PLN-R14del mutation: pathogenetic mechanism in a transgenic mouse model of dilated cardiomyopathy

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Abstract:

The sarco/endoplasmic Ca^{2+}-ATPase (SERCA2a) and its natural inhibitor phospholamban (PLN) play a pivotal role in cardiac excitation-contraction coupling. A heterozygous deletion of arginine 14 of the PLN protein (R14del) is associated with a dilated cardiomyopathy (DCM). It has been previously shown that overexpression of PLN-R14del leads to a substantial decrease in SERCA2a affinity for Ca^{2+}, thus proposing that a “superinhibitory” effect of mutant PLN on SERCA2a may lead to the DCM phenotype. This theory is not consistently supported by recent experimental evidence, thus suggesting alternative pathogenetic mechanisms.

The aim of the study is to shed light on the debated pathophysiological mechanisms of PLN-R14del DCM exploiting a heterozygous transgenic model (Mut) that recapitulates the clinical human phenotype.

SERCA2a ATPase activity and intracellular Ca^{2+} dynamics have been measured in cardiac homogenates and cardiomyocytes (CMs) isolated from 8-12 weeks old Mut mice and WT littermates. To compare mutation effect with pharmacological SERCA2a modulation, CMs were perfused with a pure SERCA2a activator (PST-3093). To test the involvement of metabolic alterations, oxidative phosphorylation and glycolysis have been investigated.

In myocardial homogenates, the Ca^{2+} dissociation constant (Kd_{Ca}) of SERCA2a ATPase activity was lower in Mut. In isolated CMs, the Ca^{2+} transient decay time (τdecay) was shorter and diastolic Ca^{2+} was lower in Mut compared to WT cells. When applied to WT CMs, PST-3093 decreased τdecay; in Mut, PST-3093 had no effect. In Mut cells O_2 consumption and glycolytic acidification were reduced.

These results indicate enhancement of SR Ca^{2+} uptake rate in Mut, which is compatible with diminished PLN inhibitory function. Future work will be directed to establish if the metabolic abnormalities may be related to altered Ca^{2+} dynamics, or be an independent mechanism for PLN-R14del DCM.