

Self-propagation and transmission of misfolded mutant SOD1

Prion or prion-like phenomenon?

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The hallmark of both sporadic and familial forms of amyotrophic lateral sclerosis (ALS), a common and inevitably fatal motor neuron disease, is the presence of proteinaceous deposits in motor neurons. Mutations in the gene encoding the abundantly expressed cytosolic superoxide dismutase-1 (SOD1) cause aggregation of the protein in some familial forms of the disease.¹ While it is clear that misfolding of mutant SOD1 is central to the disease and somehow leads to the degeneration of motor neurons, what elicits aggregation of mutant SOD1 in ALS is unknown. ALS has an adult onset and is rapidly progressive. Likewise, both the deposition of SOD1 aggregates and the appearance of symptoms are progressive in mouse models of ALS.² Curiously, just like in motor neurons prior to the onset of the disease, SOD1 mutants do not spontaneously form the disease-characteristic deposits in cell culture.²

In a study recently published in *The Proceedings of the National Academy of Sciences*,³ we report that exogenous aggregates prepared from highly purified recombinant SOD1 protein, penetrate inside cells with a surprising efficiency. Like some viruses, SOD1 aggregates use macropinocytosis to enter cells and then rapidly escape this compartment to reach the cytosol. Just like the disease deposits, the internalized SOD1 aggregates are ubiquitinated. Once they have penetrated inside the cytosol, mutant SOD1 aggregates convert the otherwise soluble, intracellular protein to their aberrant conformation.

This is a point of no return. The newly synthesized mutant SOD1 proteins are inevitably corrupted by the internalized

aggregates. Furthermore, aggregates are continuously released by cells and taken up by neighboring cells, hence endlessly continuing this vicious cycle: penetration of aggregates into cells, seeding aggregation of the cellular, normally soluble, homologous protein and transmission of the misfolding pathology to neighboring cells. Once induced by very small amounts of exogenous seeds, mutant SOD1 aggregation is a self-propagating[†] phenotype that stably persists in dividing cells, long after the disappearance of the seeds. Thus, mutant SOD1 is the second mammalian protein to fully recapitulate, in cells, the cycle of events characteristic of prions.

Prion disorders such as, Bovine Spongiform encephalopathy (BSE), scrapie in sheep and Creutzfeldt-Jakob disease in humans are infectious diseases caused by the aggregated form of the prion protein, PrP^{Sc}, which endlessly self-propagate by imposing its altered conformation to the cellular protein PrP^C.⁴ Like the prion, mutant SOD1 aggregates can infect cells: penetrate inside cells, seed aggregation of the homologous protein and replicate.³ Similar to the scrapie agent, mutant SOD1 aggregates display hydrophobic surfaces,^{5,6} a feature that may underlie their ability to cross cellular membranes. However, unlike prions, there is no evidence that SOD1 aggregates could be transmitted between individuals.

The prion realm is not restricted to metazoans and is not necessarily associated with fears of epidemics. A few unrelated yeast prion proteins can adopt self-propagating conformations, responsible for a non-mendelian, cytoplasmic, “protein-only” mode of inheritance.⁷ Mutant SOD1

displays the defining properties of a prion, according to the definition proposed by Reed Wickner: “any protein that indefinitely propagates an altered form of itself and is transmissible.”⁸

Can there be more human prions? Recent studies have revealed that the misfolding pathology characteristic of Alzheimer, Parkinson and Huntington disease can be transmitted experimentally in animal or cellular models (reviewed in ref. 9). These observations are reminiscent of the seeding property of prions and have led to the proposal that misfolding diseases could all be prion-like disorders. However, it remains to be established whether the misfolded proteins associated with Alzheimer, Parkinson and Huntington disease have the ability to self-propagate a change in their conformation in the absence of exogenous seeds, like prions. Further investigations will help defining a clearer distinction between prion and prion-like phenomena.

Note

[†]Self-propagation indicates that the protein indefinitely replicates its altered conformation.

References

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