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

Benjamin Barthela, Mads G Stemmerikb, Nanna R Andersenb, Sofie V Skriverb, Alan J Russellb, John Vissingu

*These authors contributed equally to this work, aEdgewise Therapeutics, Boulder, CO, USA, bNeuromuscular Center, Department of Neurology, University of Copenhagen, Copenhagen, DK

Introduction

Several inherited muscular dystrophies are characterized 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 set of inherited myopathies that differ in their underlying pathophysiology. Using the SomaScan 7K high-throughput analysis platform, we characterized both baseline differences 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 Becker muscular dystrophy (BMD) and the Limb Girdle muscular dystrophies 2I and 2L (LGMD2I and LGMD2L), as well as a healthy cohort. Individuals were challenged with a high-intensity, bimodal exercise regimen consisting of both aerobic and strength components. Blood samples 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.

Exercise Study Design and Analysis

The exercise challenge consisted of an assessment phase, in which aerobic threshold (VO2max) and measures of protein concentrations in the sample.

Validation of the Signature in a Large Cross-Sectional Dataset

Figure 4. Baseline Proteomic Differences in Each Indication Relative to Healthy

Figure 5. Expression and Post-Exercise Dynamics of the Baseline Signature

Figure 6. Baseline Signature in Samples from Newcastle Biobank

Figure 7. Trends of Biomarker Changes with Age

Identification of the Baseline Signature and Post-Exercise Dynamics


Validation of the Signature in a Large Cross-Sectional Dataset

Figure 6. Baseline Signature in Samples from Newcastle Biobank

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 the significantly associated, injury signature proteins decreased with age (right). However, with the exception of muscle-derived myomesin 3, all of the exercise nonresponsive proteins increased with age, suggesting one or more non-muscle sources for baseline increases in this subset.

Conclusions

We identified a shared circulating baseline biomarker signature amongst the 3 neuromuscular disorders studied, despite unique genetic etiology. Within that signature, we described a proteomic signature of muscle injury that further elevates upon exercise in BMD and LGMD2I and that this injury signature tends to be negatively associated with age. Conversely, the subpopulation or proteins that are baseline-elevated but are not responsive to exercise or derived from muscle tend to increase with age, raising the possibility that these proteins may serve as direct markers of disease progression.

References


