IGF-1/GH axis enhances losartan treatment in Lama2-related muscular dystrophy.

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**IGF-1/GH axis enhances losartan treatment in Lama2-related muscular dystrophy.**

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**Abstract**

As the complexities of dystrophic pathology have been elucidated over the last few years, it has become increasingly clear that primary monogenetic defects result in multiple secondary pathologies capable of autonomously driving disease progression. Consequently, single-mode therapies fail to comprehensively ameliorate all aspects of pathology. **Lama2-related muscular dystrophy** (MDC1A) is a devastating congenital muscular dystrophy caused by mutations in the LAMA2 gene that results in multi-faceted secondary pathologies that include inflammation, fibrosis, apoptosis, and necrosis leading to severe muscle weakness and minimal postnatal growth. This study sought to implement a novel combinatorial treatment utilizing losartan, previously shown to ameliorate fibrosis and inflammation in conjunction with transgenic IGF-1 overexpression to improve postnatal growth. We found that dual-therapy rescued inflammation and fibrosis, improved weight gain, and led to remarkable restoration of muscle architecture and locomotory function in DyW mice (mouse model of MDC1A). We further showed using murine growth hormone that postnatal intervention with both therapies also yielded impressive amelioration of dystrophic pathology. Our results suggest for the first time that a combinatorial anti-fibrotic and pro-myogenic therapy could be the foundation of future therapies to a population of afflicted children in serious need.