Positive Role for a Negative Calcineurin Regulator in Cardiac Hypertrophy

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Calcineurin is protein phosphatase with characteristic calci-um- and calmodulin-dependent activation through its regulatory subunits.1 Activated calcineurin dephosphorylates downstream transcription factor nuclear factor of activated T cells (NFAT), which leads to its nuclear translocation and transcriptional activation.1 Calcineurin-NFAT signaling axis is initially discovered as an essential pathway for T-cell activa-tion1 but has now been implicated in a broad range of cellular processes and cell types ranging from fungus to plants. In the heart, calcineurin-mediated signaling is recognized as a common intracellular pathway leading to cardiac hypertrophy and pathological remodeling, thus adding yet another negative regulator for calcineurin signaling after T-cell receptor induction. In addition to its inhibitory effect on calcineurin activity, carabin/EPI64C is also reported to have additional inhibitory role for Ras-mediated mitogen-activated protein kinase activation through an intrinsic Ras GTPase-activating protein activity.8 In a recent report by Bissierer et al7 using both genetic knockout mouse model and adenovirus-mediated cardiac targeted gene transfer, carabin/EPI64C is shown to be both necessary and sufficient to attenuate pressure-overload–induced cardiac hypertrophy and pathological remodeling, thus adding yet another negative regulator of calcineurin into the player list in the cardiac hypertrophy regulatory network. In this issue, Zhu et al9 further advance this notion that carabin/EPI64C is a critical regulator of cardiac hypertrophy by offering several important new lines of evidence.7 First, these investigators generated cardiac specific knockout and cardiomyocyte-specific transgenic mouse models to demonstrate in vivo that carabin/EPI64C-mediated regulation of cardiac hypertrophy and pathological remodeling is a cardiomyocyte cell-autonomous process. Second, the underlying mechanism seems to involve direct interaction and inhibition of calcineurin signaling rather than Ras-mitogen-activated protein kinase pathway as originally reported. Finally, carabin/EPI64C-mediated hypertrophy regulation is conserved across different species, and its expression exerts cardiac protection against pressure-overload–induced cardiac hypertrophy and dysfunction in both mice and nonhuman pri-mates. These findings further demonstrate the translational potential of carabin/EPI64C as a therapeutic target for pathological hypertrophy in the stressed human heart.

As an endogenous feedback regulator for calcineurin, carabin/EPI64C is both a downstream target of calcineurin/NFAT-mediated transcriptional induction and an upstream negative inhibitor for calcineurin signaling.5 Because calcineurin/NFAT-mediated signaling is a common pathway significantly elevated in the diseased heart, we should expect to

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observe an induced expression of carabin/EPI64C in stressed hypertrophic myocardium as observed for RCNA1. Yet, both reports by Bisserier et al.9 and Zhu et al.3 showed a significantly reduced expression of carabin/EPI64C in the pathologically stressed heart and the human failing heart. Therefore, the loss of carabin/EPI64C (but not RCAN1)–mediated negative feedback may represent an interesting new mechanism underlying the hyperactivity of calcineurin in cardiac hypertrophy and pathological remodeling. It is not clear why carabin/EPI64C expression is downregulated in the diseased heart and whether restoring its expression in established hypertrophic heart is able to reverse the pathogenic progression. Understanding the uncoupling mechanism between calcineurin and carabin/EPI64C and testing the therapeutic effect of restoring carabin/EPI64C expression in established hypertrophy may uncover a truly translational path to treat cardiac hypertrophy and pathological remodeling. It is important to note that although pharmacological inhibition of calcineurin has proved to be effective in clinic to suppress immune response and is widely used for organ transplant and other immune disorders, they have not been demonstrated efficacious to treat heart failure or hypertrophic cardiomyopathy in humans. Considering the hypertensive effect of cyclosporine (a pharmacological inhibitor of calcineurin) at systemic level,10 cautions must be taken to translate these insights learnt from tissue-specific and precision genetic manipulations to clinical applications. Clearly, there are a lot more sciences still waiting to be done.

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**References**
