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Content

TWO MAIN SKELETAL MUSCLE MOLECULAR PHENOTYPES OF MOUSE DM1 MODELS: A COMPARATIVE TRANSCRIPTOMIC ANALYSIS

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Introduction: Myotonic dystrophy type 1 (DM1) is a rare, incurable multisystemic disease, with the main symptoms being skeletal muscle weakness, atrophy, and myotonia. It is caused by CTG expansion in the 3' UTR of the *DMPK* gene whose RNA acquires toxic functions and sequesters MBNL proteins, resulting in globally altered RNA metabolism. To better understand the DM1 transcriptome, we systematically analyzed gene expression in the skeletal muscles of various mouse DM1 models.

Methods: We retrieved 13 publicly available RNA-seq datasets from mouse models expressing expanded CTG repeats (HSALR, CTG480KI, TREDT960I) and *Mbnl* knockout models (SKO, DKO, TKO). Our bioinformatic pipeline with unified parameters consisted of preprocessing, differential expression (DESeq2), gene network analysis (WGCNA), comparison of gene network interactions with the STRING database, and network node enrichment analysis (Cytoscape).

Results: In models expressing CTG repeats, the average number of up-regulated genes was 787, compared to 676 in Mbnl knockout models, while there was 642 and 380 down-regulated genes, respectively (log2FC>1, padj>0.05). Both model groups had network modules whose nodes were enriched for muscle and secretory functions (FDR<0.05). There were modules related to immune response, lipid transfer, and insulin in models expressing repeats and modules related to immunoglobulins and extracellular matrix in knockout models.

Conclusion: Gene expression patterns separated *Mbnl* knockouts from models expressing CTG repeats that had a greater number of smaller functionally distinct network modules. Our results revealed novel pathway changes in DM1 skeletal muscles, among which immunological and secretory are particularly interesting as molecular targets for further investigation.

Key words: Myotonic dystrophy type 1; comparative transcriptomics; DM1 mouse models; gene co-expression networks

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