**Calcineurin Inhibition and Cardiac Hypertrophy**

Mark A. Sussman *et al.* (1) report that the immunosuppressants cyclosporin (CsA) and FK506 prevent the development of hypertrophy in transgenic mouse models of intrinsic cardiomyopathy and, of more general import, in a rat model of extrinsic pressure-overload hypertrophy caused by banding of the abdominal aorta. This appears to add further evidence to the recent postulate that activated calcineurin is both necessary for and sufficient to induce cardiac hypertrophy (2). To assess the physiological role of calcineurin-mediated signaling in vivo, we studied the effect of cyclosporin in a mouse model of extrinsic pressure-overload hypertrophy induced by transverse aortic constriction (TAC) (3). Despite high CsA-serum levels in the treated animals (2901 ± 218 ng/ml) (4), all operated animals developed hypertrophy within 3 weeks. There was no significant difference in the degree of left ventricular hypertrophy between untreated and CsA-treated TAC mice (Fig. 1). In a similar study, Luo *et al.* (5) found that administration of CsA to Sprague-Dawley rats “had no effect on their heart-weight/body-weight ratio.”

Beyond possible age-, timing-, or species-related differences, the contrasting outcomes in these studies could be the result of different sites of banding. It has been shown recently that constriction of the abdominal aorta, but not the aortic arch, activates the renin-angiotensin-system in a rat pressure-overload model (6). Taking into account that angiotensin signaling is in part mediated by the activation of phospholipase C and mobilization of intracellular calcium (7), it is probably not unexpected that inhibition of the downstream target calcineurin prevents hypertrophy in animal models that activate or overexpress these pathways.

Mechanical stress, however, also causes hypertrophy in angiotensin receptor knockout mice (3), as well as in CsA-treated mice with TAC, which indicates that in this context the hypertrophic response is mediated at least in part by signaling pathways different from the calcium-calcineurin cascade. Thus, activated calcineurin is sufficient but not necessary for the induction of cardiac hypertrophy.

**Joachim G. Müller**
**Shintaro Nemoto**
**Martin Laser**
**Blase A. Carabello**
**Donald R. Menick**

Gazes Cardiac Research Institute, Medical University of South Carolina, Charleston, SC 29425, USA

E-mail: menickd@musc.edu

*Fig. 1. Effect of calcineurin inhibition on the development of pressure-overload hypertrophy in C57BL/6 mice. *P = 0.01 versus respective non-TAC controls.*

**References and Notes**
3. Pressure overload was produced by transverse aortic constriction as described before [M. Hamawaki *et al.*, Am. J. Physiol. **274**, H468 (1998)]. Male C57BL/6 mice (age 3 to 5 months) were anesthetized with ketamine (50 mg/kg) and xylazine (2.5 mg/kg), and respiration was artificially controlled. The transverse aorta was constricted by tying a 6-0 nylon suture around the vessel over a blunted 27G needle. Three weeks after surgery, animals were killed by removal of the heart in deep anesthesia. Left ventricular (LV) weight was determined directly after the left ventricle was dissected free of the atria and right ventricle. The body weight at the end of the study was used for indexing purposes. ANOVA with Scheffé’s F procedure for post-hoc testing was performed for statistical analysis.
4. Cyclosporin A was injected subcutaneously at a dose of 25 mg/kg twice daily. Administration was initiated 2 days before surgery, maintained during the entire study period, and terminated 12 hours before killing the animals. CsA serum levels were determined in 250-μl blood samples obtained by direct cardiac puncture immediately before cardiac excision.

Response: We agree with Müller *et al.* that calcineurin is not necessary for the induction of pressure overload hypertrophy. Since our report (1) was published, we have extended our studies of abdominal aortic banded rats treated with cyclosporin and have noted that the effect of hypertrophy attenuation by cyclosporin is temporally regulated, such that rats treated with cyclosporin for longer treatment periods (21 days) did not show a significant prevention of the response (2). Our original description demonstrated a positive correlation after a 6-day study (1). A more comprehensive model would suggest that calcineurin is a parallel pathway involved in pressure overload hypertrophy, and that inhibition with cyclosporin may blunt the magnitude of the response (reducing the time available for achieving maximal response). It would be unexpected if one pathway were sufficient to explain all aspects of cardiac hypertrophy, given the vast number of stimuli and disease states that are known to be involved. Countless studies have elucidated critical roles for other signaling factors such as PKC, MAPK (ERKs, JNKs, p38s), PKA, CamK, ras, adrenergic receptors, angiotensin II receptors, specific G-α proteins, and calcium itself.

**Jeffery D. Molkentin**

Division of Molecular Cardiovascular Biology, Children’s Hospital Medical Center, 3333 Burnet Avenue, Cincinnati, OH 45229–3039, USA

*References*  
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