This article by Collet et al is a good example of the type of proteomics study currently populating this body of literature.

The authors performed a case-control study with 5 samples of patient GBM tissue and 5 samples of microscopically normal tissue from patients who had cortical excisions secondary to a seizure disorder. Comparison of tissue proteins present in the 2 samples was performed using 2-dimensional difference gel electrophoresis together with matrix-assisted laser desorption/ionization time-of-flight mass spectrometry. Their results are important because they not only confirm the upregulation of multiple proteins in GBM tissues that previously have been reported (eg, HSP 27 and Mn-SOD) but also describe the upregulation of proteins not previously reported (eg, alkaline dehydrogenase) that warrant further investigation as potential therapeutic targets.

The major limitations of the study are that it is a single-center study with examination of a small number of specimens, and this is the major limitation of many of the currently published proteomics studies related to GBM. These limitations, together with the lack of standardized methods, have resulted in relatively inconsistent or invalidated information. In response to these limitations, the National Cancer Institute has developed the Proteome Characterization Centers, a collaborative aimed at providing validated, comprehensive genomic and proteomic information about multiple tumor types (including GBM) and developing and improving proteomic technologies.[1]

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Reference

1. Kalinina J, Peng J, Ritchie JC, Van Meir EG. Proteomics of gliomas: Initial biomarker discovery and evolution of technology. *Neuro Oncol*. 2011;13:926-942.

A yeast functional screen predicts new candidate ALS disease genes

Couthouis J, Hart MP, Shorter J, et al (Univ of Pennsylvania School of Medicine, Philadelphia; et al)

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Amyotrophic lateral sclerosis (ALS) is a devastating and universally fatal neurodegenerative disease. Mutations in two related RNA-binding proteins, TDP-43 and FUS, that harbor prion-like domains, cause some forms of ALS. There are at least 213 human proteins harboring RNA recognition motifs, including FUS and TDP-43, raising the possibility that additional RNA-binding proteins might contribute to ALS pathogenesis. We performed a systematic survey of these proteins to find additional candidates similar to TDP-43 and FUS, followed by bioinformatics to predict prion-like domains in a subset of them. We sequenced one of these genes, *TAF15*, in patients with ALS and identified missense variants, which were absent in a large number of healthy controls. These disease-associated variants of TAF15 caused formation of cytoplasmic foci when expressed in primary cultures of spinal cord neurons. Very similar to TDP-43 and FUS, TAF15 aggregated in vitro and conferred neurodegeneration in *Drosophila*, with the ALS-linked variants

having a more severe effect than wild type. Immunohistochemistry of postmortem spinal cord tissue revealed mislocalization of TAF15 in motor neurons of patients with ALS. We propose that aggregation-prone RNA-binding proteins might contribute very broadly to ALS pathogenesis and the genes identified in our yeast functional screen, coupled with prion-like domain prediction analysis, now provide a powerful resource to facilitate ALS disease gene discovery.

▶ Amyotrophic lateral sclerosis (ALS), as well as other neurodegenerative diseases, has been shown to be associated with an accumulation of misfolded proteins in neurons and glia in the central nervous system. Spreading of misfolded protein conformations present in Alzheimer's disease, similar to the mechanism of infectious prions, was demonstrated approximately 2 decades ago. Since that time, a significant amount of evidence has been generated supporting the idea that multiple neurodegenerative diseases, including ALS, progress clinically and neuropathologically via a mechanism similar to prions. In addition, it is now clear that the accumulation of 2 RNA binding proteins (FUS and TDP-43), which have domains similar to prions, is responsible for the development of ALS in some patients.

The findings reported in this article by Couthouis et al are important for 2 major reasons. First, they describe another RNA-binding protein, TAF-15, which demonstrates characteristics similar to FUS and TDP-43 both in vitro and in vivo, thus making it a good candidate for involvement in the pathogenesis of ALS. Second, the investigators describe methods for screening and testing candidate proteins that will most likely be highly useful for identifying additional proteins potentially involved in the pathogenesis of ALS as well as with the pathogenesis of other neurodegenerative diseases known to involve accumulations of misfolded proteins.

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Progression of Tau Pathology in Cholinergic Basal Forebrain Neurons in Mild Cognitive Impairment and Alzheimer's Disease

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Tau is a microtubule-associated protein that forms neurofibrillary tangles (NFTs) in the selective vulnerable long projection neurons of the cholinergic basal forebrain (CBF) in Alzheimer's disease (AD). Although CBF neurodegeneration correlates with cognitive decline during AD progression, little is known about the temporal changes of tau accumulation in this region. We investigated tau posttranslational modifications during NFT evolution within the CBF neurons of the nucleus basalis (NB) using tissue from subjects with no cognitive impairment, mild cognitive impairment, and AD. The pS422 antibody was used as an early tau pathology marker that labels tau phosphorylated at Ser422; the TauC3 antibody was used to detect later stage tau