THE HARTWELL FOUNDATION

2019 Individual Biomedical Research Award

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Mechanisms of Contracture in Cerebral Palsy: Tissue Architecture and Stem Cell Mechanobiology

Cerebral palsy (CP) is the result of injury to the immature or developing brain before, during or after birth. It occurs in 1 out of every 350 babies and there is no single cause. Children affected by CP sustain deficits in muscle function such as decreased force production, muscle control, coordination, tone and reflex, including posture and balance issues; problems swallowing; an inability to visually focus on an object, and various developmental disabilities related to epilepsy and autism. As a spectrum disorder with a range in severities, CP is permanent but not unchanging; and there is no cure. Adaptations of the musculoskeletal system progressively culminate in joint contractures (shortening and hardening of muscles), where the stiffness of muscle limits its range of motion. Highly invasive surgeries can improve joint mobility, but they further weaken muscle and contractures often recur. Contractures are usually due to the inability of skeletal muscle to accommodate bone growth, where the more the muscle is stretched, the stiffer it becomes. Based on muscle biopsies, the stiffness of the muscle is in large measure derived from the collagen-rich connective tissue matrix that attaches and supports the muscle fibers; and while scar tissue forms in the extracellular space during periods of excessive strain of contracture, stiffness does not correlate with the amount of scar tissue. Healthy muscle can lengthen in response to stretch due largely to its own mechanosensitive stem cell population, which act to support muscle fiber growth and regeneration. In CP by contrast, there is an abundance of connective tissue stem cells and a dearth of proliferating muscle stem cells, where the mechanical stiffness of the extracellular environment is an important mediator of cellular phenotype and a defining feature of contracture. To combat muscle contractures in children with CP, it is essential to understand how alterations in these factors combine to regulate muscle stiffness. Lucas proposes to determine the relationship between extracellular matrix architecture and muscle stiffness including quantity, crosslinking, density, and alignment of extracellular collagen fibrils that can alter the mechanical properties of muscle. He will determine qualitative shifts in resident muscle cells measured by single cell RNA-sequencing in human muscle biopsies of patients diagnosed with CP versus healthy controls; and using engineered hydrogels that can mimic the stiffness in typically-developing muscle, determine the sensitivity of muscle and connective tissue stem cells present in CP muscle tissue to mechanical stimuli. If successful, he will identify promising therapeutic targets to reduce muscle contractures, which if translated clinically would improve the mobility and quality of life of those children who endure the life-long debilitating effects of CP.