“Propagated misfolding of SOD1 in ALS: A new prion-like disorder?”

Approximately 10% of ALS cases are familial, with ~20% of these due to mutations in the gene encoding Cu/Zn superoxide dismutase (SOD1), a ubiquitous free-radical defense enzyme. A consequence of SOD1 mutation and/or oxidation is a propensity of the protein to misfold and aggregate. Human wild-type (wt) SOD1 is known to co-aggregate with mutant SOD1 in familial ALS, in double transgenic mouse models, and in cell culture systems, but the structural determinants of this process and its functional consequences are unclear. We sought to molecularly dissect the effects of intracellular obligately misfolded SOD1 mutant proteins on natively structured wild-type SOD1.

Expression of the enzymatically inactive, natural familial ALS SOD1 mutations G127X and G85R in human mesenchymal and neural cell lines induced misfolding of wild-type natively-structured SOD1, as indicated by: 1) acquisition of immunoreactivity with SOD1 misfolding-specific monoclonal antibodies; 2) markedly enhanced protease sensitivity suggestive of structural loosening; and 3) non native disulfide-linked oligomer and multimer formation. Cytosolic mislocalizing mutations of FUS and TDP43, two proteins implicated in familial and sporadic ALS, also triggered SOD1 misfolding. Expression of G127X and G85R in mouse cell lines did not induce misfolding of murine wtSOD1, and a species restriction element for human wtSOD1 conversion was mapped to a region of sequence divergence in loop II and beta-strand 3 of the SOD1 beta-barrel (residues 24-36), then further refined surprisingly to a single tryptophan residue at codon 32 in human SOD1. Aggregated recombinant G127X is capable of inducing misfolding of recombinant human wtSOD1 in a cell-free system in buffered saline containing reducing and chelating agents.

Transmission of SOD1 misfolding in vitro was abrogated by extracellular pan- and misfolding-specific SOD1 antibodies. G37R Tg mice treated with misfolding-specific SOD1 antibodies displayed prolonged survival of ~11 days (p < 0.001). On quantitative immunoprecipitation, misfolded wtSOD1 was found to constitute ~5% of total SOD1 in spinal cord samples from SOD1 familial as well as sporadic ALS. SOD1 misfolding and toxicity can propagate within and between cells, prompting novel targeted therapies for all forms of ALS. ALS now joins company with Alzheimer’s, Parkinson’s, and other neurodegenerative and systemic diseases as a “prion-like” disorder that transmits from cell to cell – and perhaps also between individuals.

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