

BIOLOGY COLLOQUIUM

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3:50 PM, Room 111, Life Sciences

“Using Yeast to Study Mad Cow and Alzheimer's Disease”

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The recent epidemics of "mad cow", Creutzfeldt-Jakob and chronic wasting disease have put the so-called prion diseases firmly in the public eye. These neurodegenerative illnesses are each transmitted in a very unusual way. In each case the infectious agent lacks any traditional genetic material (nucleic acid.). Rather, infectivity depends upon the shape into which the highly conserved PrP protein is folded: when some PrP is in its disease-causing ("prion") shape, it converts normal PrP into that form too.

In recent years it has become clear that several genetic traits in the single celled eukaryotic organism, yeast, are propagated by this unusual "protein only" mechanism. Although the yeast traits involve proteins distinct from PrP, the term prion has been expanded to include them because the traits are controlled by an infectious protein shape, rather than by an altered nucleic acid sequence. Since it is so much easier to experiment with yeast than mammals, the yeast model system provides a great opportunity for studying prions.

In my laboratory we use yeast to elucidate the factors that influence prion inheritance and to look for new prions. One yeast prion we study, [PSI+], is caused by an altered shape of a protein called Sup35 (a translational release factor). When Sup35 is in the prion shape it aggregates and loses its normal activity and this causes the [PSI+] phenotype. An important piece of evidence for this prion hypothesis was our finding that a transient excess of the Sup35 protein induces the permanent appearance of [PSI+]. Presumably this occurs because the excess of Sup35 increases the chance that some Sup35 molecules will accidentally fold into the prion shape creating a "seed" that starts a chain reaction affecting most of the Sup35. Our finding that an intermediate level of the Hsp104 chaperone is required for the propagation of [PSI+] also provides dramatic support for the prion hypothesis, since the only known function of Hsp104 is to facilitate protein folding. This finding has spawned considerable interest in the role of other chaperones in the maintenance of various prions.

Surprisingly the same PrP protein molecule with the identical amino acid sequence can take on more than one heritable prion shape! These different prion shapes have been called "strains". The relationship between different prion strains and their effects on prion infectivity are of great interest. This phenomenon can now be studied in yeast because we found and characterized different [PSI+] "strains" and [PIN+] "strains" with distinct heritable phenotypes. We are also studying factors that influence the appearance of yeast prions. The most intriguing of these is a new prion, [PIN+], which we found to be required for the de novo appearance of [PSI+]. Interestingly, [PIN+] is only required for the generation of [PSI+], but does not influence the propagation of [PSI+]. We believe that the [PIN+] prion can inefficiently "seed" the de novo formation of the heterologous prion, [PSI+]. This finding suggests that altered protein in one of the conformation based diseases such as Creutzfeldt-Jakob, Alzheimers' or Huntington's disease, may influence the appearance of another conformation based disease even though a different heterologous protein is involved.