The diverse roles of phospholamban and sarcolipin in skeletal muscle: From adaptive thermogenesis to muscle myopathy

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Phosopholamban (PLN) and sarcolipin (SLN) are small sarcoplasmic reticulum (SR) proteins that regulate SERCA pump function through physical interactions. My research program aims to advance fundamental understanding of the physiological roles of PLN and SLN in skeletal muscle. In 2008, we began a program of research to investigate the hypothesis that the primary physiological function of SLN in skeletal muscle may be to regulate thermogenesis by SERCA pumps. Overall, we have established that SERCA pumps are important contributors to muscle metabolic rate (Smith *et al.*, 2013) and that SLN, by uncoupling Ca^{2+} transport from ATP hydrolysis by SERCAs (Bombardier *et al.*, 2013b), is protective against diet-induced obesity, providing a novel mechanism of adaptive thermogenesis within skeletal muscle (Bal *et al.*, 2012; Bombardier *et al.*, 2013a; Gamu *et al.*, 2014). We also published the first study on SLN in human skeletal muscle revealing its co-expression with SERCA isoforms, PLN and myosin heavy chain isoforms in *vastus lateralis* (Fajardo *et al.*, 2013). Therefore, research in our laboratory has contributed very significantly to the elucidation of the physiological function of SLN in skeletal muscle but the role of PLN in skeletal muscle is not well understood. We are utilizing single and double knock-out models to examine the physiological role of PLN in adaptive thermogenesis. Our preliminary data indicate that the response of PLN to diet overload differs from that of SLN. We have also discovered that PLN overexpression in mouse slow-twitch skeletal muscle (Pln^{OE}) causes centronuclear myopathy (CNM) with core-like lesions and dystrophic features, a phenotype that is associated with significant up-regulation of muscle SLN content, impaired SERCA function and increased Ca^{2+}-activated proteolysis (Fajardo *et al.*, 2015). Interestingly, SLN protein is also up-regulated in other mouse models of myopathy including Duchenne muscular dystrophy (*i.e.* mdx mice). Therefore, targeting SLN and PLN may represent novel therapeutic approaches to improve SERCA function and oppose skeletal muscle myopathy. We are currently testing these hypotheses using Pln^{OE}/*Sln*-null and *mdx/Sln*-null mice and our findings have uncovered a novel physiological role of SLN in skeletal muscle.

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