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PRIONS

Prying into prions

Prion proteins switch between a normal conformation and an aggregated form, and they can propagate this conformational change among other molecules of the same protein. Although this intriguing ability allows prions to confer a heritable phenotype to other yeast cells independently of DNA, only a few prions have been identified to date. A recent study suggests that prions might have a much broader role in biology than previously thought. Alberti *et al.* now describe their systematic survey of the *Saccharomyces cerevisiae* genome for prion candidates, revealing a novel amino acid bias for predicting prion proteins and a new prion-forming protein called Mot3.

An initial bioinformatics scan identified around 200 proteins that contain a candidate prion-forming domain (cPrD). Among these, 19 new prion candidates were identified on the basis of their ability to form amyloid (insoluble fibrous protein aggregates) *in vitro* and *in vivo*, and to replicate indefinitely in cells as self-perpetuating epigenetic elements, thus satisfying the main criterion of prion behaviour.

Next, the sequences of cPrDs were compared. Surprisingly, although defined PrDs have been characterized as Asn and Gln rich, aggregation-prone cPrDs were strongly enriched for Asn, whereas non-aggregating cPrDs were abundant in Gln, Pro and charged residues. The spacing of Pro and charged residues also influences prion formation. Contrary to previous findings, these data suggest that it is not the amino acid composition alone but also the exact sequence that determines prionogenesis.

Finally, the authors rigorously assessed Mot3, a globally acting transcription factor that contains a cPrD, for its ability to operate as a prion in a physiologically relevant manner. Data reveal that the Mot3 prion protein can confer its phenotype to prion-free cells independently of DNA, and that intracellular Mot3 readily engages in self-renewing prion aggregation. In short, the authors have identified Mot3 as a novel prion-forming protein in yeast, and they have discovered new sequence features for prionogenesis, which will help to characterize prion proteins in the future. Further assessment of other cPrD-containing proteins will reveal if these, too, truly behave as prions.

> “...19 new prion candidates were identified...”

Katharine H. Wrighton

ORIGINAL RESEARCH PAPER Alberti, S. *et al.* A systematic survey identifies prions and illuminates sequence features of prionogenic proteins. *Cell* **137**, 146–158 (2009)