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Therapeutic Approaches for Treatment of Duchenne Muscular Dystrophy: Exploring the Compensatory Role of DP71 in the Early Stages of Muscle Development

Summary

Duchenne muscular dystrophy (DMD) is a severe muscle-wasting disorder affecting 1 in 5,000 boys, leading to premature death around age 30. It is caused by mutations in the *DMD* gene, resulting in the loss of the full-length dystrophin isoform DP427. In about 10% of cases, a short DP71 isoform, synthesized ubiquitously in myoblasts, is also absent, and these patients tend to show more severe phenotype. The DP427 paralog, utrophin UP395, generated during fetal muscle development, can partially compensate for DP427 deficiency in patients. In contrast, the roles of DP71 in control and DMD muscle cells are not known. Our research focused on explaining limitations of current dystrophin- and utrophin-based therapeutic approaches in DMD, identifying the roles of DP427 and DP71 in cell proliferation and myofiber differentiation, determining compensatory potential of DP71 in DP427-deficient muscle fibers, and evaluating therapeutic roles of various DP71 splice variants.

We analyzed key dystrophin and utrophin domains for DMD treatment, identifying regions in utrophin that limit its compensatory function and potential immune triggers in dystrophin-based therapies. Next, using various DMD models, we found that loss of DP427 in myofibers and DP71 in proliferating myoblasts led to similar cellular defects and apoptosis. Further investigation showed that DP71 can compensate for DP427 loss during the early stage of myofiber differentiation, with its synthesis increasing in cells lacking DP427. This upregulation reduced ROS, calcium influx, and improved cell viability. We also explored the impact of different DP71 splice variants, revealing variations in their stability, localization, and ability to restore cellular functions, though some increased ROS levels in specific compartments.

In summary, we demonstrated the significance of specific dystrophin and utrophin domains in both treatment efficacy and immune response regulation. Our analysis also highlighted similar and distinct functions of DP427 and DP71, providing new insights into the therapeutic potential of DP71 during the early stages of muscle fibers lacking all dystrophins.

Keywords: dystrophin, utrophin, muscles, DMD therapies, splicing variants