Delivery of SERCA2a as a Treatment for Heart Failure

A number of cardiac abnormalities are associated with advanced heart failure (HF), all leading to a reduced ability of the heart to pump blood and supply adequate oxygenated blood to the body. Reduced contractility of the individual cardiomyocytes is the main factor resulting in reduced global cardiac output, and intracellular calcium (Ca^{2+}) flux is central to this cellular abnormality.

Regulation of excitation–contraction coupling in cardiomyocytes is driven by Ca^{2+} flux between the sarcoplasmic reticulum (SR) and the cytosol. Electrical excitation of the sarcolemma leads to the opening of voltage gated L-type Ca^{2+} channels, allowing the entry of a small amount of Ca^{2+} into the cell (Figure below). This influx leads to opening of the ryanodine receptors located on the SR membrane and a large amount of Ca^{2+} is released from the SR into the cytosol. The resulting increase in cytosolic Ca^{2+} activates the myofilaments resulting in contraction. [1, 2] During relaxation, Ca^{2+} is pumped back into the SR by the SR Ca^{2+} ATPase (SERCA2a) pump and extruded extracellularly by the sarcolemmal Na^{+}/Ca^{2+} exchanger. The contribution of SERCA2a in humans for removing intracellular calcium is ~75% and ~25% for the Na^{+}/Ca^{2+} exchanger. The Ca^{2+} pumping activity of SERCA2a is regulated by phospholamban. In the unphosphorylated state, phospholamban inhibits the Ca^{2+}-ATPase, whereas phosphorylation of phospholamban by cAMP-dependent protein kinase and by Ca^{2+}-calmodulin dependent protein kinase releases the inhibition.

In summary, in the mammalian heart, the intracellular Ca^{2+} movements are tightly regulated at various levels within the cell. SERCA2a plays a central role in regulating contraction and relaxation by its role in controlling the level of Ca^{2+} in the cytosol and SR in the cardiomyocyte. [3]

Defects in Excitation-Contraction coupling, due to abnormal expression and/or function of calcium handling and transport proteins, are a hallmark of cardiac dysfunction. These defects manifest in changes in the calcium transient: reduced amplitude, increased duration, and prolonged decay – the consequence of which is decreased contractility and reduced cardiac output. Regardless of the etiology of heart failure, the role of reduced SR calcium load has been well established in terms decreased SR calcium uptake, decreased SR calcium content, and calcium leak from the SR. [4] [5] This is primarily due to a decrease in SR calcium uptake because of SERCA2a dysfunction. In both animal models of and patients with heart failure, there is a reduction in SERCA2a expression (mRNA and protein levels) and activity. [6]

Increasing the levels of SERCA2a protein in cardiomyocytes has been shown in human cells, experimental rodent and large animal models to normalize the abnormally high diastolic levels of cytosolic calcium typical of HF and improve contractile and clinical outcomes, as described below. [7-9] [10-13]

SARDOCOR proposes to investigate gene transfer as a method to restore SERCA2a function in heart failure patients using a recombinant adeno-associated viral vector (AAV), which consists of an AAV serotype 1 capsid and contains the human SERCA2a cDNA flanked by ITRs derived from AAV serotype 2 (AAV1/SERCA2a).

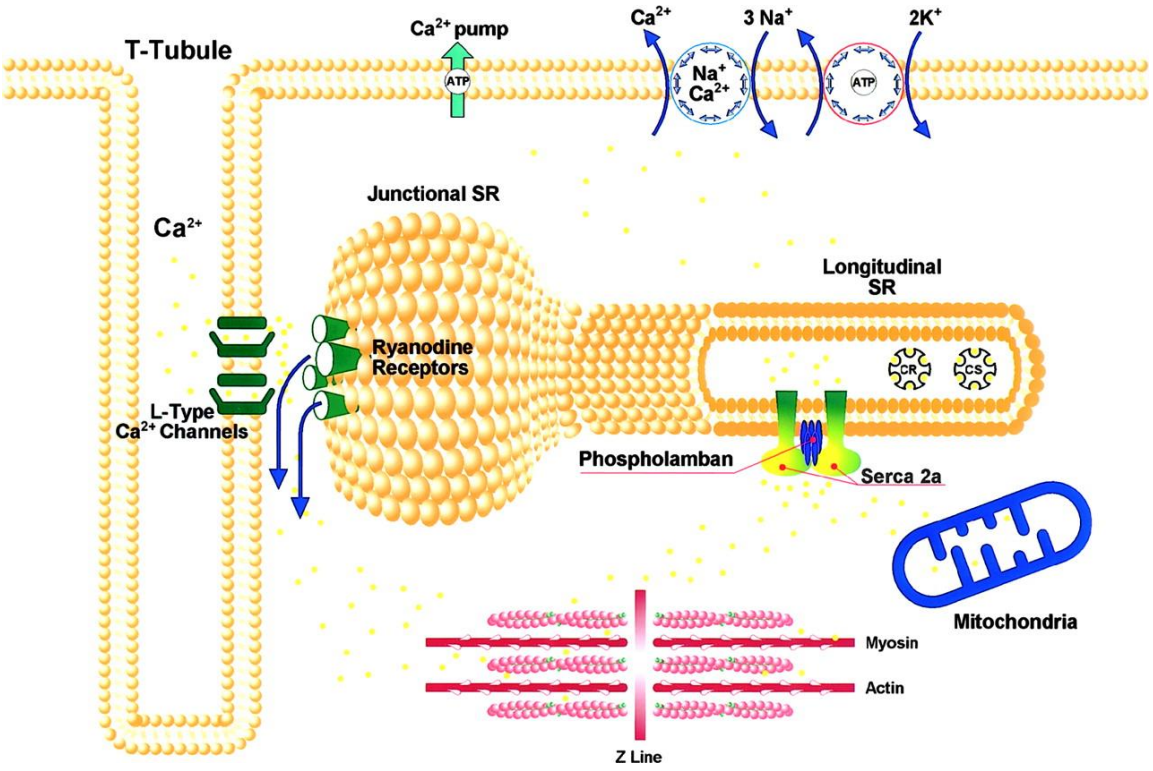

Figure : Ca^{2+} Handling Proteins Involved in Intracellular Ca^{2+} Movement

In addition to the role in cardiomyocytes, SERCA2a also has a role in skeletal muscle, the diaphragm, vascular smooth muscle, and endothelial cells. Both moderate and high intensity exercise increase the relative SERCA2a isoform expression in cardiac and skeletal muscle cells. SERCA2a gene transfer also results in increased coronary blood flow in a diabetic rat model. Finally, increasing SERCA2a levels via gene transfer inhibits vascular smooth muscle proliferation.

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