Use of an exercise challenge system to define a universal proteomic signature of muscle injury in a diverse set of adult individuals with inherited myopathy

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Introduction

Several inherited muscular dystrophies are defined by an enhanced injury response to exercise. However, the molecular definition of muscle injury and how injury relates to the underlying genetic lesion remain poorly understood.

To address these questions, we utilized an established exercise intervention system in a diverse set of adult individuals with a range of inherited myopathies. Using the SomaScan 7K high-throughput analysis platform, we characterized both baseline changes from healthy, as well as the proteomic signatures of injury during the 24 hours following an exercise challenge.

The subjects selected for the study included healthy, Becker muscular dystrophy (BMD), the Limb Girdle muscular dystrophies 2I and 2L (LGMD2I and LGMD2L), as well as an unrelated metabolic myopathy, McArdle’s disease. Individuals were challenged with a high intensity, bimodal exercise regimen consisting of both aerobic and strength components. Blood tests were collected prior to exercise and at controlled intervals up to 24 hours post-exercise, after which the plasma was analyzed by SomaScan for the concentrations of approximately 7,000 proteins.

Study Design

A bimodal exercise regimen consisting of both aerobic and strength components. Blood tests were collected prior to exercise and at controlled intervals up to 24 hours post-exercise, after which the plasma was analyzed by SomaScan for the concentrations of approximately 7,000 proteins.

Validation of Profile in a Large Cross-Sectional Dataset

The universal baseline signature is applicable to a cross-sectional set of 55 BMD serum samples from the Newcastle Biobank. The signature shows equal elevation over healthy in both datasets and, individually, most proteins in the signature are within 1.5-fold of the levels seen in the exercise dataset.

Opposing Age Dynamics of Injury Signature and Exercise Nonresponsive Proteins

Proteins in the injury signature and exercise nonresponsive proteins in BMD were analyzed for correlation with age (left). Among those that significantly associated, all injury signature proteins decreased with age (right). However, with the exception of muscle-derived myosin 3, all of the exercise nonresponsive proteins increased with age, suggesting that these non-muscle sources for baseline increases in this subset.

Conclusions

We identified a shared circulating baseline biomarker signature amongst the 4 neuromuscular disorders studied, despite unique genetic lesions and symptom profiles accompanying each. Within that signature, we described a proteomic signature of muscle injury that further elevates upon exercise in BMD, LGMD2I, and McArdle and that this injury signature tends to be negatively associated with age. Conversely, the population that are baseline-elevated but are not responsive to exercise or derived from muscle increase with age, raising the possibility that these proteins may serve as less variable markers of disease progression.

References


