Determinants of rapid disease progression in ALS
Koji Yamanaka and Don W. Cleveland
Neurology 2005;65;1859-1860
DOI: 10.1212/01.wnl.0000192717.25980.b5

This information is current as of May 8, 2006

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://www.neurology.org/cgi/content/full/65/12/1859
Determinants of rapid disease progression in ALS

Koji Yamanaka, MD, PhD; and Don W. Cleveland, PhD

It has now been 12 years since mutations in superoxide dismutase (SOD1), an abundant, ubiquitously expressed protein, were identified as causes of 20% of dominantly inherited ALS. The long-known involvement of this enzyme in oxidative chemistry (converting superoxide produced primarily by errors within mitochondria to hydrogen peroxide and water) fueled an initial view that selective toxicity to motor neurons resulted from loss of dismutase activity. This is not the case, however. Some mutations are fully active, whereas others are completely inactive, and no correlation has been found between retention of dismutase activity and age at disease onset or duration of disease. Moreover, with at least 114 different mutations now reported, there is a conspicuous absence of the simple null mutations that would decrease dismutase activity by precluding the synthesis of a full-length, or nearly full-length, mutant polypeptide. Finally, expression of ALS-linked SOD1 mutations in rodents provokes progressive motor neuron disease independent of dismutase activity, whereas total absence of SOD1 by gene deletion does not cause motor neuron disease in mice.

This has led to the widely believed view that SOD1 mutant-mediated ALS arises from acquisition of an as-yet unidentified toxic property shared among the many mutants. But what is it? In this issue of Neurology, Sato et al. report what may be a pivotal and counterintuitive discovery regarding the nature of such a toxic property. By using antibody methods to rapidly purify SOD1 and coupling this with mass spectrometry that is capable of distinguishing the mutant and wild-type SOD1 proteins, these investigators have measured the relative accumulated levels of wild-type and mutant SOD1 in erythrocytes of 29 SOD1-mutated familial ALS patients and four presymptomatic mutant carriers. SOD1 extracted from red blood cells of patients had been analyzed previously (e.g., Deng et al.), albeit these earlier efforts were never very satisfying in light of the inability to distinguish the mutant and normal SOD1 polypeptides and the very harsh isolation methods used that probably denatured many of the mutants.

The new study covers 22 different SOD1 mutations, including SOD1A4V, which accounts for approximately 50% of SOD1-mutated patients in North America. Because enucleated erythrocytes survive approximately 120 days but do not continue to synthesize proteins, remaining protein levels provide a measure of protein stability. Ratios of mutant to wild-type SOD1 ranged from a high of 0.61 to undetectable, with no mutant at all measured in 13 patients. The patients with undetectable SOD1 mutant had the shortest disease durations. Although age at disease onset was found to be uncorrelated with the amount of mutant SOD1, the evidence convincingly shows a strong inverse correlation (with one outlier) between disease duration and mutant accumulation (and hence mutant polypeptide stability). Said another way, an accelerated disease course is found for mutants that are less stable.

What does this surprising discovery imply? In biosynthetically active cells, including spinal motor neurons and their nonneuronal neighbors, mutant and wild-type SOD1 proteins are synthesized at equivalent levels. Consequently, when they have accumulated to their steady state levels, there will be the same number of molecules of mutant and wild type undergoing degradation in any unit of time: models of toxicity from choking the protein degradation machinery (e.g., the proteasome) by the sheer mass of mutant proteins to be degraded cannot be right.

There are two further lessons. That patients accumulating less mutant have a more rapid disease course implies that it is the misfolded, unstable forms of SOD1 mutants that contribute to toxicity underlying disease progression. Notwithstanding the difficulties in obtaining appropriate samples, an essential extension of the current effort will be to test
the stability of the SOD1 mutants in the tissues most affected in ALS. A second, even more surprising insight is that despite its apparent importance for progression, SOD1 mutant stability is not correlated with disease onset.

All of this raises something only hinted at previously: are the mechanisms for onset different than the mechanisms for disease progression? Compelling evidence for this divergence emerged earlier this year through suppressing mutant SOD1 synthesis selectively in motor neurons by using lentivirus-mediated RNA silencing. This markedly delayed onset of disease in SOD1 mutant–expressing mice but at the same time was deeply disappointing from a therapeutic standpoint because disease progression after onset was accelerated. Failure of viral methods to slow disease progression after onset after targeting only motor neurons is most readily explained by the inability of that approach to suppress mutant action in the nonneuronal cells. Toxicity to motor neurons is known to be non–cell autonomous, with wild-type nonneuronal cells capable of delaying or eliminating degeneration and death of mutant-expressing motor neurons and wild-type neurons acquiring damage from mutant-expressing neighbors.

So what is toxic in SOD1 mutant–mediated ALS? Linkage of mutant instability to rapid disease progression fits well with discovery that unstable, misfolded mutant SOD1 is accumulated onto the cytoplasmic face and within mitochondria only in affected tissues. This is most pronounced for the least stable mutants, which cause disease in rodent models and familial ALS spinal cord at more than 50 times lower accumulated levels than are needed for stable, dismutase active mutants. The accumulated evidence, especially in light of the study of Sato et al., is that the focal association of a small proportion of misfolded SOD1 mutant with spinal mitochondria provokes disease-initiating damage within motor neurons. This is then compounded by subsequent mutant action within nonneuronal neighboring cells whose dysfunction accelerates disease progression.

References
Determinants of rapid disease progression in ALS
Koji Yamanaka and Don W. Cleveland
Neurology 2005;65;1859-1860
DOI: 10.1212/01.wnl.0000192717.25980.b5

This information is current as of May 8, 2006

Updated Information & Services
including high-resolution figures, can be found at:
http://www.neurology.org/cgi/content/full/65/12/1859

Related Articles
A related article has been published:
http://www.neurology.org/cgi/content/full/65/12/1848

Permissions & Licensing
Information about reproducing this article in parts (figures, tables)
or in its entirety can be found online at:
http://www.neurology.org/misc/Permissions.shtml

Reprints
Information about ordering reprints can be found online:
http://www.neurology.org/misc/reprints.shtml