Sodium pump and intracellular sodium in healthy and failing hearts

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The sodium pump (Na/K ATPase) uses the free energy of hydrolysis of ATP to exchange three intracellular sodium ions (Na) for two extracellular potassium ions (K), thus setting the electrochemical gradient for both Na and K across the cell membrane. As the only quantitatively significant Na efflux pathway from cardiac cells, the sodium pump is the primary regulator of intracellular Na. The transmembrane Na gradient it establishes is essential for normal electrical excitability as well as for active transport of many other ions, amino acids and substrates into the cell. Intracellular Na concentration is also critical for the control of intracellular calcium (Ca) *via* the Na/Ca exchanger, thereby determining sarcoplasmic reticulum Ca content and cardiac contractility. As sodium influx varies with electrical excitation, heart rate and pathology, the dynamic regulation of intracellular Na efflux is essential.

Our group has demonstrated that phospholemman (FXYD1), a 72 amino acid accessory protein which forms part of the sodium pump complex, is the key nexus linking cellular signaling to pump regulation. Phospholemman is the target of a variety of post-translational modifications (phosphorylation, palmitoylation and glutathionation) and these can dynamically alter the activity of the sodium pump. Our goal now is to decipher the role that phospholemmann plays in regulation of intracellular Na in normal physiology but also in cardiac hypertrophy and heart failure. As dysregulation of intracellular Na contributes to contractile and metabolic dysfunction during cardiac failure, a complete understanding of the mechanisms that control the cardiac sodium pump activity is vital if we are to develop novel treatments for cardiac hypertrophy and heart failure.