Aberrant Caspase Activation in Laminin-α2-Deficient Human Myogenic Cells is Mediated by p53 and Sirtuin Activity.

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Abstract

BACKGROUND: Mutations in the LAMA2 gene encoding laminin-α2 cause congenital muscular dystrophy Type 1A (MDC1A), a severe recessive disease with no effective treatment. Previous studies have shown that aberrant activation of caspases and cell death through a pathway regulated by BAX and KU70 is a significant contributor to pathogenesis in laminin-α2-deficiency.

OBJECTIVES: To identify mechanisms of pathogenesis in MDC1A.

METHODS: We used immunocytochemical and molecular studies of human myogenic cells and mouse muscles-comparing laminin-α2-deficient vs. healthy controls-to identify mechanisms that regulate pathological activation of caspase in laminin-α2-deficiency.

RESULTS: In cultures of myogenic cells from MDC1A donors, p53 accumulated in a subset of nuclei and aberrant caspase activation was inhibited by the p53 inhibitor pifithrin-alpha. Also, the p53 target BBC3 (PUMA) was upregulated in both MDC1A myogenic cells and Lama2-/- mouse muscles. In addition, studies with sirtuin inhibitors and SIRT1 overexpression showed that caspase activation in MDC1A myotubes was inversely related to sirtuin deacetylase activity. Caspase activation in laminin-α2-deficiency was, however, not associated with increased phosphorylation of p38 MAPK.

CONCLUSIONS: Aberrant caspase activation in MDC1A cells was mediated both by sirtuin deacetylase activity and by p53. Interventions that inhibit aberrant caspase activation by targeting sirtuin or p53 function could potentially be useful in ameliorating MDC1A.

KEYWORDS: Congenital muscular dystrophy Type 1A; MAPK; MDC1A; laminin-α2; myotube; p38; p53; sirtinol; sirtuin; skeletal muscle

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