THE HARTWELL FOUNDATION

2016 Individual Biomedical Research Award

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Treating Skeletal Muscle Wasting with Novel Growth-Promoting Myokines to Improve Disease Prognosis

Many of the most prevalent and debilitating pediatric diseases (e.g., neuromuscular disorders, cancer, and infections) and their common therapies (e.g., glucocorticoids and chemotherapy) induce skeletal muscle wasting (decrease in muscle mass), a debilitating feature of life-saving interventions that can independently shorten patient survival. Regrettably, for the many children who endure muscle wasting there is no cure and no therapy. Although much is known about the molecular mechanisms of the disorder, it has proven difficult to test effective drugs that could target the proteins and intracellular signaling pathways involved in the wasting process. This is because many protein families that are known to be pivotal in muscle wasting, such as transcription factors, are notoriously undruggable, whereas others cannot be safely targeted since they are necessary for normal tissue function. Recent identification of small extracellular proteins secreted by skeletal muscle (myokines) have however, emerged as potential mediators of muscle function and offer new opportunity. For example, the genetic knockout of a myokine called myostatin in adult mice results in a significant increase in muscle mass, albeit with significant adverse effects that include brittle tendons and thickening of the heart muscle. Unfortunately, due to experimental obstacles in high-throughput screening of myokine gene function in mouse models, the role of myokines in muscle wasting continues to remain largely unknown. To address this problem, Fabio proposes using mice in combination with the fruit fly Drosophila melanogaster, another established model organism that is particularly amenable to large-scale transgenic RNAi screens. Using this system, he was able to screen more than 100 evolutionarily conserved myokines with over 300 RNAi transgenic fly stocks. He demonstrated that genes regulating muscle growth and wasting in mice elicit similar effects during developmental muscle growth in the fruit fly. In preliminary observations, he has also identified several fruit fly genes that code for myokines and regulate developmental muscle growth. Leveraging availability to produce synthetic versions of the myokines he identified by means of recombinant protein technology (protein resulting from the expression of recombinant DNA within living cultured cells), he now seeks to evaluate whether any of the myokines will promote muscle fiber growth and overcome muscle wasting in mouse models and ultimately, in humans. If Fabio is successful, uncovering the role of growth promoting myokines will advance clinical translation, with the potential for preventing and curing skeletal muscle wasting in children, thus reducing morbidity and mortality as a side-effect of essential life-saving interventions in so many pediatric diseases.