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Dystrophin deficiency combined with reduced muscle stem cell reserve in mdx/mTR mice models Duchenne Muscular Dystrophy

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In Duchenne Muscular Dystrophy (DMD), *dystrophin* mutation leads to progressive lethal skeletal muscle degeneration. Eventually in patients functional muscle tissue is supplanted by fibrosis, calcium deposits and adipose accumulation that coincides with clinical manifestations. Although clearly initiated by dystrophin deficiency, the pathophysiological cause of eventual failure of the tissue repair process is unknown. Unfortunately dystrophin deficiency does not recapitulate DMD in mice (mdx), which have mild skeletal muscle defects and potent regenerative capacity. The absence of a mouse model for DMD that faithfully mimics key features of the human disease has limited our understanding of its pathophysiology and tests of potential therapies. We postulated that human DMD progression is a consequence of loss of muscle stem cell function and that the mild mouse mdx phenotype results from greater reserve fueled by longer telomeres. To test this hypothesis, we crossed dystrophic mdx mice with mice lacking the RNA component of the telomerase enzyme Terc. We report that this novel mouse model has severe muscular dystrophy with profound muscle weakness, elevated serum enzyme levels, and increased muscle fibrosis and calcium deposits. Their muscle stem cells exhibit reduced proliferative and regenerative capacity in vitro and in vivo upon transplantation and their progeny has shortened telomeres. These data suggest that DMD progression results from a cell autonomous failure of muscle stem cells to maintain the damage-repair cycle initiated by dystrophin deficiency. The essential role of muscle stem cell function has implications for treatment approaches for DMD.