

Presence and Nature of “Tau” Immunoreactivity in Normal Myonuclei and Inclusion Body Myositis

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Introduction It has been widely stated that sarcoplasmic accumulation of phosphorylated forms of the microtubule associated protein tau (MAPT) occurs in and contributes to the pathogenesis of the muscle disease in inclusion body myositis (IBM). The goal of our study was to further explore the extent and nature of reactivity against “tau” antibodies in normal and diseased human muscle.

Methods Muscle samples from 20 patients with inflammatory myopathies and 10 from subjects without a neuromuscular disease were studied using immunohistochemical methods with anti-“tau” antibodies tau-5, pS422, and SMI-31. A range of other tissues were also examined for pS422 and SMI-31 immunoreactivity. Myonuclear and cytoplasmic fractions were prepared from whole muscle lysates using a differential solubilization protocol, as well as from muscle sections by direct visualization and isolation using laser capture microdissection. Immunoblots of these materials were performed with pS422 and SMI-31 antibodies.

Results Anti-“tau” immunoreactivity with tau-5, pS422, and SMI-31 was present in most myonuclei from all normal and diseased muscle specimens but not seen in nuclei in a range of other human tissues examined. Western blots performed on myonuclear preparations, prepared through both differential solubilization and removal of myonuclei by laser capture microdissection, showed that pS422 and SMI-31 react to a number of nuclear proteins in regions other than those expected for MAPT. A 200 kDa protein, the same size as phosphorylated neurofilament H which is the primary target of SMI-31, was identified as a normal myonuclear constituent.

Conclusion Previous experiments with antibody reagents have been interpreted as indicating that the microtubule associated protein tau is abnormally present in IBM myofiber sarcoplasm. We found that these reagents react to myonuclei in normal and IBM muscle and recognize myonuclear proteins other than tau. Normal human myonuclei contain neurofilament H or other unidentified 200 kDa proteins with similar phosphorylated amino acid motifs accounting for SMI-31 immunoreactivity.

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