To achieve the necessary sharper imaging, astronomers have resorted to a 'shadowgram' technique, using a metal mask encoded with a pattern of holes to cast a shadow on a large camera (Fig. 1). By correlating the observed shadow with the known pattern in the coded mask, the position of the γ-ray source can be pinpointed. The viability of the technique was demonstrated by a pathfinder Russian–French telescope that flew on the Russian GRANAT mission in 1989.

Coded-mask telescopes need large radiation-collecting areas to detect the faint sources, and this in turn requires a big, heavy space observatory. For more than two decades, astronomers could only dream of the potential of such a γ-ray telescope for solving the mystery of our Galaxy's γ-ray glow. ESA took up the challenge in the mid-1990s and led the development of the INTEGRAL observatory. In October 2002, it was launched on a Russian Proton rocket.

The INTEGRAL observations reported by Lebrun *et al.* reveal many dozens of sources, most of them quite faint. The sum of their γ-radiation matches the γ-ray flux previously attributed to the diffuse glow. Many of the newly discovered sources seem to be either black holes or neutron stars. They show absorption spectra — corresponding to their radiation being absorbed by some intervening material between these sources and INTEGRAL, meaning that they stand out only at γ-ray wavelengths. The absorbing material may be either the accretion flow from a companion star, or a molecular cloud in which the source is embedded. Now we know where these objects are, follow-up observations using other telescopes, such as ESA's XMM–Newton Observatory, will uncover their nature more fully.

Over the coming years, INTEGRAL will make a complete census of the buried populations of black holes and neutron stars in the Milky Way. Exploiting its capabilities to the full, the observatory will be able to search nearby galaxies for supermassive black holes buried in their centres, pick up γ-ray bursts and detect the radioactive decay of newborn elements in the fires of exploding supernovae. The Universe will appear to be a very different place when viewed clearly with γ-ray eyes. ■

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Cell biology

The strain of being a prion

Mick F. Tuite

Prions are remarkable infectious agents associated with certain brain diseases. But they also occur in fungi, experiments with which now provide plausible answers to some critical questions about prion biology.

A widely (but not universally) accepted dogma about the agents known as prions is that they are protein-based entities that are self-perpetuating, 'infectious' and devoid of any transmissible nucleic acids. Yet despite intensive research into this 'protein only' hypothesis[1], two crucial challenges have remained unanswered. Can infectivity with purified prion protein be demonstrated? And how can different prion 'strains' be generated without any underlying change in the amino-acid sequence of the prion protein or in the genetic make-up of the host? Papers in this issue by King and Diaz-Avalos[2] and Tanaka *et al.*[3] (pages 319 and 323) address these challenges. They provide the most dramatic demonstration to date of the validity of the protein-only hypothesis.

Infection of the host by a prion can, over time, lead to the replication and subsequent transmission of an aggregated fibrous form of the infectious protein known as an amyloid. In mammals, the only known prion protein (PrP) is associated with a group of neurodegenerative diseases that include Creutzfeldt–Jakob disease in humans and bovine spongiform encephalopathy in cows[4]. Prion proteins have also been linked with stable, heritable traits in two fungi (*Saccharomyces cerevisiae* and *Podospora anserina*), although none of the four known fungal prions can be considered 'disease-causing' — some may in fact be beneficial to the host[5].

King and Diaz-Avalos[2], and Tanaka *et al.*[3], have exploited the prion properties of the Sup35p protein of *S. cerevisiae*. Sup35p is an essential factor required by the protein-synthesizing organelles— the ribosomes — to terminate synthesis of a polypeptide chain. Cells in which most of the Sup35p protein molecules have been converted to their prion form ([*PSI*$^+$] cells) are defective in this crucial termination phase.

[*PSI*$^+$] cells can be readily detected in a population of 'normal' genetically marked [*psi*$^-$] cells by a simple screen involving cell colour and protein analysis (Fig. 1, overleaf). Using this screen, King and Diaz-Avalos, and Tanaka *et al.*, independently developed what are essentially protein-only transformation systems and used them to demonstrate that

100 YEARS AGO

I happened to possess a small sample of a red deposit, coloured by iron, which is left by the water of the King's Spring, at Bath. It occurred to me that it might be worth while to test this for radio-activity. The result was to show that the deposit was markedly active. On leaving it in the testing vessel (which was closed airtight) for a few days, the activity was found to increase to several times its initial value. This shows that the deposit gives off an emanation freely, even without heat. Experiments were then made to test the rate of decay of this emanation. It proved to be identical with the rate of decay of the emanation of radium… The presence of radium in the Bath water and deposits is of special interest because of the occurrence of helium in the gas which arises from the spring… There can be little doubt that the helium owes its origin to the same store of radium that supplies the water.
From *Nature* 17 March 1904.

