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Physiological Importance of Functional Coupling between TRPC3 and Nox2 in Cardiac Homeostasis

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Summary

Chronic stresses induces pathological cardiac remodeling in which production of reactive oxygen species (ROS) plays a critical role. We have revealed that those ROS were produced by NADPH oxidase 2 (Nox2), despite low Nox2 expression levels in the normal heart. We demonstrate that transient receptor potential canonical 3 (TRPC3) Ca^{2+}-permeable channel acts as a positive regulator of Nox2 in both enzymatic activation and protein expression in cardiomyocytes during pathological remodeling. TRPC3 physically interacts with Nox2 through TRPC3 carboxyl-terminal regions, escaping Nox2 from proteasomal degradation, resulting in amplification of Ca^{2+}-dependent Nox2 activation. This TRPC3-Nox2 coupling mediates mechanical stress-induced cardiac fibrosis and a chemotherapy agent Doxorubicin-induced cardiac atrophy in mice. Inhibition of TRPC3-Nox2 coupling in cardiomyocytes could significantly suppressed Dox-induced cardiac atrophy. Furthermore, voluntary exercise which has a beneficial effect on cardiac function significantly reduced the level of TRPC3 and Nox2 protein expression. Exercised mouse heart increased their elasticity which resulted in improvement of cardiac function. These results suggest that functional and physical coupling of TRPC3 and Nox2 mediates various stress-induced cardiac remodeling and inhibition of TRPC3-Nox2 coupling will be a promising therapeutic target for the treatment of pathological muscle remodeling.