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Dolichol-phosphate mannose synthase depletion in zebrafish leads to dystrophic muscle with hypoglycosylated α-dystroglycan.

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Abstract

Defective dolichol-phosphate mannose synthase (DPMS) complex is a rare cause of congenital muscular dystrophy associated with hypoglycosylation of alpha-dystroglycan (α-DG) in skeletal muscle. We used the zebrafish (Danio rerio) to model muscle abnormalities due to defects in the subunits of DPMS. The three zebrafish ortholog subunits (encoded by the dpm1, dpm2 and dpm3 genes, respectively) showed high similarity to the human proteins, and their expression displayed localization in the midbrain/hindbrain area and somites. Antisense morpholino oligonucleotides targeting each subunit were used to transiently deplete the dpm genes. The resulting morphant embryos showed early death, muscle disorganization, low DPMS complex activity, and increased levels of apoptotic nuclei, together with hypoglycosylated α-DG in muscle fibers, thus recapitulating most of the characteristics seen in patients with mutations in DPMS. Our results in zebrafish suggest that DPMS plays a role in stabilizing muscle structures and in apoptotic cell death.

KEYWORDS: Congenital muscular dystrophy; Glycosylation; Mannosylation; Zebrafish; α-dystroglycan

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