50 YEARS AGO

At a meeting of the Geological Society held at Burlington house on February 24, Mr. A. T. Marston exhibited a number of flints which he had attempted to stain with chromic acid or potassium dichromate in order to assist appreciation of the condition of the Piltdown flint recently described by Drs. Oakley and Weiner (*Nature*, December 12, 1953). Mr. Marston pointed out that though some types of these flints would not stain at all, others became deeply stained. In the latter case, however, the stain was very difficult to remove. As the stain on the Piltdown flint had apparently been easily removed by acid, Mr. Marston queried whether it had indeed been artificially produced, and also inquired whether there was any possibility that traces of chromium might exist naturally in the ferruginous Piltdown gravels. Dr. Oakley then exhibited specimens of flint from Piltdown, and described tests that had been made on all the flints illustrated in the original paper by C. Dawson and A. Smith Woodward. All these flints had a ferruginous stain which was easily removed by acid, in contrast to the other 'natural' flints from the Piltdown area collected at the same time… Dr. Oakley believed that the illustrated flints had been stained artificially with a ferruginous solution, and in one case a chromic solution had also been used in order to make the flint less red, and so resemble more closely the 'natural' flints.
From *Nature* 20 March 1954.

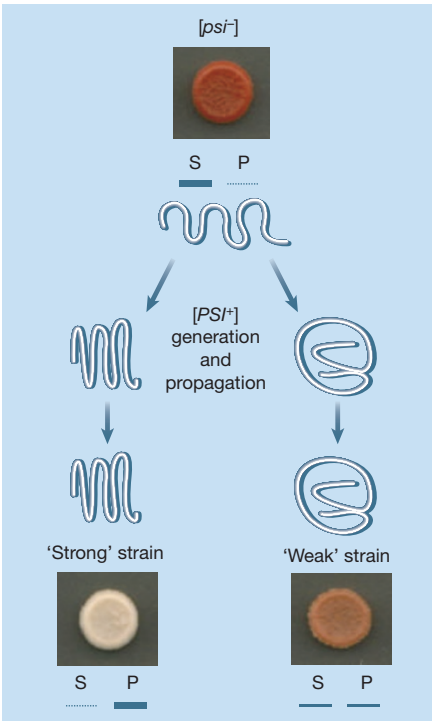

Figure 1 **Prion behaviour in the yeast *S. cerevisiae*. Tell-tale colony colours are shown, along with an indication of the amount of Sup35p protein in soluble (S lane) or aggregated (P lane) form. [*psi*⁻] yeast cells contain a soluble form of the Sup35p protein. Such cells fail to suppress the *ade1-14* mutation, because of effective translation termination, leading to red colonies being formed on agar plates. Two different [*PSI*⁺] strains can be generated *de novo*; they differ not only in the conformation of Sup35p, but also in the extent to which the Sup35p protein is aggregated. In the 'strong' [*PSI*⁺] strain, more than 95% of the Sup35p protein is in the non-functional, aggregated fraction (lane P). These cells produce white colonies because translation termination is impaired and the *ade1-14* mutation is suppressed. In the 'weak' [*PSI*⁺] strain, a significant level of Sup35p is also seen in the soluble fraction (lane S). The 'weak' strain therefore shows a partial restoration of translation termination and concomitantly less efficient suppression of the *ade1-14* mutation giving pink colonies. Once a particular strain has been generated, it is stably replicated in that conformation.**

[*psi*⁻] cells can be 'infected' — that is, turned into [*PSI*⁺] cells — with an amyloid form of part of the Sup35p protein. The part they use is one end of the protein, the N region, which contains all the structural information needed for maintaining the [*PSI*⁺] state *in vivo* and can readily assume an amyloid form *in vitro*[5]. By generating amyloid forms of the protein that are free from any other yeast protein, and by showing that the resulting infectivity is not affected by treatment with agents that destroy nucleic acids, the authors' findings leave little doubt that a single protein species can act as an infectious agent based on its conformation. Moreover, previous work with Sup35p in *S. cerevisiae*[6] and with a different fungal prion protein (the HET-s protein of *P. anserina*)[7], did indeed provide some evidence in favour of the view that it is the amyloid form of the protein that transmits infectivity[8]. That evidence fell short of being compelling, but the gap is now filled by the new results[2,3].

