PLN- R14DEL, A CONTROVERSIAL CARDIOMYOPATHY - OBSERVATIONS FROM PATIENT-DERIVED CARDIOMYOCTES AND TRANSGENIC MICE

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Phospholamban (PLN) phyis the natural inhibitor of SERCA2a function, decreases its Ca^{2+} affinity and mediates the effect of its phosphorylation-dependent modulation. The heterozygous R14del PLN mutation (PLN-R14del) is associated with an arrhythmogenic dilated cardiomyopathy (DCM) with clinical onset at middle age. Initial heterologous expression studies (microsomal preparations) detected a sharp decrease in SERCA2a affinity for Ca^{2+} in the presence of heterozygous PLN-R14del; this led to interpret DCM as the consequence of SERCA2a "super-inhibition" by mutant PLN. This interpretation has been assumed in a number of later studies attempting therapeutic approaches. We have recently evaluated intracellular Ca^{2+} dynamics in cardiomyocytes derived (hIPSCMs) from a symptomatic heterozygous PLN-R14del carrier. The results obtained surprisingly pointed to enhancement of sarcoplasmic reticulum (SR) Ca^{2+} transport, i.e. opposite to what expected from SERCA2a superinhibition. To test whether these results might have a more general value, we have further investigated Ca^{2+} dynamics in a transgenic PLN-R14del murine model. Preliminary results from this model are fully consistent with our observations in hiPSCMs. My presentation will discuss these new findings and their impact on the interpretation of the mechanism by which PLN-R14del results in DCM.