The role of phospholamban in heart failure

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A pair of phospho-specific antibodies to PLN were first described in 1994 [1]. These have been in continual use by the entire cardiac excitation-contraction coupling research community since that time, and have underpinned a series of discoveries concerning the aetiology and potential management of heart failure.

In the early days, research focused on defining the normal physiological situation in the heart and the role of PLN phosphorylation in the response to stress. PLN is a small transmembrane protein expressed in the sarcoplasmic reticulum (SR) of cardiac myocytes, which interacts with the Ca^{2+}-pump of the SR and inhibits Ca^{2+} transport by this pump. This inhibition is relieved upon PLN phosphorylation at Ser-16 or Thr-17 sites, Ca2+-transport into the SR is accelerated and the contraction cycle quickens and generates more force [2-4].

Next, the focus turned to a comparison between normal and disease states in an effort to define the molecular basis of dysfunction. These studies were performed in many mammalian species, including man, and found that PLN was overbearing in heart failure. PLN concentration was maintained, whilst its state of phosphorylation was reduced [4-6]. At the same time SERCA expression was reduced, and thus Ca^{2+}-pumping was reduced by both the relative lack of SERCA and the relative overbearing activity of dephosphorylated PLN [7-12]. This combination underpinned small Ca^{2+}-transients in the myocytes, leading to low contractile force and slow kinetics: phenomena central to the poor muscle performance in this disease.
It should be noted this pattern of changes in protein abundance was not universally observed, with existing reports of unchanged levels of PLN and SERCA in HF [5, 6, 13, 14].

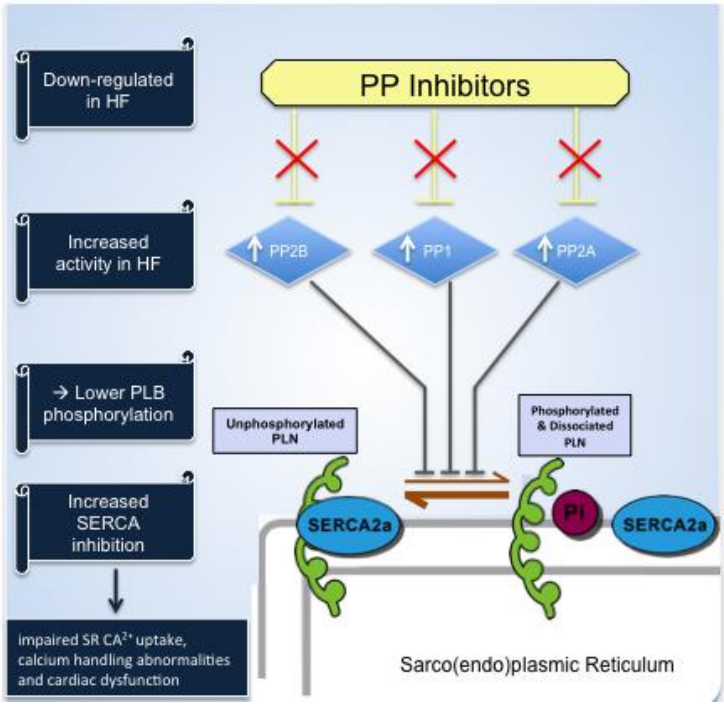
Low phosphorylation of PLN makes it overbearing in HF

What prompts low PLN phosphorylation in HF?

HF is a disorder of low contractile performance of the heart. The fight or flight response (or sympathetic drive) is a response deployed to increase muscle performance at times of stress. In HF, this normally transient response is deployed chronically as the muscle is underperforming chronically. Beta-adrenergic receptors (the target of sympathetic ligands epinephrine and nor-epinephrine) are down-regulated in the plasma membrane, a consequence of the chronic exposure to ligand [13]. This reduces the stimulus for Ser-16 phosphorylation of PLN. In addition, the protein phosphatases focused on PLN (PP1, PP2A, and calcineurin (PP2B)) are up-regulated [5, 13, 15, 16] and the natural inhibitors of these phosphatases are down-regulated [17]. These adaptations together suppress the phosphorylation of PLN at Ser-16 and Thr-17 and suppress Ca2+-pump performance. This cascade of events is summarized in Figure 1.

Following establishment of the molecular basis underlying heart failure, research turned to new therapeutic approaches. Benefits have accrued from strategies that inhibit PLN function, strategies that increase PLN phosphorylation, and strategies that increase SERCA expression.

Figure 1. Involvement of Protein Phosphatases (PP's) and their inhibitors (PPI's) in HF



Strategies that depress PLN expression relative to SERCA include exercise training (ET), ET in

combination with beta blocker use, [10, 18, 19] and gene transfer inhibiting overexpression of PLN [11].
Approaches that have allowed us to enhance phosphorylation of PLN include targeted inhibition of protein phosphatases delivered by increased expression of their natural inhibitors [17]. Other therapies increasing PLN phosphorylation include: B-type natriuretic peptide (BNP) infusion combined with b-blocker use [20], gene transfer, exercise training (ET) alone and ET in combination with beta-blocker.

The final strategy which is closest to clinical application, bypasses PLN altogether, and increases the concentration of SERCA protein in cardiac muscle cells by gene therapy. A clinical trial led by Roger Hajjar in New York (CUPID2 study: Calcium Up-regulation by Percutaneous Administration of Gene Therapy in Cardiac Disease Phase 2b) is currently underway.

Clinical trials involving SERCA2 gene therapy in humans.

This trial is exploring the ability of a single intracoronary infusion of DRP AAV1/SERCA2a to improve the clinical outcome in HF patients with reduced ejection fraction [21].
Enhanced SERCA2 expression in the heart appears safe (in man) and improves left ventricular function, whilst reducing cardiovascular events. Completion of the phase 2b trial is expected by mid2015 [21].

Over the last 21 years, our knowledge and understanding of the role of PLN and its modulation of sarcoplasmic reticulum (SR) function has advanced significantly. It is clear that PLN modulation appears to be of paramount importance in humans, and further detailed investigation into PLN function may provide insights into its potential as a therapeutic target in heart failure. Many challenges remain but patients with heart disease will benefit from the worldwide research effort and together we look forward to another 21 years of innovative PLN discoveries.

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