Biomarker Discovery in Duchenne Muscular Dystrophy Through Global Metabolomic Analysis

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Introduction

Duchenne muscular dystrophy (DMD) is an X-linked recessive disorder resulting from a mutation in dystrophin and is characterized by progressive muscle deterioration, loss of functional abilities and reduced life expectancy. With no current cure, promising clinical trials are in progress, however, FDA approved clinical and functional outcome measures of DMD are effort based and insensitive to therapeutic efficacy. As a result, there is a pressing need for a non-invasive measure for tracking therapeutic efficacy in DMD There have been few studies, which have compared metabolic profiles in vivo tissues to global changes in the serum and *ex vivo* tissue metabolomes[1,2] in the most commonly used preclinical model of DMD, the *mdx* mouse. In this study, we propose a minimally invasive global metabolomics investigation using magnetic resonance (MR) spectroscopy for biomarker discovery tracking disease progression in DMD.

Experimental

Preclinical studies include 1) *in vivo* MR imaging performed on the 11.1 T Agilent horizontal bore, 2) ex vivo tissue samples analyzed on the 4mm high-resolution magic angle spinning (HR-MAS) probe on the 600 MHz Avance III and 3) spectroscopy on mouse serum performed on the 600MHz Agilent with a 1.5mm high resolution high temperature superconducting (HTS) probe. *In vivo* experiments include ^{1}H spectroscopy and T_2 measurements. One-dimensional (1D) serum spectra and 1D HR-MAS spectra on *ex vivo* intact muscle tissue was collected and analyzed by multivariate statistical analysis, including statistical correlation spectroscopy (STOCSY) as seen in Figure 1.

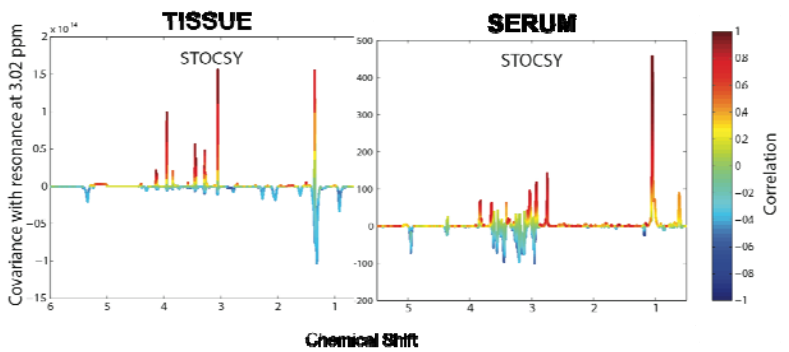

Figure 1. Multivariate analysis of serum and tissue show similar metabolites changing between *mdx* and control.

Results and Discussion

We found similar metabolic profiles *in vivo* studies, *ex vivo* intact tissue and serum. Previously, our lab[3] has showed MRI T_2's as a biomarker to track disease progression. Investigating the T_2 difference further by *in vivo* spectroscopy we found metabolite changes between *mdx* mice and control. Further investigation into the serum and intact tissue revealed a metabolic profile in serum that is found to change similarly to the metabolic profile in the tissue (Figure 1).

Conclusions

These results provide a foundation to target specific changes seen within the muscle for further investigation including age comparisons and targeted mass spectrometry.

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References

[1] Griffin, et al. Magn Reson Med 2001, [2] Griffin et al. NMR Biomed 2009 [3] Mathur et al. Muscle Nerve. 2011