PATHOLOGY

Two of a kind

sarcomas from the mouse models of muscular dystrophy ... [had] ... frequent and recurrent cancer-associated alterations

All muscular dystrophies are characterized by progressive muscle wasting, despite being a genetically heterogeneous group of inherited disorders. Reginald Bittner and colleagues now propose that genomic instability (which is more commonly associated with cancer) may be a unifying pathomechanism in genetically distinct muscular dystrophies.

Schmidt *et al.* observed that different mouse models of muscular dystrophy, which harboured mutations in some of the most commonly mutated muscular dystrophy-associated genes — dystrophin (*Dmd*), dysferlin (*Dysf*), calpain 3 (*Capn3*) or like-glycosyltransferase

(*Large*) — were prone to develop age-related mixed rhabdomyosarcomas, fibrosarcomas and liposarcomas. Furthermore, *Dmd*^{-/-}*Dysf*^{-/-} and *Dmd*^{-/-}*Capn3*^{-/-} double-knockout mice suffered from accelerated sarcomagenesis, prompting the authors to suggest that muscular dystrophy-associated genes may act as tumour suppressors. Indeed, array comparative genomic hybridization (CGH) and quantitative-PCR of DNA from sarcomas from the mouse models of muscular dystrophy revealed frequent and recurrent cancer-associated alterations: amplification of loci harbouring the oncogenes *Met* and *Jun*; loss of loci harbouring the tumour suppressors cyclin-dependent kinase inhibitor 2A (*Cdkn2a*) and neurofibromatosis 1 (*Nf1*); and whole-chromosome duplication of chromosomes 8 and 15. Elevated levels of chromosome 8 and/or chromosome 15, together with highly proliferative microscopic tumour masses, were found in muscles of clinically tumour-free muscular dystrophy mice, suggesting that preneoplastic lesions are already present in dystrophic muscle.

Although increased tumour susceptibility of muscle has not been reported in human patients with muscular dystrophy, is gross genomic instability also present in human muscular dystrophy? Array-CGH and interphase fluorescence *in situ*

hybridization analyses of primary myoblast lines and muscle biopsy samples from patients with muscular dystrophy revealed multiple changes in copy number, which increase in frequency with disease progression. Could this somatic aneuploidy, which is observed in dystrophic muscle from both mice and humans, arise from unrepaired double-strand breaks (DSBs)? To investigate, immunostaining of dystrophic muscle from *Dmd*^{-/-} mice, as well as muscle biopsy samples from patients with muscular dystrophy, revealed the occurrence of phosphorylated histone H2AX (known as γH2AX), which indicates the presence of DSBs. The induction of γH2AX was additionally seen in pre-pathological muscle from very young patients with muscular dystrophy, suggesting that DSBs occur in dystrophic muscle prior to the onset of the clinical symptoms of muscular dystrophy.

The observations of Schmidt *et al.* suggest that genetically distinct muscular dystrophies in humans and mice may share a common pathology of cancer-like DNA damage and genomic instability. Although it remains to be determined how DNA damage and genomic instability may promote muscle wasting and degeneration, these similarities between muscular dystrophy and cancer offer the potential for novel therapeutic strategies.

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ORIGINAL RESEARCH PAPER Schmidt, W. M. *et al.* DNA damage, somatic aneuploidy, and malignant sarcoma susceptibility in Muscular Dystrophies. *PLoS Genetics* 7, e1002042 (2011)