9. Milestones and frontiers in muscular physiology: Ca2+ handling in T-tubules

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The plasma membrane of skeletal muscle is highly specialised and exists mostly as what is known as the tubular (t-) system, an invagination of the plasma membrane. The t-system accounts for approximately 80% of the plasma membrane with the remaining membrane forming what is known as the sarcolemma. In skeletal muscle the t-system is a complex network consisting of longitudinal and transverse tubules. The transverse tubules form a junction with the sarcoplasmic reticulum, a highly specialized Ca2+ storage organelle of muscle. Muscle contraction is regulated by tightly controlled changes in Ca2+ levels within a muscle fiber. The movement of Ca2+ into and out of the fiber occurs across the t-system. It is therefore valuable to gather information on the spatial organisation and structure of this system and to describe quantitatively the Ca2+ movements that are critical to muscle function. We developed a new single muscle fiber fluorescence based method that is sensitive enough to calibrate and measure Ca2+ within the t-system. This technique utilizes the mechanically skinned fiber preparation which traps Ca2+ indicating dyes within the t-system. This method was used to perform 3D reconstructions of the t-system ultrastructure and perform Ca2+ measurements in exercised human muscle and describe highly novel physiological changes in response to heavy exercise regimens. The regulation of Ca2+ is believed to differ in healthy and diseased muscle and can influence factors such as reactive oxygen (ROS) production. Currently, my work focuses on how changes in Ca2+ and redox signaling within micro domains of mouse skeletal muscle fibers alters the homeostasis of these complexes in a mouse model of Duchenne Muscular Dystrophy (DMD). ROS, generated by NAD(P)H oxidase (Nox)2, play a role in DMD with early pathological involvement in inflammation, decreased muscle function and alterations in Ca2+ handling. Identifying the ROS/Ca2+ interaction in dystrophic muscle could provide pharmacological targets to a disease that has no cure.

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