Increased Myotonic Dystrophy type 1 (DM1) Disease Severity is Associated with a Dysregulated Immune System

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INTRODUCTION

- Myotonic dystrophy type 1 (DM1)
- Multisystemic disorder
- Symptoms not limited to muscle[1]
- Accelerated aging disease linked to immune dysfunction and muscle loss[1]
- CTG repeat length in DMPK gene → accumulation of RNA transcripts and splice variants
- Severity of symptoms measured by Muscle Impairment Rating Scale (MIRS) is associated with Low Quality of Life (QoL) for which biomarkers are needed as surrogate clinical outcomes
- Be aware skeletal muscles are antigen presenting cells (APCs)

APPROACH

- Stratify DM1 blood samples based on MIRS severity ratings (G1 MIRS 1-2, G2 MIRS 3-5) with the same CTG repeat expansion size (CTG<400)
- Transcriptomic data from DM1 blood samples from 2 independent cohorts at baseline (without intervention) (EU OPTIMISTIC study (n=10 per group) and Marigold foundation DMBDI study (n=6 per group)

DATA ANALYSIS

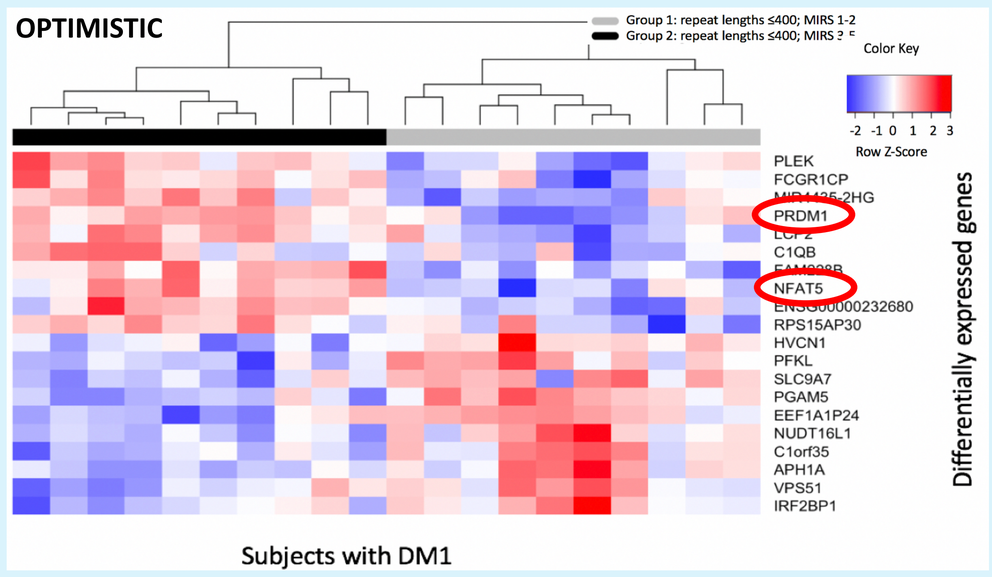
- OPTIMISTIC RNAseq + differential gene expression (DGE) analysis and DMBDI - microarray gene expression[3]

PATHWAY ANALYSIS

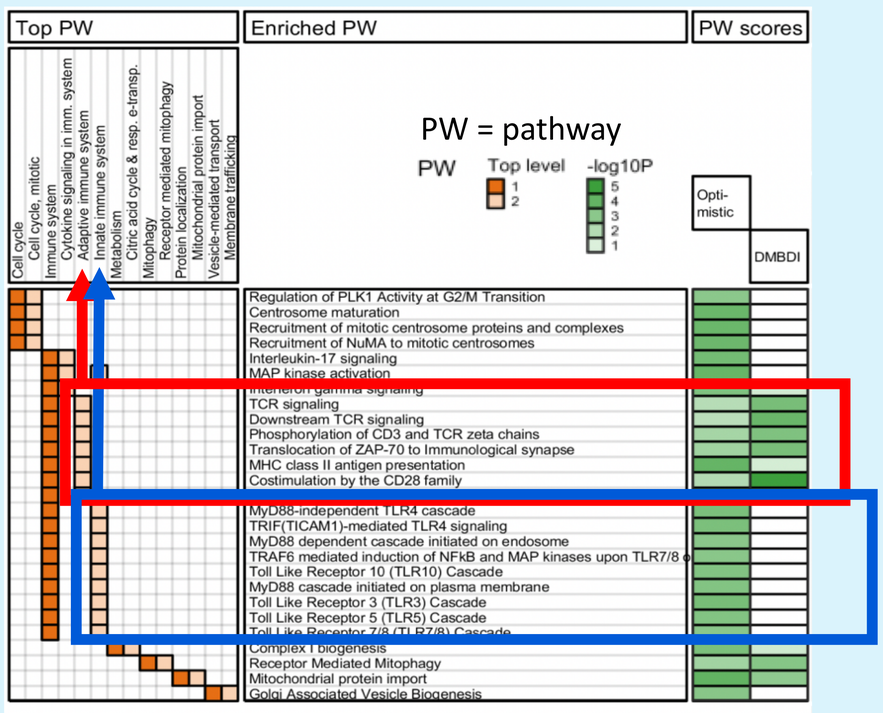
- Ingenuity Pathway Analysis (IPA), Diseases and Functions
- Reactome Pathway Analysis, Gene Ontology terms Master Regulators; causal network analysis in IPA
- Splicing

RESULTS

GENE EXPRESSION



PATHWAY ANALYSIS



RESULTS

MASTER REGULATORS

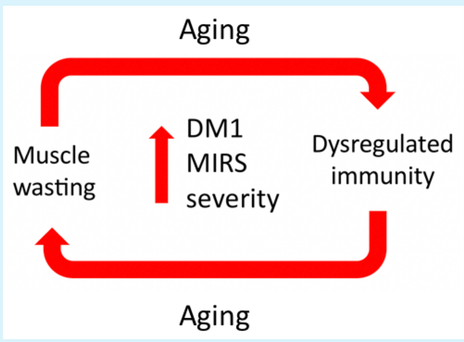
Many master regulators, e.g., FOXD1, PAX5, CIITA, QKI, VEGFA, VIM, IL4, MLX are implicated in muscle differentiation and/or repair processes. These two processes are essential for muscle wasting observed in DM1.

SPLICING

This study demonstrates no significant splicing changes.

CONCLUSION

The current study demonstrates that muscle wasting together with aging deteriorate immunity leading to increasing DM1 severity.



PRDM1 and NFAT5 which both play a role in immunity are among the top 20 DE genes in OPTIMISTIC.

Pathway analysis (Reactome) demonstrates that adaptive immunity plays a key role in both OPTIMISTIC and DMBDI datasets (red box in pathway analysis figure).

Furthermore, these analysis also demonstrates a role for innate immunity which is the first line of immunity is seen in several TLR cascades (blue box).
Both activated and inhibited Master Regulators also support a role for inflammatory and immune signaling.

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