Letter to the Editor

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Calcium, Calpains, and Cardiac Hypertrophy: A New Link

To The Editor:

In the March 28, 2008 issue of *Circulation Research*, Letavernier et al assessed the effects of calpain inhibition on angiotensin (Ang) II–induced cardiovascular remodeling.[1] These authors used transgenic mice expressing high levels of calpastatin to inhibit Ang II–dependent calpain activation. They show that prevention of Ang II–induced calpain activation is associated with impaired nuclear factor (NF)-κB activation in heart tissue, which eventually leads to decreased Ang II–induced cardiac hypertrophy. This finding adds substantial novel information to our understanding of how calpains might be involved in the complex regulation of cardiac hypertrophy. However, compelling evidence as to how calpains are activated by Ang II in the myocardium and how the calpain/calpastatin system is linked to NF-κB activation is not provided. In the May 23, 2008 issue of *Circulation Research*, we show that Ang II induces calcium release via the inositol 1,4,5-trisphosphate receptor ($InsP_3R$) pathway in cardiomyocytes and that impaired $InsP_3R$-dependent calcium release after chromogranin B (CGB) knockdown attenuates NF-κB activation and leads to decreased production of brain natriuretic peptide (BNP).[2] Here, we discuss the convergent results of these 2 studies and show that calpain/calpastatin and CGB may be important for developing new strategies in the prevention and treatment of cardiovascular disease.

The calpain/calpastatin system in the heart, and particularly its potential role in the complex regulation of cardiac hypertrophy, is only poorly understood. Calpains are calcium-activated cysteine proteases present in the cytosol as inactive proenzymes. Two isoforms (μ- and m-calpain) are ubiquitously expressed, whereas the other isoforms are tissue-specific. Calpain activity is tightly controlled by its endogenous inhibitor calpastatin.[3] Although these common principles in calpain regulation are well described, activation and downstream signaling of calpain in the myocardium are not fully understood. In the heart, 2 transcription factors play central roles in the regulation of cardiac hypertrophy, nuclear factor of activated T-cells (NFAT) and NF-κB.[4] It is generally accepted that calpain-dependent activation of the serine/threonine protein phosphatase calcineurin controls NFAT activity in cardiomyocytes[5]; however, the role of calpain-dependent NF-κB activation in the heart is not established. Recent in vitro studies suggest calpain mediates degradation of the cytosolic NF-κB inhibitor IκBα, a step that is a prerequisite in the activation of NF-κB.[6]

We show that impaired $InsP_3R$-dependent calcium release in CGB knockdown cardiomyocytes attenuates both NF-κB activation and production of BNP on Ang II stimulation.[2] CGB is a positive modulator of $InsP_3R$ activity that we showed is expressed in neonatal cardiomyocytes and adult mice ventricular myocardium.[2,7] $InsP_3$ functions as a key second messenger in the regulation of cardiac hypertrophy in which both the $InsP_3R$ and CGB are upregulated.[2,4,8] BNP is widely used as an established marker of hypertrophy in vitro and in vivo.[4] In light of our findings, the in vivo study by Letavernier et al[1] suggests that the missing link in calcium-dependent NF-κB activation in the heart is the calcium-activated protease calpain. Decreased activation of calpain in calpastatin transgenic mice impairs NF-κB activity and attenuates Ang II–induced hypertrophy, just as we observed for impaired $InsP_3R$-dependent calcium release in CGB knockdown cardiomyocytes on Ang II stimulation.[1,2] The parallels of the 2 studies become even more obvious when 2 observations are highlighted: neither calpain inhibition by calpastatin overexpression nor impaired $InsP_3R$-dependent calcium release impaired NFAT signaling but rather selectively targeted NF-κB. Therefore, calpain might not just be the missing link in cardiomyocyte calcium-dependent NF-κB activation but may also be of crucial importance in the differential activation of calcium-activated transcription factors such as NFAT and NF-κB.

Although the intriguing parallels of the 2 independent studies suggest that the missing link in calcium-dependent NF-κB activation in the context of Ang II–induced cardiac hypertrophy is the calcium-activated protease calpain, further studies are needed for a detailed and comprehensive description of the underlying signaling pathway. Including the calpain/calpastatin system in the complex signaling network that controls cardiac hypertrophy will be a challenging task for ongoing research but is likely to be a key to our understanding of the pathophysiology and will ultimately lead to the development of novel therapeutic agents in the treatment of cardiovascular disease.

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