Structural determinants for the regulation of SERCA by Calumenin

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In the cardiac muscle, Ca^{2+} plays a fundamental role both in signalling and in muscle contraction. The cardiac sarcoplasmic reticulum (SR) serves as a calcium store, enabling quick release/uptake of Ca^{2+} resulting in cytoplasmic Ca^{2+} concentrations varying by orders of magnitude with every heart beat. The SR protein calumenin, a Ca^{2+} binding/sensing protein, is involved in the regulation of this process and its abnormal expression is associated with various pathological conditions such as cardiomyopathy.

Calumenin consists of 6 EF-hand motifs expected to arrange around calcium ions in a similar fashion to Calmodulin. Both proteins interact with P-type Ca^{2+}-ATPases, albeit through remarkably different mechanisms. Calmodulin binds and inhibits the Plasma Membrane Ca^{2+} ATPase (PMCA) at low Ca^{2+} concentration. Increase of intracellular Ca^{2+} levels induce a major rearrangement of Calmodulin which detaches from PMCA and relieves inhibition. Calumenin only binds the sarcoplasmic reticulum Ca^{2+} -ATPase (SERCA) when the calcium concentration is high, thereby altering the calcium affinity of the pump.

Our aim is to provide a structural explanation of this phenomenon and the possible physiological implication.

SR-CD experiments at Diamond's beamline B23 showed that, within the physiological range of Ca^{2+} concentrations, Calumenin shifts between a random coil and an alpha helical conformation. We conclude that Calumenin senses high Ca^{2+} concentrations, initiating a reversible folding process which mediates the regulation of SERCA sensitivity to the ion.

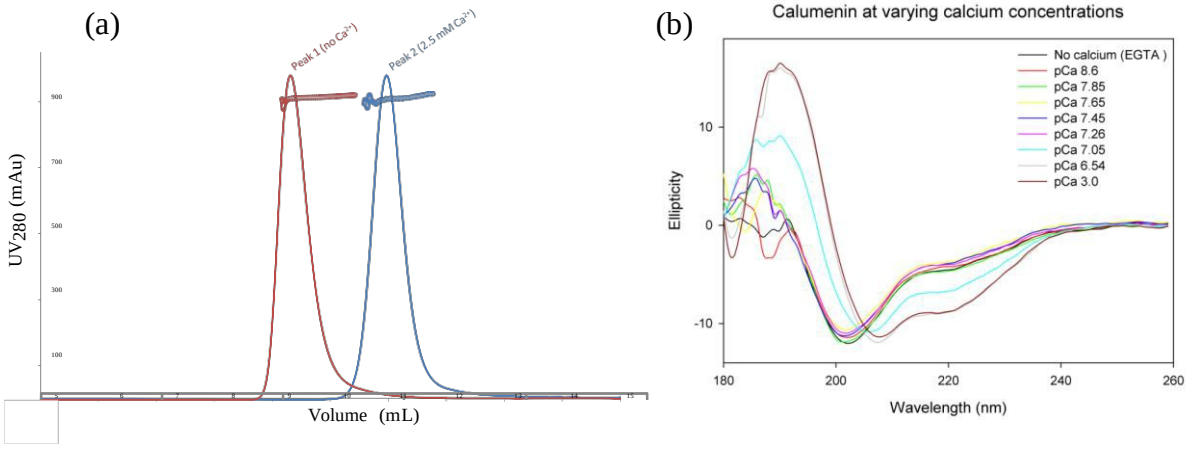

Figure 1 (a) Analytical gelfiltration profiles of Calumenin in the absence (red curve) and in the presence of 2.5 mM Ca^{2+} (blue curve) highlight major structural rearrangements upon binding of the metal. (b) SR-CD titration curves in Ca-EGTA buffered system evidence the increase in alpha helical content for Ca^{2+} concentrations above 100 nM (pCa = 7.0).

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