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Impaired fetal muscle development and JAK-STAT activation mark disease onset and progression in a mouse model for merosin-deficient congenital muscular dystrophy.

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Abstract

Merosin-deficient congenital muscular dystrophy type 1A (MDC1A) is a dramatic neuromuscular disease in which crippling muscle weakness is evident from birth. Here we use the dyW mouse model for human MDC1A to trace the onset of the disease during development in utero. We find that myotomal and primary myogenesis proceed normally in homozygous dyW^{-/-}embryos. Fetal dyW^{-/-}muscles display the same number of myofibers as wildtype muscles, but by E18.5 dyW^{-/-}muscles are significantly smaller and muscle size is not recovered post-natally. These results suggest that fetal dyW^{-/-}myofibers fail to grow at the same rate as wildtype myofibers. Consistent with this hypothesis between E17.5 and E18.5 dyW^{-/-}muscles display a dramatic drop in the number of Pax7- and Myogenin-positive cells relative to wildtype muscles, suggesting that dyW^{-/-}muscles fail to generate enough muscle cells to sustain fetal myofiber growth. Gene expression analysis of dyW^{-/-}E17.5 muscles identified a significant increase in the expression of the JAK-STAT target gene Pim1 and muscles from 2-day and 3-week old dyW^{-/-}mice demonstrate a dramatic increase in pSTAT3 relative to wildtype muscles. Interestingly, myotubes lacking integrin $\alpha 7 \beta 1$, a laminin-receptor, also show a significant increase in pSTAT3 levels compared to wildtype myotubes, indicating that $\alpha 7 \beta 1$ can act as a negative regulator of STAT3 activity. Our data reveal for the first time that dyW^{-/-}mice exhibit a myogenesis defect already in utero. We propose that overactivation of JAK-STAT signaling is part of the mechanism underlying disease onset and progression in dyW^{-/-}mice.

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