NEUROMUSCULAR DISEASE

TDP-43 in inclusion body myositis

New research examining the skeletal muscle cells of patients with inclusion body myositis (IBM) has revealed that the nucleic acid-binding protein TDP-43, which is normally restricted to the nucleus, is clearly present in the muscle cell cytoplasm (Figure 1). "In cross-sections of muscle biopsies from patients with IBM, a large percentage (23%) of muscle fibers show abnormal redistribution of TDP-43 from nuclei to muscle sarcoplasm," notes senior author Steven Greenberg, who predicts that TDP-43 could facilitate the diagnosis of IBM.

IBM is a progressive degenerative disease typified by the development of rimmed vacuoles inside skeletal muscle cells and infiltration of muscle by immune cells. The earliest pathological studies of IBM muscle in 1968 emphasized distinctive myonuclear abnormalities. In 1994, a nucleic acid-binding protein was found in the lining of IBM vacuoles, but further characterization of this protein has proved difficult.

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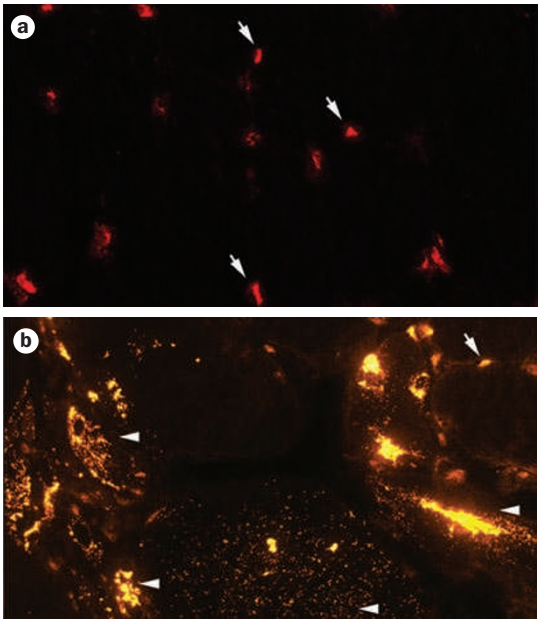
TDP-43 was recently identified as a potential diagnostic marker; it is present in normal muscle nuclei and has been noted around some of the rimmed vacuoles in IBM. The present study set out to compare the immunoreactivity of TDP-43 with other reported histochemical markers. "By demonstrating the redistribution of TDP-43 … from its normal localization in the myonucleus to the sarcoplasm, the current findings continue a string of observations pertaining to structural and molecular abnormalities of myonuclei in IBM," comments Greenberg.



◀ **Figure 1** | TDP-43 in myofibers. **a** | Normal muscle. The myonuclei (arrows) contain TDP-43 but the sarcoplasm is devoid of visible TDP-43. **b** | Muscle from a patient with IBM. TDP-43 is present in fewer IBM myonuclei (arrow). Many myofibers contain TDP-43 within the sarcoplasm (arrowheads). Abbreviation: IBM, inclusion body myositis.Image provided by Dr Steven Greenberg.

Several groups have reported abnormalities of TDP-43 in IBM muscle, but this study differs in that it quantitates these findings. "We have shown that non-nuclear sarcoplasmic accumulation of TDP-43 is highly sensitive and specific for sporadic IBM," explains Greenberg. He hopes that studying TDP-43 distribution could help to elucidate some of the mechanisms that result in myofiber injury in IBM. "TDP-43 redistribution has the potential to alter normal translation of RNA or normal function of microRNAs in IBM myofibers in a manner that could result in myofiber injury. The next step would be to further expand our understanding of the role of TDP-43 in IBM pathogenesis," he suggests.

Kathryn Senior

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