, intense interest was recently evoked by the elucidation of a new cardiomyocyte signal transduction pathway that could initiate cardiac hypertrophy and failure. Molkentin et al3 demonstrated that the calcium calmodulin– dependent protein phosphatase calcineurin can activate hypertrophic signals in vitro using neonatal cardiomyocytes and in vivo using transgenic mice that overexpressed components of the pathway in a cardiac-specific postnatal manner. Inhibition of this pathway by cyclosporine in these experimental settings prevented hypertrophy and failure. Subsequently, cyclosporine administration also appeared to ameliorate the development of cardiac hypertrophy in additional lines of transgenic mice with cardiac-specific overexpression of a variety of mutant sarcomeric proteins.4 Differing perspectives on the role of the calcineurin pathway among the hierarchy of signal transduction systems from these and other recently published studies are presented as point/counterpoint articles in this issue of Circulation Research.5,6

Of even greater interest for those in the field are original studies published in this issue of the Journal from three separate laboratories that have examined the potential role of calcineurin inhibition by cyclosporine in the prevention of cardiac hypertrophy and failure in conventional genetic and hemodynamic overload rodent models of cardiac hypertrophy. In each case, the result is negative or incomplete abrogation of the pathological process. Zhang et al7 tested the ability of the calcineurin inhibitors cyclosporin A and FK 506 to prevent pressure-overload left ventricular hypertrophy using two widely accepted rat models: the spontaneously hypertensive rat and suprarenal aortic banding. Importantly, these investigators examined multiple time points in the hypertrophy process and different times for initiation of drug administration. Despite elevated calcineurin phosphatase activity in the hearts of the two rodent hypertrophy models and nearly complete inhibition (90%) of phosphatase activity by cyclosporine in the hypertrophied myocardium of the treated groups, neither the amount of cardiac hypertrophy nor cardiac function was appreciably altered. Ding et al8 also report the effects of cyclosporine administration on the degree of pressure-overload hypertrophy induced by 4 weeks of ascending aortic banding in mice. Similar to the study presented by Zhang et al7, this group failed to observe any increase in the amount of cardiac hypertrophy between cyclosporine–treated and control banded mice, despite similar elevations of left ventricular systolic pressure. However, in contrast to all prior studies, Ding et al8 measured a decrease in calcineurin phosphatase activity in hypertrophied compared with normal hearts that was further reduced by cyclosporine administration. Finally, Meguro et al9 report the effects of calcineurin inhibition by cyclosporine on the degree of hypertrophy produced by transverse aortic banding in mice. Calcineurin phosphatase activity in the myo-

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cardium did not differ between hypertrophied and control hearts but was depressed by cyclosporine inhibition. Cyclosporine administration modestly attenuated the degree of cardiac hypertrophy in response to pressure overload, depressed isovolumic left ventricular function, and accelerated mortality of the banded animals. The differences in these latter two mouse studies may, in part, reflect differences in mouse strains, location of the aortic band, and the numbers of mice that were used in each experimental group (much larger in the study presented by Meguro et al"). Two other preliminary studies also failed to demonstrate a beneficial effect of cyclosporine administration on the development of cardiac hypertrophy in the supraprenal aortic-banded rat or transverse aortic-banded mouse.10,11

In balance, it would appear that cyclosporine inhibition can prevent cardiac hypertrophy when it is induced by transgenic overexpression of one of the constituents of the calcium-calcineurin-NFAT3-GATA4 pathway in mice or when some mutated sarcomeric proteins are similarly overexpressed in this species. However, there are no available data that demonstrate that calcineurin inhibition can reverse cardiac hypertrophy and failure under these experimental conditions. Calcineurin inhibition fails to prevent or only modestly attenuates the development of acquired pressure-overload hypertrophy in rats and mice with no change or impaired cardiac function.

Unanswered Questions and Directions for Future Research

How can we reconcile the striking disparity between the results derived from in vitro neonatal cardiomyocytes and in vivo transgenic studies with the disappointing results presented herein from conventional animal models of in vivo acquired or genetic rodent hypertrophy? Congestive heart failure is a clinical syndrome that represents the final common phenotype of diverse pathological stimuli. It is unlikely that any single molecular or biochemical event will explain its common forms. Instead, investigators will pursue hierarchical mechanisms that may or may not be targets for drug development. The initial appeal for a primary role of the calcineurin pathway in cardiac hypertrophy and failure was derived from multiple clinical studies that have demonstrated elevated basal calcium levels in cardiomyocytes enzymatically extracted from hearts of patients with clinical congestive heart failure2 and the fact that this phosphatase is calcium dependent. However, none of the available studies has measured basal or cyclic calcium levels in the various model systems in which this pathway has been examined in the myocardium. There are also no available data regarding the role of the calcineurin pathway in volume-overload hypertrophy, ischemic models of cardiomyopathy, or myocarditis, in which T-cell activation may play a more prominent role. Experience with other putative mediators of cardiac hypertrophy and failure has taught us that there may be striking model-, species-, and/or cardiac chamber–specific differences.12 Only after such studies are completed will we definitively understand what role, if any, calcineurin-NFAT3-GATA4 activation plays in the development of clinically relevant cardiac hypertrophy and failure. In this regard, it will also be critically important to determine whether and to what extent calcineurin activation occurs in human cardiomyopathic heart failure.

One final problem with all available studies is the use of cyclosporine and FK 506 to inhibit the calcineurin pathway. Recently, Hojo et al13 have demonstrated that cyclosporine may directly induce cancer progression (a well-known complication of this form of immunosuppressive therapy after orthotopic transplantation) by stimulating the production of transforming growth factor-β (TGF-β). Although the mechanism for enhanced TGF-β production is unknown, the cardiotoxic effects of this growth factor may offset the results of cyclosporine inhibition of calcium-calcineurin-NFAT3-GATA4 in vivo.

The evolving information regarding the potential role of the calcineurin pathway in the production of cardiac hypertrophy and failure illustrates the importance of multidisciplinary studies in this arena. Use of neonatal cardiomyocytes, genetically engineered mice, and conventional experimental animal models and analysis of cardiomyopathic human tissues each has its advantages and disadvantages. Evidence for a mechanism that is present from each approach is more compelling than a role from any one approach taken in isolation. For example, recent studies in neonatal cardiomyocytes, genetically engineered mice, and human cardiomyopathic tissue suggest a potential role for protein kinase C activation in the development of cardiac hypertrophy, contractile depression, and heart failure.14–19

References


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