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.

See p 2265

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 waned as many laboratories have focused attention on this pathway with sometimes discrepant results. The administration of calcineurin-inhibitory drugs has proven ineffective or counterproductive in preventing hypertrophy or heart failure in several animal models. 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.

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 al 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 al 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

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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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