Positive Role for a Negative Calcineurin Regulator in Cardiac Hypertrophy

Chen Gao, Yibin Wang

Calcineurin is a calcium- and calmodulin-dependent protein phosphatase that is activated downstream of T-cell receptor signaling through the nuclear factor of activated T cells (NFAT) pathway. Calcineurin-NFAT signaling is a key mediator of various cellular processes, including cell division, differentiation, and stress response. Calcineurin-mediated signaling can have a significant ameliorative effect on cardiac hypertrophy and pathological remodeling.

In this issue, Zhu et al. add a new piece of evidence to a significant body of literature and further demonstrate that calcineurin signaling can have a significant ameliorative effect on the pathogenesis of cardiac hypertrophy and dysfunction in response to various stresses.

Like many stress-induced signaling pathways, calcineurin pathway is also tightly controlled by a cohort of endogenous negative regulators in cells. The prototypic regulator of calcineurin-1 (RCAN1) is transcriptionally controlled by NFAT and serves as a negative feedback regulator for calcineurin signaling. In addition to RCAN1, many other negative regulators for calcineurin-NFAT signaling have been identified, including cain/cabin1 (calcineurin inhibitor 1), RCAN2, RCAN3 (also known as DSCR1L2, MCIP2, RCN2, ZAKI-4, and ZAKI4), RCAN3 (also known as DSCR1L2, MCIP3, RCN3, and hRCN3), four-and-a-half LIM domain protein 2, CHP1 (calcineurin B homologous protein 1), known as SLC9A1BP, Sid470p, p22, and p24), and CHP2. Most of them function through direct interaction with calcineurin as a scaffold. However, specific inhibitory function for calcineurin has also been identified for muscle-specific RING (Figure) as an E3 ubiquitin ligase through targeted calcineurin degradation and plasma membrane calcium ATPase as membrane calcium pump. Different from RCAN1, many of these endogenous inhibitors are not necessarily bona fide negative feedback regulators for calcineurin signaling as they are not directly induced by calcineurin-NFAT-mediated transcription on stimulation, but nevertheless modulate calcineurin signaling under different extracellular stimuli. Indeed, like RCAN1, manipulating many of these endogenous calcineurin inhibitors can have a significant effect on cardiac hypertrophy and pathological remodeling.

In 2007, Pan et al. identified yet another negative feedback regulator for calcineurin, termed carabin or EPI64C, which fulfills the criteria of both negative inhibitory function to calcineurin and induction by calcineurin-mediated 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. In a recent report by Bisserier et al. using both genetic knockout mouse model and adeno-associate virus-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 al. further advance this notion that carabin/EPI64C is a critical regulator of cardiac hypertrophy by offering several important new lines of evidence. 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 primates. 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. Because calcineurin/NFAT-mediated signaling is a common pathway significantly elevated in the diseased heart, we should expect to
observe an induced expression of carabin/EPI64C in stressed hypertrophic myocardium as observed for RCNA1. Yet, both reports by Bisserier et al9 and Zhu et al3 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


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