

## **Functional impairments in dystrophic muscles: lateral transmission of force and sarcomere dynamics**

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Early interpretations of muscle contractions were based on the premise that forces produced within fibres were transmitted longitudinally from fibres to proximal and distal tendons. In 1983, Street demonstrated with muscles of frogs that lateral transmission of force was equally effective. Dystrophin and the dystrophin-associated glycoprotein (DAG) complex are in a position to transmit force laterally from fibre to fibre through the ECM and ultimately to the epimysium of muscles. Experiments were conducted in accordance with University guidelines on Use and Care of Animals. Mice were housed in specific-pathogen-free conditions and fed food and water *ad libitum*. Mice were anesthetized with an intraperitoneal injection of Avertin (400 mg/kg). Deep anesthesia was maintained throughout experiments by additional doses. Mice were euthanized by an overdose of anesthetic followed by creation of a pneumothorax. Compared with the longitudinal transmission of force, muscles of wild type mice transmit force laterally to the epimysium without decrement, whereas muscles of *mdx* mice, that lack dystrophin and DAG complex, exhibit a large, 40% deficit indicative of impaired lateral transmission of force. In muscles of dystrophic animals, the relative strengths of sarcomeres varies both longitudinally within myofibrils and laterally from fibre to fibre. During a maximum isometric contraction, particularly when muscles are stretched, the dystrophin and the DAG complex facilitate the stabilization of the lengths of weak sarcomeres by shunting the load laterally onto adjacent sarcomeres. In the absence of dystrophin and the DAG-complex, sarcomeres within dystrophic muscles are highly susceptible to excessive strains due to their inability to shunt strains laterally to adjacent stronger groups of sarcomeres. Consequently, the weaker sarcomeres undergo severe stretches that rupture titin within sarcomeres and cause contraction-induced injury to fibres. Dystrophin and the DAG complex appear to be critical for the successful transmission of force laterally and for the stability of sarcomeres.

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