Pax7, Pax3 and Mamstr Genes are Involved in Skeletal Muscle Impaired Regeneration of dy2J/dy2J Mouse Model of Lama2-CMD.

Yanay N¹, Elbaz M², Konikov-Rozenman J¹, Elgavish S³, Nevo Y³, Fellig Y⁴, Rabie M¹, Mitrani-Rosenbaum S⁵, Nevo Y¹.

Abstract

Congenital muscular dystrophy type-1A (Lama2-CMD) and Duchenne Muscular dystrophy (DMD) result from deficiencies of laminin-α2 and dystrophin proteins, respectively. Although both proteins strengthen the sarcolemma, they are implicated in clinically distinct phenotypes. We used RNA-deep sequencing (RNA-Seq) of dy2J/dy2J, Lama2-CMD mouse model, skeletal muscle at 8 weeks of age to elucidate disease pathophysiology. This study is the first report of dy2J/dy2J model whole transcriptome profile. RNA-Seq of the mdx mouse model of DMD and WT mouse was carried as well in order to enable a novel comparison of dy2J/dy2J to mdx. A large group of shared differentially expressed genes (DEG) were found in dy2J/dy2J and mdx models (1834 common DEG, (FDR) < 0.05). Enrichment pathway analysis using Ingenuity Pathway Analysis (IPA) showed enrichment of inflammation, fibrosis, cellular movement, migration and proliferation of cells, apoptosis and necrosis in both mouse models (p-values 3E-10-9E-37). Via Canonical pathway analysis; Actin cytoskeleton, Integrin, ILK, NF-kB, Renin-angiotensin, EMT, and calcium signaling were also enriched and upregulated in both models (FDR < 0.05). Interestingly, significant downregulation of Pax7 was detected in dy2J/dy2J compared to upregulation of this key regeneration gene in mdx mice. Pax3 and Mamstr genes were also downregulated in dy2J/dy2J compared to WT mice. These results may explain the distinct disease course and severity in these models. While the mdx model at that stage shows massive regeneration, the dy2J/dy2J shows progressive dystrophic process. Our data deepen our understanding of the molecular pathophysiology and suggest new targets for additional therapies to upregulate regeneration in Lama2-CMD.

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