Calcineurin Signaling in Human Cardiac Hypertrophy

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On the basis of studies in cell and animal models, a great diversity of signaling molecules have been implicated in stimulus–response pathways by which hypertrophic growth of the myocardium is controlled. It remains unclear, however, which signal transduction pathways are pertinent to the common forms of cardiac hypertrophy that lead to heart failure and sudden death in humans.

The initial observation in 1998 that calcineurin, a calmodulin-dependent protein phosphatase, is capable of driving cardiac hypertrophy, heart failure, and death in experimental animal models received special attention for several reasons. Previous evidence suggested that dysregulation of calcium metabolism is an integral feature of stresses that promote hypertrophy, and calcineurin was known to be abundant in cardiomyocytes, reinforcing the plausibility of its proposed role as a key mediator of hypertrophic signaling. Perhaps most intriguing is the fact that calcineurin is the target of drugs already approved for use in humans to inhibit T-cell activation and prevent rejection of transplanted organs, validating the concept that nodal points in complex signaling networks exist and can indeed serve as targets for clinically efficacious drugs. Initial studies indicated that calcineurin-inhibitory drugs could prevent or repress pathological forms of cardiac hypertrophy induced by a variety of stimuli.

Over the past 3 years, enthusiasm for calcineurin as a potential target for drugs to prevent heart failure in humans has waxed and waned3–7 as many laboratories have focused attention on this pathway with sometimes discrepant results.8–15 The administration of calcineurin-inhibitory drugs has proven ineffective or counterproductive in preventing hypertrophy or heart failure in several animal models.14,15 On the other hand, overexpression in cardiomyocytes of calcineurin-inhibitory proteins, arguably a better test than the administration of drugs with systemic toxicity, has produced favorable consequences in several models of hypertrophy.16–18 The debate goes on, but animal models of increasing sophistication should help to clarify our understanding.

Ultimately, of course, principles established in animal models must be evaluated for their relevance to the disease processes that affect our patients. A study presented in this issue of Circulation takes a step in this direction. Ritter et al19 acquired myocardial tissue samples at the time of surgery from patients with hypertrophic obstructive cardiomyopathy (HOCM) or aortic stenosis (AS). They assessed the enzymatic activity of calcineurin, the abundance of immunoreactive calcineurin A protein (the catalytic subunit), and the phosphorylation state of nuclear factor of activated T cells-2 (NF-AT2), an important substrate of calcineurin that participates in downstream signaling to control gene transcription. Compared with a set of control samples from normal myocardium, a uniform increase in the enzymatic activity of calcineurin measured under conditions of calcium excess was noted. The results of this enzymatic assay in vitro measure peak catalytic capacity of calcineurin and bear no predictable relationship to the activation state of calcineurin in vivo (where calcium concentrations are limiting), and therefore, this finding is not in itself very persuasive in supporting a role for calcineurin signaling in human cardiac hypertrophy. However, the electrophoretic mobility of NF-AT2 from HOCM and AS patients also was increased, presumably representing dephosphorylation of NF-AT2 and providing biochemical evidence of increased calcineurin activity in vivo.

The analysis by Ritter et al19 of calcineurin A protein abundance in human myocardial specimens produced an apparent contradiction: A monoclonal antibody directed against an amino terminal epitope suggested an increased abundance of calcineurin A in hypertrophic hearts (111% to 278%), whereas an antibody recognizing a carboxyl terminal epitope produced the opposite result: reduced abundance of calcineurin A in hypertrophic hearts (17% to 88% of control values). The authors interpret this result to reflect posttranslational modification of calcineurin A in human hypertrophic hearts through proteolytic processing to remove the carboxyl terminal region, within which resides an autoinhibitory domain, and thereby to increase catalytic activity, as measured in their in vitro assay. Truncated forms of calcineurin A produced through genetic engineering are, in fact, constitutively active, lending credence to this notion. Proteolytic processing of calcineurin in the manner proposed by Ritter et al19 would represent a novel mechanism of activation that potentially could prolong or augment calcineurin-dependent signaling events.

These results are intriguing, but additional studies are required to test this hypothesis more rigorously. Important controls and confirmatory experiments were omitted from the article by Ritter et al but may have been unfeasible because of the limited mass of tissue available for biochemical studies. The putative truncated form(s) of calcineurin eventually must be isolated to confirm the immunoblot results and to map the precise site(s) of proteolytic processing. Depending on the site of cleavage, it would be possible to produce truncation products that are enzymatically inactive, as well as others that...
may have constitutive activity. Ultimately, testing the relevance of calcineurin signaling to pathological forms of cardiac hypertrophy in humans will require the development of novel measures to modulate this signaling pathway that can be applied safely to human subjects. Current immunosuppressive drugs that inhibit calcineurin are unsuitable to the task because of noncardiac effects. Further exploration of calcineurin-dependent signaling pathways is revealing new drug targets, some of which are expressed selectively in cardiomyocytes. If proteolytic processing of calcineurin is indeed a mechanism for activating the enzyme in human cardiac hypertrophy, other new targets may become evident.

**References**


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