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Heart, Vascular Smooth Muscle, Excitation-Contraction Coupling (E-CC), Cytoskeleton, Cellular Dynamics and Ca^{2+} Signaling

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Abbreviations : AP: Action Potential, ARVD2: arrhythmogenic right ventricular cardiomyopathy type 2, CaMKII: Ca^{2+}/Calmodulim-dependent protein kinase II, CICR: Ca^{2+} induced Ca^{2+} release, CM: Calmodulin, CPVT: Catecholaminergic polymorphic ventricular tachycardia, ECC: Excitation–Contraction Coupling, FKBP12/12.6: FK506 Binding Protein, HF: Heart Failure, LCC: L-type Ca^{2+} Channel, P-1 or P-2: Phosphatase inhibitor type-1 or type-2; PKA: Protein Kinase A; PLB: Phosphoplamban; PP1: Protein Phosphatase 1, PP2A: protein Phosphatase 2A, RyR1/2: Ryanodine Receptor type-1/type-2, SCD: Sudden Cardiac Death, SERCA: Sarcoplasmic Reticulum Ca^{2+}ATPase, SL: Sarcolemma, SR: Sarcoplasmic Reticulum.

Mini Review

We previously discussed common MOTIFs across cell-types that are essential for cell division, embryogenesis, cancer metastasis, osteogenesis, musculoskeletal function, vascular compliance, and cardiac contractility. We now turn to specific functionalities for cardiac contractility based on Ca^{2+} signaling in excitation-contraction coupling. The modifications discussed apply specifically to cardiac muscle and not to skeletal muscle. The observations described might raise questions specifically to address the unique requirements of smooth muscle, abundant in the GI tract and responsible for motility in organ function, and in blood vessel compliance or rigidity. Due to the distinctly different aspects of the cardiac contractility and contraction force, and the interactions with potential pharmaceutical targets, there are two separate articles on calcium signaling and cardiac arrhythmias or heart failure. The study focuses on the ryanodine role in cardiac Ca^{2+} signaling and its effect in heart failure. It takes up other aspects of heart failure and calcium signaling with respect to phosporylation/dephosphorylation. I add a single review and classification of genetic cardiac disorders of the same cardiac Ca^{2+} signaling and the initiation and force of contraction. Keep in mind that the heart is a syncytium, and this makes a huge difference compared with skeletal muscle dynamics. There was some discussion of the importance of Ca^{2+} signaling on innate immune system, and the immunology will be further expanded in a fourth of the series [1-3].

Manuscript Click here to download Manuscript: Heart, Vascular Smooth Muscle, Excitation-Contraction Coupling (E-CC), Cytoskeleton, Cellular Dynamics and Ca^{2+} Signaling.

This second article on the cardiomyocyte and the Ca^{2+} cycling between the sarcomere and the cytoplasm, takes a little distance from the discussion of the ryanodine that precedes it. In this discussion we found that there is a critical phosphorylation/dephosphorylation balance that exists between Ca^{2+} ion displacement and it occurs at a specific amino acid residue on the CaMKIId, specific for myocardium, and there is a 4-fold increase in contraction and calcium release associated with this CAM kinase (ser 2809) dependent exchange. These events are discussed in depth, and the research holds promise for therapeutic application. We also learn that Ca^{2+} ion channels are critically involved in the generation of arrhythmia as well as dilated and hypertrophic cardiomyopathy. In the case of arrhythmiagenesis, there are two possible manners by which this occurs. One trigger is Ca^{2+} efflux instability. The other is based on the finding that when the cellular instability is voltage driven, the steady-state wavelength (separation of nodes in space) depends on electrotonic coupling between cells and the steepness of APD and CV restitution. The last article is an in depth review of the genetic mutations that occur in cardiac diseases. It is an attempt at classifying them into reasonable groupings [4-8].

What are the therapeutic implications of this? We see that the

molecular mechanism of cardiac function has been substantially elucidated, although there are contradictions in experimental findings that are unexplained. However, for the first time, it appears that personalized medicine is on a course that will improve health in the population, and the findings will allow specific targets designed for the individual with a treatable impairment in cardiac function that is identifiable early in the course of illness. This article is a continuation to the following articles on tightly related topics:

Canine cardiac sarcoplasmic reticulum is phosphorylated by

- adenosine 3,5-monophosphate (cAMP)-dependent and
- calcium calmodulin-dependent protein kinases on

a proteolipid, called phospholamban.

Both types of phosphorylation are associated with

- an increase in the initial rates of Ca^{2+} transport by SR vesicles
- which reflects an increased turnover of elementary steps of the calcium ATPase reaction sequence.

The stimulatory effects of the protein kinases on the calcium pump may be reversed by an endogenous protein phosphatase, which

- can dephosphorylate both the CAMP-dependent and the calcium calmodulin-dependent sites on phospholamban.

Thus, the calcium pump in cardiac sarcoplasmic reticulum appears to be under reversible regulation mediated by protein kinases and protein phosphatases [9-11].

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