Amyotrophic lateral sclerosis, frontotemporal lobar dementia, and p62

A functional convergence?

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Amyotrophic lateral sclerosis (ALS) is a familial disease in 10% of cases and is sporadic in 90%; investigations prior to the early 1990s focused on the more prevalent sporadic disease. A paradigm shift in approaches to disease pathogenesis began almost 2 decades ago, with the publication of 2 articles[1,2] that documented the presence of mutations in Cu/Zn superoxide dismutase–1 in 20% of familial cases. These seminal studies refocused investigative efforts to patients with familial ALS, unleashing the power of genetics to illuminate the many different ways neurons succumb to the degenerative process. Discoveries of novel genetic mutations have also provided cogent evidence that ALS is linked to frontotemporal lobar dementia (FTLD), with reports of genes linked to rare cases of familial ALS and ALS-FTLD such as valosin-containing protein (*VCP*), TAR DNA binding protein TDP-43 (*TARDBP*), fused in sarcoma (*FUS*), optineurin (*OPTN*), and ubiquilin 2 (*UBQLN2*).[3] Overall, many different mutations have been linked to ALS, to FTLD, or to both, supporting the etiologic diversity and clinical, pathologic, and genetic heterogeneity of these disorders. Recently, 2 study reports noted that the most common cause of familial ALS and FTLD is an expanded hexanucleotide repeat of GGGGCC in a noncoding region of the C9Orf72, accounting for almost 40% to 50% of familial ALS and 4% to 6% of sporadic ALS, providing further support for the linkage between ALS and FTLD.[4,5]

An important addition to the genes implicated in the spectrum of ALS/FTLD is *SQSTM1*. Early publications described *SQSTM1* mutations in both familial and sporadic ALS. The contribution by Rubino et al.[6] in this issue of *Neurology*® provides evidence from a large Italian cohort that mutations in *SQSTM1*, albeit rare, are also present in some patients with FTLD. Six missense mutations in the coding region and 7 novel noncoding variants, including 4 variations in the promoter region of *SQSTM1*, were found in patients with ALS or FTD, none of which were found in healthy controls or patients with Paget disease of bone. The key question raised by this report and warranting further investigation is whether *SQSTM1* is a major contributor to the pathogenesis of disease in the FTLD/ALS spectrum.

SQSTM1 encodes p62 (also called sequestosome 1), a novel ubiquitin-binding protein that has an important role in protein degradation via the proteasome and autophagy, the latter being a major pathway of lysosomal digestion for cellular constituents. Accumulation of p62 is not specific for ALS and FTLD; ubiquitin-positive inclusions containing p62 have been reported in Alzheimer disease (AD), Parkinson disease (PD), multisystem atrophy, and Pick disease. The p62 also colocalizes with TDP-43-positive cytoplasmic inclusions, ubiquitin, and UBQLN2 in patients with FTLD with motor neuron disease.[6] The presence of p62 in ubiquitin-positive inclusions in many different neurodegenerative diseases, including ALS/FTD, focuses attention on a potentially important common theme in these disorders, namely, misfolded proteins and impaired proteasomal digestion and autophagy.[7]

Misfolded aggregated proteins are a prominent pathologic feature in many neurodegenerative diseases. After polyubiquitination, misfolded proteins resulting from mutations in SOD1, TDP-43, or *FUS* in ALS and α-synuclein or parkin in PD accumulate in cytoplasmic inclusions.[8] TDP-43 is degraded by both the ubiquitin-protein system and autophagy, and overexpression of p62 reduces TDP-43 aggregation in a process that involves both proteasomes and autophagy. In AD phosphorylated tau accumulates as neurofibrillary tangles in the hippocampus and cortex. The ubiquitin binding protein p62 colocalizes with these ubiquitinated tau aggregates and shuttles them to the proteasome for degradation. Mice deficient in p62 accumulate aggregated polyubiquitinated hyperphosphorylated tau and develop neurofibrillary tangles and neurodegeneration.[9]

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Discovery of many of these misfolded aggregated proteins was made possible by identifying the mutated genes, with subsequent demonstration that the protein products, even in wild-type configurations, participate in the neurodegenerative pathways in sporadic disease.

The p62 may promote the formation of ubiquitin-containing inclusions and may play a role in protecting cells from the toxicity of misfolded proteins. It now joins other proteins such as ubiquilin 2 as relevant to the functional convergence of ALS and FTLD[10]; mutations in ubiquilin 2, and now possibly p62, may alter or impair proteasomal digestion and autophagy, leading to accelerated neurotoxicity as the catabolic mechanisms of proteasomal degradation and lysosomal-mediated autophagy are overwhelmed and undigested misfolded proteins wreak havoc in the cell.

Clearly, we have much to learn about *SQSTM1* and whether the reported mutations of p62 alter proteasomal digestion and autophagy; the use of transgenic mice may allow modeling the effects of p62 mutations on protein degradation via autophagy and the proteasome. The focus on discovering relatively common as well as rare mutations in ALS and FTLD has had a tremendous payoff in the last several decades, and we can hope that future investigations will translate into new therapeutic targets for both familial and sporadic disease.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. **Go to Neurology.org for full disclosures.**

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