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Mad yeast disease?

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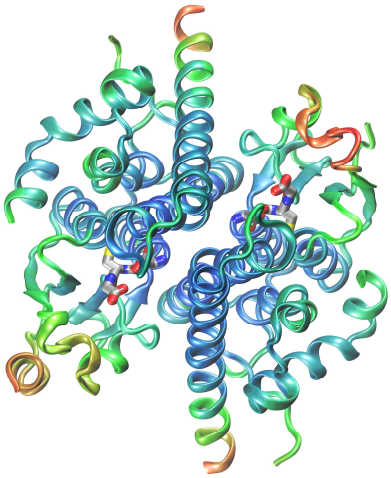
When referring to prions, most of us think 'Mad Cow disease' (Bovine Spongiform Encephalopathy or BSE). Which is not incorrect but narrow-minded. The term 'prion' – coined in the early 1980s by the American biochemist Stanley Prusiner – simply means 'infectious protein', from which were derived the letters which make up the word. Prion proteins are found not only in cattle, sheep and humans, but also in other vertebrates as well as yeast and certain fungi. And will no doubt continue to be discovered in many other organisms, if not all. The URE2 protein – a candidate prion in *Saccharomyces cerevisiae* – was the first prion to be crystallised. Clearly, the understanding of a prion's 3D structure and the conformational changes it undergoes – and passes onto its peers – is of great interest in the search for therapeutic treatments of diseases caused by these volatile proteins.



Dimer of the prion Ure2P

Courtesy of Fabrice David, SIB Geneva

Scrapie – the fatal neurodegenerative disease which affects sheep and goats – and which could very well be named the 'Mad Sheep disease', was first described in the 1700s but its infectious nature was only recognised in the 1930s. It took a further 70 years before it was discovered that the infectious agent of such diseases was actually a protein. Prusiner made the discovery and tentatively suggested it to the scientific community.

The concept that a protein could be infectious was far from popular. The media helped to kindle disagreement, and it was some time before the idea was generally accepted. Despite a rough ride, Prusiner was ultimately rewarded the Nobel Prize in Medecine in 1997 for his discovery, where he humbly noted that '…while it is quite reasonable for scientists to be sceptical of new ideas that do not fit within the accepted realm of scientific knowledge, the best science often emerges from situations where results carefully obtained do not fit within the accepted paradigms.'

Contrary to popular belief, prion proteins do not necessarily bring on disease; they are not 'infectious' in the common sense. What a prion can do is undergo a conformational change that it can transmit to an identical neighbouring protein, which can transmit the same modification to yet another identical neighbour, and so on. It is in this sense of 'transmission' that a prion is said to be infectious. In BSE, prions form fibrillar structures in the cells, which are harmful to the organism. This type of infection is also termed a conformational disease. On the other hand, other prions are absolutely harmless to the cell and the organism as a whole; despite the 'infection', there is no disease. It may be that some organisms use prion infection as a regulator of function, i.e. the 'infection' causes a function to be switched on at a given time. In *S.cerevisiae* for instance, a

conformational change of the prion URE2 and hence its neighbours, disrupts the protein's function but causes no subsequent harm to the yeast.

What function does URE2 have in its native form? It does bear sequence similarity and even structural similarity to glutathione S-transferases but no one has yet been able to show that this is actually its function. However it is required for detoxification of glutathione S-transferase substrates and cellular oxidants. What is known is that URE2 has a role in nitrogen metabolism, where it regulates a number of transcription factors. When there is plenty nitrogen, yeast turns off enzymes and transporters needed in the event of a poor nitrogen source, and URE2 helps out in this process by binding to transcription factors in the cytoplasm, thereby preventing their entry into the nucleus where they would promote the transcription of a certain number of genes.

Structurally, URE2 is a globular protein with a flexible cap region and a poorly structured N-terminal region. The belly of the protein sports a cleft – like the glutathione S-transferases – and could well be there for an unknown ligand. In its active form, URE2 acts as a dimer, where it seems likely that the N-terminal region of one monomer interacts with the belly (functional) region of the other to hold the dimer together in an appealing embrace.

The poorly-structured N-terminus is also known as the prion region; this region may interact with the globular region to prevent the protein from converting into its prion form. What molecular changes ease URE2 into its prion form: URE2p? We do not know. What happens though is that the structural change causes the subsequent loss of URE2 function altogether and promotes the assembly of URE2p into fibrils through the interaction of URE2p monomers. It is not known to date whether it is the subtle change in conformation which causes the loss of URE2 function or whether the novel fibril formation simply hinders the URE2/GLN3 interaction.

The 'infection' is then propagated from one yeast cell to another by cytoplasmic mixing. When yeast mates, the cytoplasm of the parental strains mix even though the nucleii do not fuse. When the URE2p of one strain flows into the other, it infects the second strain by transmitting the URE2p conformational change. Understanding in detail how a prion protein such as URE2p becomes infectious and assembles into fibrils, how it loses its function and it ultimately affects an organism will help in the future design of drugs which could counter neurodegenerative diseases such as BSE and the unfortunate human form: Creutzfeldt-Jakob disease.

Cross-references to Swiss-Prot

URE2 protein, *Saccharomyces cerevisiae* (Baker's yeast) : P23202

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