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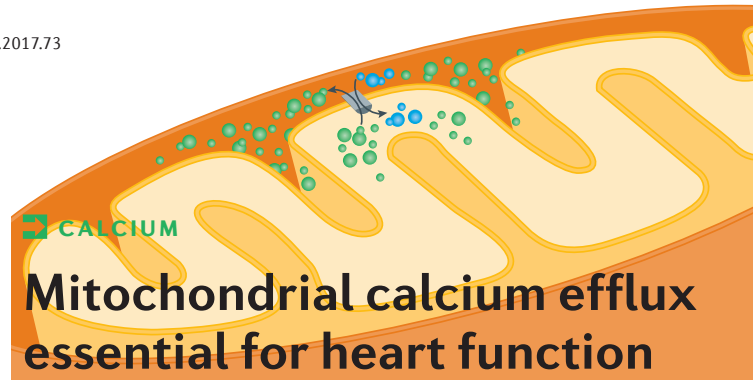

Mitochondrial calcium efflux essential for heart function

> cardiomyocyte-specific overexpression of NCLX reduced infarct size in a mouse model of ischaemia–reperfusion injury

Calcium signalling in mitochondria has a crucial role in cell physiology, both in health and disease, but its function in the cardiovascular system is controversial. John Elrod and colleagues now show that loss of the mitochondrial sodium–calcium exchanger (NCLX), encoded by the *Slc8b1* gene, in mice induces heart failure via necrotic cell death.

Involvement of mitochondrial calcium signalling in cardiac tissue homoeostasis has been called into question by studies showing that deletion of a recently discovered mitochondrial calcium uniporter (MCU) did not result in major cardiac phenotypes; effects were limited to inhibition of stress-responsive signalling pathways. Elrod and colleagues hypothesized that other MCU-independent calcium-uptake mechanisms were responsible for normal mitochondrial function. They focused their attention on NCLX, a mitochondrial exchanger thought to be the primary mediator of calcium extrusion from mitochondria in excitable cells.

By using a conditional, cardiomyocyte-specific *Slc8b1*-knockout mouse model, Elrod and colleagues showed that deletion of NCLX resulted in the sudden death of mice within 2 weeks, which was preceded by ventricular dilatation and decreased left ventricular function. Furthermore, hearts from NCLX-deficient mice were characterized by increased mass and cardiac fibrosis compared with those from control mice.

To investigate the mechanisms underlying these findings, the investigators focused on the mitochondrial permeability transition pore (mPTP), which is known to be involved in necrotic cell death in the heart. Mitochondrial swelling, an indicator of mPTP opening, was increased in mitochondria isolated from *Slc8b1*-knockout mice compared with those isolated from control mice. Consistent with this finding, the investigators found that cellular necrosis, measured by analysis of sarcolemmal integrity, was increased in cardiomyocytes from NCLX-deficient mice compared with those from control mice.

To confirm *in vivo* the involvement of mitochondrial calcium overload and subsequent necrosis following the deletion of NCLX, Elrod and colleagues analysed *Slc8b1*-knockout mice crossed with mice deficient in *Ppif*, which encodes cyclophilin D, a component of the mPTP. Survival of these double-knockout mice was significantly increased compared with NCLX-deficient mice. In addition, the investigators found that cardiomyocyte-specific overexpression of NCLX reduced infarct size in a mouse model of ischaemia–reperfusion injury, an effect that correlated with improved contractile function and reduced superoxide generation. Furthermore, NCLX overexpression in a mouse model of heart failure resulted in decreased left ventricular dilatation and improved left ventricular function compared with control, as well as a reduction in cardiac hypertrophy, fibrosis, and inflammation.

These findings demonstrate that mitochondrial calcium efflux, controlled by NCLX, is indispensable for normal cardiac function, and suggests that enhancement of mitochondrial calcium efflux might be a novel therapeutic strategy in cardiac disease.

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ORIGINAL ARTICLE Luongo, T. S. *et al.* The mitochondrial Na^+/Ca^{2+} exchanger is essential for Ca^{2+} homeostasis and viability. *Nature* http://dx.doi.org/10.1038/nature22082 (2017)
FURTHER READING Brown, D. A. *et al.* Expert consensus document: Mitochondrial function as a therapeutic target in heart failure. *Nat. Rev. Cardiol.* **14**, 238-250 (2017)