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Cardiac Hypertrophic Signaling Mediated by the Interaction between Na^+/H^+ Exchanger and the Neuronal Ca^{2+} Sensor NCS-1

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Summary

Activation of the sarcolemmal Na^+/H^+ exchanger 1 (NHE1) is increasingly documented as a process involved in cardiac hypertrophy and heart failure (HF). We have previously reported that transgenic (Tg) mice overexpressing a constitutively active form of human NHE1 in hearts, developed cardiac hypertrophy and HF. Elevation of intracellular Ca^{2+} levels followed by increase in Na^+ level, and subsequent activation of Ca^{2+}-dependent hypertrophic signaling is the molecular mechanism of NHE1-induced cardiac hypertrophy (Circ Res 2008).

Like this, intracellular Ca^{2+} regulates variety of cellular processes, including cardiac remodeling and the functions of Ca^{2+} is mediated by Ca^{2+}-binding proteins. NCS-1 (Neuronal Ca^{2+} sensor-1) is one of these EF hand Ca^{2+}-binding proteins, which plays an important role in neuronal functions. Although NCS-1 is also expressed in the heart, little is known about its functions. Since our preliminary observations using NCS-1 knock-out (KO) mice suggested that NCS-1 is involved in hypertrophy, we studied whether NCS-1 actually mediates cardiac hypertrophy and if so, what the molecular mechanism is, by using both NHE1 Tg and NCS-1 KO mice. Immunofluorescence analysis revealed that NCS-1 is predominantly localized to the Ca^{2+} handling organelles, such as plasma membrane, nuclear envelope and sarcoplasmic reticulum in cardiac muscle. Over-expression of NCS-1 induced cardiac hypertrophy concomitant with increased spontaneous beating rate of cultured myocytes. In contrast, KO myocytes exhibit less sensitive to hypertrophic stimuli; i.e. receptor stimulation-induced increases in intracellular Ca^{2+} transient and cardiac hypertrophy were both prevented in KO hearts, suggesting that NCS-1 mediates hormone-induced cardiac hypertrophy. Mice overexpressing NHE1 but lacking NCS-1 protein, however, had little effect on preventing NHE1-induced hypertrophy. These results suggest that the signaling pathway involving NCS-1-mediating hypertrophy may be different from NHE1-mediating one, where CaMKII/HDAC pathway is the main pathway. We are now investigating the possible involvement of calcineurin/NFAT pathway as a main signaling pathway mediating NCS-1-induced hypertrophy.