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Dystrophin as a tumor suppressor in cancers with myogenic programs

The dystrophin gene is the largest known human gene, comprising 2.2 Mb of the genome and 79 coding exons. Through the use of multiple tissue-specific promoters and alternative splicing of RNA, several isoforms of the protein dystrophin are encoded by the dystrophin (DMD) gene. The primary 427-kDA dystrophin isoform (Dp427) is found in the cytoplasm of skeletal and cardiac muscle cells, where it is involved in physically linking the cytoskeleton to protein structures outside the cell and, therefore, strengthens and protects muscle fibers during contraction and relaxation. Inherited mutations in the DMD gene are associated with a variety of muscle disorders, including both Duchenne and Becker muscular dystrophy and dilated cardiomyopathy. The authors revealed an unexpected role for DMD as a tumor suppressor in malignancies of myogenic origin. They used a genome-wide SNP array to study potential shared mechanisms of tumorigenesis in cancers that display myogenic differentiation, including gastrointestinal stromal tumor (GIST), rhabdomyosarcoma, and leiomyosarcoma. The authors found that intragenic deletions in the DMD gene were present in 63 percent (25 of 40) of such tumors but not in companion, non-neoplastic tissue, proving the somatic origin of these deletions within the tumors. Furthermore, the same DMD deletions identified in a primary GIST were found in corresponding metastatic lesions. Deletions of DMD were not found (none of 58) in sarcomas of nonmyogenic origin and were found very infrequently (4.3 percent of 905) in nonsarcoma human cell lines. An evaluation using multiplex ligation-dependent probe amplification identified intragenic deletions of DMD in 43 percent (24 of 56) of cases of high-grade myogenic cancers, predicting the loss of expression of the largest isoform (Dp427) of dystrophin. Western blot analyses confirmed the loss or severely decreased expression of Dp427 in 96 percent of metastatic GISTs, 100 percent of metastatic embryonal rhabdomyosarcomas (eRMS), and 62 percent of metastatic leiomyosarcomas, while demonstrating strong expression in normal tissue and benign counterparts of the myogenic cancers. Significantly, re-expression of dystrophin via transfection of an artificial DMD construct previously shown to restore dystrophin function in people with muscular dystrophy inhibited the invasiveness and migration of GIST, embryonal rhabdomyosarcoma, and leiomyosarcoma. It also inhibited the anchorage-independent growth of DMD-inactivated GIST, embryonal rhabdomyosarcoma, and leiomyosarcoma cells. Together, these findings suggest that DMD acts as a tumor suppressor in myogenic cells and that somatic inactivation of DMD may act as a driver event in the development of myogenic cancers. This raises the intriguing possibility that the trend of cross-walking targeted therapeutic options between cancers of different origin may expand even further to include the use of therapies developed for classical inherited diseases in the oncology realm.

Wang Y, Marino-Enriquez A, Bennett RR, et al. Dystrophin is a tumor suppressor in human cancers with myogenic programs. *Nat Genet.* 2014;46(6):601–606. Correspondence: Jonathan A. Fletcher at jfletcher@partners.org