The existence of different prion 'strains' has always cast a shadow on the protein-only hypothesis. In mice, for example, at least 20 prion strains have been described which produce different disease characteristics but are not the result of a change in host genetic make-up[9]. It has been proposed that prion strains could arise through the existence of distinct, self-propagating conformers of otherwise identical PrP polypeptide chains. But no direct experimental evidence was forthcoming[9] — until now.

There are at least two distinct [*PSI*⁺] strains (or 'variants'), as defined by the degree of suppression of a host nonsense mutation (*ade1-14*), and biochemically by the proportion of Sup35p that remains soluble and hence free to participate in the termination process (Fig. 1). During the *de novo* appearance of the [*PSI*⁺] prion, both types of strain can emerge within a population of otherwise genetically identical [*psi*⁻] cells. Once a prion strain has emerged, it is stably propagated and efficiently transmitted to daughter cells during cell division. Evidence already exists that Sup35p may be in a different conformational state in different strains; for example, Sup35p from different [*PSI*⁺] strains has different amyloid seeding propensities *in vitro*[10].

King and Diaz-Avalos[2], and Tanaka *et al.*[3], provide the first direct evidence that conformationally distinct, amyloid forms of Sup35p underlie the transmissible differences in the [*PSI*⁺] strains. They show that at least two distinct conformers of Sup35p can be generated *in vitro* as defined by various biophysical measurements. By demonstrating that the 'infection' of [*psi*⁻] cells with the different conformers each generates different [*PSI*⁺] variants, both groups firmly establish the link. Furthermore, these conformational differences are propagated *in vivo*[3].

At least for yeast prions, attention can now turn to the baffling matter of how the amyloid form is propagated, thereby ensuring stable transmission to daughter cells. Two basic mechanisms, known as template-directed refolding and seeded nucleation, have been widely touted[11]. But what is the molecular nature of the propagating unit (or seed)? Is it a conformationally altered monomeric form of the protein, or the highly aggregated amyloid form? These questions can now be tackled using the new prion transformation assays, and there are already candidates. For example, high-molecular-weight Sup35p aggregates in [*PSI*⁺] cells can be broken down into smaller, detergent-insoluble Sup35p-based polymers, and the size of the polymer depends on the [*PSI*⁺] strain[12]. Could these detergent-insoluble polymers be the active seeds? We now have a powerful way of approaching the remaining mysteries of prion propagation in yeast, and one that could equally be applied to the cells of higher organisms. ■

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1. Prusiner, S. B. *Science* **216,** 136–144 (1982).
2. King, C.-Y. & Diaz-Avalos, R. *Nature* **428,** 319–323 (2004).
3. Tanaka, M., Chien, P., Naber, N., Cooke, R. & Weissman, J. S. *Nature* **428,** 323–328 (2004).
4. Collinge, J. *Annu. Rev. Neurosci.* **24,** 519–550 (2001).
5. Uptain, S. M. & Lindquist, S. L. *Annu. Rev. Microbiol.* **56,** 703–741 (2002).
6. Sparrer, H. E., Santoso, A., Szoka, F. & Weissman, J. S. *Science* **289,** 595–599 (2000).
7. Maddelein, M. L., Reis, S. D., Duvezin-Caubet, S., Coulary-Salin, B. & Saupe, S. J. *Proc. Natl Acad. Sci. USA* **99,** 7402–7407 (2002).
8. Liebman, S. W. *Proc. Natl Acad. Sci. USA* **99,** 9098–9100 (2002).
9. Bruce, M. E. *Br. Med. Bull.* **66,** 99–108 (2003).
10. Uptain, S. M., Sawicki, G. J., Caughey, B. & Lindquist, S. *EMBO J.* **20,** 6236–6245 (2001).
11. Tuite, M. F. & Cox, B. S. *Nature Rev. Mol. Cell Biol.* **4,** 878–889 (2003).
12. Kryndushkin, D. S., Alexandrov, I. M., Ter-Avanesyan, M. D. & Kushnirov, V. V. *J. Biol. Chem.* **278,** 49636–49643 (2003).

Cancer

Survival pathways meet their end

Frank McCormick

Conventional chemotherapeutic approaches to treating tumours can be hit-and-miss. One way to ensure successful treatment may be to go for the jugular of cancer-cell survival signalling as well.

Chemotherapy uses powerful drugs designed to induce cancer cells to commit suicide. So why don't all tumours succumb to these drugs? The answer is that cancer cells have an inbuilt urge to survive, so any genetic change that favours survival amidst adverse conditions will be selected for. The outcome, of course, is that some tumours survive exposure to even the most potent therapeutic agents. But by increasing our knowledge of the components involved in the pathways that mediate survival, the hope is that targeting specific molecules will impart sensitivity to chemotherapy — a combinatorial approach. Wendel and co-workers, reporting