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TDP-43 Immunoreactivity in Neurodegenerative Disease: Disease- versus Mechanism-Specificity

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Recently, the TAR DNA binding protein 43 (TDP-43) has been shown to be present in neuronal inclusions in frontotemporal lobar degeneration with ubiquitin-immunoreactive inclusions (FTLD-U), as well as in amyotrophic lateral sclerosis (ALS) [17]. TDP-43, a nuclear DNA binding protein that is involved in transcriptional regulation, is aberrantly deposited in filamentous cytoplasmic inclusions subsequent to a series of post-translational modifications including proteolysis, phosphorylation and ubiquitination [17]. Neuronal cytoplasmic inclusions have been known to be a consistent feature of motor neuron degeneration in ALS for over a decade [12,14], but their molecular composition was not known. Prior to this discovery, the motor neuron inclusions of ALS were only known to be immunoreactive for ubiquitin [12,14] and the ubiquitin-binding protein p62/sequestosome [15], but these markers are not disease-specific and can be detected inclusions in a wide range of other disorders as well as inclusions and other pathology in the normal aged brain. Consequently, it was difficult to determine what was disease-specific in these cases, especially for inclusions that were present in extra-motor regions of the nervous system. This problem has apparently been resolved with the discovery of TDP-43, which has been suggested to be a specific marker for ALS. It is present in the neuronal (and glia) inclusions in all cases of ALS that have been studied, except for those that are found in the setting of familial ALS due to mutations in the superoxide dismutase-1 gene [13,19]. At present it is unknown if TDP-43 will be present in inclusions in familial ALS due to mutations in other genes.

Degeneration of upper or lower motor neurons, or both (as in ALS), occurs in a wide range of other disorders, including frontotemporal lobar degeneration with motor neuron disease (FTLD-MND) and Guam ALS and Parkinson dementia complex (PDC). Guam PDC is a neurodegenerative disorder associated with neurofibrillary tangles in widespread parts of the central nervous system [11]. In some patients, PDC is accompanied by clinical features of ALS. The pathogenesis of ALS on Guam has been debated over the years [10]. One school favored the idea that ALS was due to neurofibrillary pathology affecting motor neurons similar to pathology affecting higher cortical areas and correlating with dementia or pathology in the substantia nigra and correlating with Parkinsonism. The other school favored the idea that ALS on Guam was an independent disease process similar to ALS that occurred in other settings [18]. The relative specificity of TDP-43 has been used to study ALS than occurs on Guam in the study by Geser and co-workers in this issue of *Acta Neuropathologica* [7]. Spinal cord pathology was studied in a group of cases of ALS, PDC and normal controls from Guam. The motor neuron pathology was similar to that in sporadic ALS [7]. In non-motor areas neurofibrillary pathology predominated, as expected, in PDC, while the spinal cord in PDC had only sparse TDP-43-immunoreactive motor neuron pathology. These observations would tend to support the dual hypothesis of ALS and PDC being independent disease processes.

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On the other hand, TDP-43 pathology has also been reported in neurons and glia in PDC cases that have not had motor neuron pathology [8]. This might argue for the unitary hypothesis in which PDC is associated with both neurofibrillary and TDP-43 pathology, except that even in non-Guamanian ALS, neuronal inclusions have been reported outside the motor system and independent of neurofibrillary pathology. Extramotor inclusions in ALS were initially shown with ubiquitin immunohistochemistry [12,14] and more recently with p62 immunohistochemistry [15]. In another report in this issue of *Acta Neuropathologica*, Zhang and co-workers [21] have shown that TDP-43-immunoreactive inclusions are common in the basal ganglia in ALS cases with and without dementia, although they are more frequent in cases with dementia. Cases with ALS-dementia in that report are similar to what other investigators refer to as FTLD-MND. In a third paper in *Acta Neuropathologica*, Brandmeir and co-workers have also shown widespread cortical and subcortical TDP-43-immunoreactive pathology in FTLD-MND [3]. The findings from these two studies suggest that ALS and FTLD-MND are part of a common disease spectrum [4]. Crucial to this debate is the specificity of TDP-43 for the disease spectrum defined by FTLD-U, FTLD-MND and ALS. While the initial studies from Neumann and co-workers did not detect TDP-43 in a range of other neuropathologic conditions [17], more recently this view has been challenged. The first report that TDP-43 may not be specific for FTLD-U, FTLD-MND and ALS was from Arai and co-workers [2] who showed that TDP-43-immunoreactivity was present in some cases of Pick's disease. Subsequently, Amador-Ortiz and co-workers [1] found TDP-43 immunoreactivity in 20% of Alzheimer cases and over 70% of cases of hippocampal sclerosis. While Alzheimer type pathology and hippocampal sclerosis might be expected in some cases of FTLD-U, especially late-onset FTLD-U, none of the Alzheimer cases had any evidence of motor neuron disease or ALS in that series. Moreover, TDP-43 was clearly shown to co-localize with neurofibrillary tangles in a subset of Alzheimer cases [1], raising the possibility that it may be co-deposited with other disease-related proteins, analogous to the known co-deposition of α-synuclein and tau in a subset of neurons in Alzheimer's disease [20]. More recently, two groups have reported that TDP-43 occasionally co-localizes with α-synuclein in Lewy body disease [9,16]. On the other hand, not all diseases showed this phenomena; for example, several cases of progressive supranuclear palsy and corticobasal degeneration were negative for TDP-43 [9].

How a nuclear protein is deposited as cytoplasmic inclusions in FTLD-U, FTLD-MND and ALS remains a mystery, but clues to the mechanism have come from recent cell culture experiments, in which it has been shown that TDP-43 can be cleaved by caspases, which are active during programmed cell death [22]. Programmed cell death is felt to play a critical role in many neurodegenerative disorders. That programmed cell death mechanisms may also lead to post-translational modifications in TDP-43 that promote its deposition in inclusions may provide a clue as to why inclusions of this type are detected in only a subset of neurodegenerative diseases. The generation of cleaved protein fragments that have abnormal solubility properties and that aggregate can also play a role in neurodegeneration by interfering with protein degradation mechanisms. The interplay between protein degradation pathways and programmed cell death has been the focus of intensive research in recent years [5]. Interestingly, it has been shown that disruption of both ubiquitin proteasomal and autophagic pathways lead to aberrant accumulation of cytoplasmic TDP-43 [6,22]. These findings caution one to think of TDP-43 as being disease-specific any more than a given molecular mechanism is disease-specific. More likely, TDP-43 pathology will be a manifestation of a limited number of disorders that share common disease mechanisms. Neuropathologic characterization of the range of disorders with TDP-43 inclusions, which at present include FTLD-U, FTLD-MND, ALS, Guam PDC, Alzheimer's disease and Lewy body disease, will lead to a clearer understanding of pathogenesis and etiology of these disorders.

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