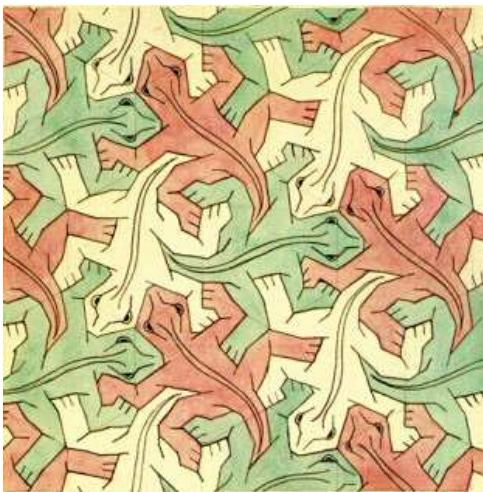


the shape of harm

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Sometimes we are forced to see things differently. But it is never easy because we are creatures of habit and, like it or not, shackled by what we were first led to believe. This is exactly what happened with the prion. Prions are proteins whose shape can change under certain conditions, and in so doing be at the heart of fatal diseases. Many afflictions are caused by a change in a protein's 3D structure, so this can hardly be considered a pioneering concept in the world of molecular biology. What is relatively new, however, is the notion that a protein can be the actual cause of infection. An infection is defined by an entity able to transmit, from one organism to another or indeed one cell to another, the information it needs to thrive and propagate. Viruses and bacteria infect organisms by multiplying inside them, killing off cells as they do so and causing havoc in their wake – such as meningitis, the classic flu or AIDS. Some prion proteins, once their shape has changed, are able to behave in the same way and cause neurodegenerative illnesses such as scrapie in sheep and Creutzfeld-Jakob disease in humans for instance. Recently, a prion of a different nature was discovered: one that refuses to change shape. Its name is PrP V¹²⁷.



Study of Regular Division of the Plane with Reptiles, by M.C. Escher

Source: Wikipedia

Contrary to popular belief, prion proteins (PrP) are not necessarily harmful. They occur naturally in organisms (PrP^c) – mainly in brain tissue – and are thought to have a role in cell-cell adhesion and intracellular signalling. It is only once they are misfolded (PrP^{Sc}) that they become pathological. It is not yet understood how the change from harmless to harmful really occurs. It could have to do with a thermodynamic barrier which causes the healthy form to be misfolded into the pathological form, and the energy required to revert back to PrP^c is so huge

that PrP^{Sc} gets trapped in its new conformation. One surprising discovery is how drastic the structural changes are between the two conformations: while PrP^c is laden with alpha helices, PrP^{Sc} bulges with beta sheets. These are striking differences for a protein whose sequence remains identical. Misfolded prions then aggregate, creating an initial PrP^{Sc} seed which stabilizes the pathological conformation of the prion protein. And the process rapidly accelerates. In the long run, oligomers assemble into fibrils, which themselves clump into larger aggregates that are ultimately deposited in the brain causing progressive neurodegeneration.

The symptoms of a prion-related affliction were described long before the prion protein was discovered. In the 18th century, Spanish shepherds remarked the odd behaviour of their Merino sheep – altered gaits, excessive licking and intense itching – which would spend hours scraping their sides against fences. They called the illness “scrapie”. In the 1920s, almost two hundred years later, the German neurologists H.G. Creutzfeld and A.M. Jakob described a neurodegenerative disease whose symptoms were similar to scrapie, and that they called Creutzfeld-Jakob disease (CJD). The affliction was slow, but progressive. What could be at the heart of such slow progression? Some scientists imagined a “slow virus” at work.

In 1967, the British biophysicist J.S. Griffith suggested that the scrapie agent was most probably proteinaceous. The notion, however, of a protein

able to act as an infectious agent met with much scepticism, and as such was largely ignored. Twenty years later, the American neurologist S.B. Prusiner uttered his belief that proteins were indeed capable of infection and coined the term “prion” – for proteinaceous infectious particle. But the scientific community continued to be dubious. Finally, towards the end of the last century and the beginning of the 21st – especially with the outbreak of Mad Cow disease – the idea of a proteinaceous infectious particle became acceptable, though a few scientists remain unconvinced. Currently, however, a finer distinction of the prion is made. Human transmission of prion-based diseases is extremely rare, and has really only occurred following the contamination of tissue grafts, surgical instruments or tainted meat products. As such, today, human prion diseases are not regarded as infectious, *sensu stricto*, but merely as disorders where aggregates form and are deposited in the brain, in a very similar manner to other neurodegenerative diseases.

This said, a neurodegenerative epidemic prion disease known as kuru was described in the 1960s by Michael Alpers, an Australian medical researcher, following field studies on the Fore tribe from Papua New Guinea. Within the tribe, the disease was known as the “laughing sickness” because those inflicted would suddenly burst out laughing. It turned out that kuru, literally “to shake”, was transmitted via funerary cannibalism, during which the flesh and the brains of the deceased were eaten. The epidemic probably sprouted in the early 1900s when a member of the population must have developed a form of CJD. There are no more cases

of kuru within the tribe today; the last person to suffer from it died in 2005. Intriguingly, further studies demonstrated that a few individuals were clearly unaffected by kuru, as though they had acquired some form of resistance. This turned out to be a PrP variant, known as PrP V¹²⁷ because a Valine replaces a Glycine at position 127 in the protein sequence. Transgenic mice expressing PrP V¹²⁷ are completely resistant to kuru and classic CJD prions. How? PrP V¹²⁷ simply refuses to convert to a pathological form of PrP, thus protecting those carrying the variant from developing a neurodegenerative disease.

There is another known PrP variant that protects individuals from developing sporadic CJD, but its mechanism of action is not the same as PrP V¹²⁷. Instead it inhibits protein-protein interactions as prion propagation progresses. Understanding how PrP V¹²⁷ has the power to resist change should help scientists grasp the molecular mechanism underlying prion pathology and propagation, and offer key insights for the development of therapeutics. Unknown to anyone at the time, the Fore population probably survived the ongoing kuru epidemic when cannibalism was banned because the path of prion transmission was interrupted. However, the mere existence of PrP V¹²⁷ seems to suggest that, given more time, kuru-resistant individuals may well have begun to flourish as a natural evolutionary response to the epidemic. Sometimes, Nature does seem to have its own way of sorting things out.

Cross-references to UniProt

Major prion protein, *Homo sapiens* (Human): P04156

References

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