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Cell Preview

Remembering the past: a new form of protein-based inheritance

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SUMMARY

A comprehensive analysis uncovered a set of yeast proteins promoting protein-based inheritance that shares many of the non-Mendelian properties of prions. Lacking any sequence or structural signatures of known prions, these proteins represent a new class of non-amyloid, protein-based epigenetic determinants that can control phenotype without impacting on genotype.

MAIN TEXT

Although originally viewed with some disbelief, protein-based inheritance is now largely accepted as a rare but significant addition to the portfolio of epigenetic mechanisms. Our knowledge of such a heretical mode of inheritance comes largely from the study of fungal prions that can generate phenotypic plasticity without compromising genotype. It now emerges that protein-based inheritance may not be so rare and that it is not just amyloid-

based prions that are the perpetrators. In this issue Chakrabortee et al (2016) add a new twist to the tale by showing that approximately 1% of the yeast proteome can undergo some form of stable molecular event that leads to the emergence of new and beneficial heritable traits. In so doing the authors have identified a new class of prion-like proteins which can establish heritable, protein-based 'molecular memories' that are sustainable over hundreds of generations yet are not amyloid associated.

The brute force approach taken by the authors was to ask whether elevating the levels of any one of 5300 or so different yeast (*Saccharomyces cerevisiae*) proteins triggered a heritable change in phenotype that was retained after the expression level had reverted back to normal. Although only relatively few phenotypes were screened, 46 different proteins satisfied the rigorous experimental criteria applied. Phenotypic changes induced by protein overexpression are not unexpected, but retention and transmission of the resulting phenotypes when the cells return to the un-induced state, is. So have the authors identified 46 new prions in yeast?

Prions are an unusual class of protein whose members can take up and perpetuate a number of distinct structural conformations with the biochemical properties of amyloid. Prions are considered infectious because the new conformer and its associated phenotype can be transmitted from individual to individual. The strategy applied to find new prions in yeast has been to first look *in silico* for proteins with the characteristic Gln/Asn-rich prion domain, then check for their amyloid-forming potential *in vitro* and finally look *in vivo* to see if there is a requirement for the protein disaggregase Hsp104 for the continued propagation of the prion state (Alberti et al. 2009). Surprisingly, the majority of the 46 proteins uncovered show none of the diagnostic sequence and biochemical features of the established yeast prions, yet they show similar non-Mendelian inheritance properties (**Figure 1**).

At this stage one can only speculate about the nature of the molecular events that lead to the establishment and inheritance of these new traits. If there is an associated change in protein conformation and/or aggregation state, that does not appear to be related to the establishment of an amyloid state. There is widespread potential for proteins in the yeast cytosol to switch to a variety of insoluble, aggregated states particularly in cells undergoing some form of stress. In some cases, e.g. CTP synthase (Ingeson-Mahar et al., 2010) proteins can even switch to a filamentous structure unrelated to amyloid. Protein aggregation is not

just the consequence of protein misfolding induced by physical or chemical stimuli or indeed protein overexpression; a number of proteins exist in a native oligomeric form (e.g. actin). Over the last decade we have also seen the emergence of a distinct class of protein assembly in the cell, the so-called droplet organelles or stress granules. These dynamic complex assemblies are typically comprised of low complexity proteins and RNA, that can assemble and disassemble and play wide ranging functional roles in the cell including response to stress and viral infection (Courchaine et al 2016).

While it remains to be established precisely what structural transitions the proteins identified by Chakrabortee et al. undergo, it is evident that most require one or other of the molecular chaperones Hsp70, Hsp90 or Hsp104 to maintain their inherited phenotype. Unlike established prions however, only a minority depend on Hsp104 although one established yeast prion, [*GAR*$^{+}$], does not require the Hsp104 disaggregase function for propagation. [*GAR*$^{+}$] is an atypical prion in several ways not least being the failure to link an amyloid-forming protein to the [*GAR*$^{+}$]-linked metabolic phenotype (Brown and Lindquist, 2009).

The newly identified prion-like proteins do however have one interesting structural characteristic that they share with known prion proteins; the presence of substantial elements of conformational flexibility associated with disordered regions of the protein. Such intrinsically disordered regions (IDRs) make important and conserved contributions to protein function (Latysheva et al., 2015) and the proteins identified by Chakrabortee et al. have significant elements of predicted disorder. IDRs also have an inherent tendency to promote the conformational flexibility that is critical to propagate the inherited prion state (e.g. Marchante et al. 2013). While IDRs are not subject to the severe evolutionary constraints placed on structured domains, there is an element of conservation of this feature in this new class of prion-like proteins, hinting that this mode of protein-based 'memory' may be wide spread in nature.

As noted by the authors, the suggestion that yeast can establish protein-based biological 'memories' is not a new one. Caudron et al. (2014) reported that yeast cells exposed to one of the mating pheromones, become refractory to that chemical signal as a consequence of a change in conformation of the Whi3 protein that in turn allows expression of the G1 cyclin, Cln3. While Whi3 has many of the hallmarks of a prion-forming protein, what makes it distinct from prions and the determinants identified by Chakrabortee et al. is that the associated trait

is retained by the mother cell and not passed on to daughter cells i.e. is asymmetrically distributed at mitosis (**Figure 1**). Consequently, the mother cell retains the 'memory' and fails to respond to this chemical signal for its remaining life span. The term mnemon was coined for the high molecular weight form of Whi3 but Chakrabortee et al would not have uncovered such proteins in their screen.

As so eloquently argued by Mark Ptashne, the term epigenetics implies memory in that "....a *transient signal or event triggers a response that is then perpetuated in the absence of the original signal...*" (Ptashne, 2013). The protein-based biological memories uncovered by Chakrabortee et al fit this definition precisely, but with the caveat that the 'transient signal' in question is the engineered over expression of a specific protein. Is there a natural 'transient signal' that triggers these memories? While a chemical signal has been indicated – but not yet identified – that induces the [*GAR*$^{+}$] prion (Jarosz et al., 2014) and the mating pheromone triggers the Whi3-based mnemon (Caudron et al. 2014), what the natural signal for establishing this new cohort of prion-like epigenetic traits remains to be established. That wild strains carry such traits at least suggest that they are not artefacts of laboratory domestication.

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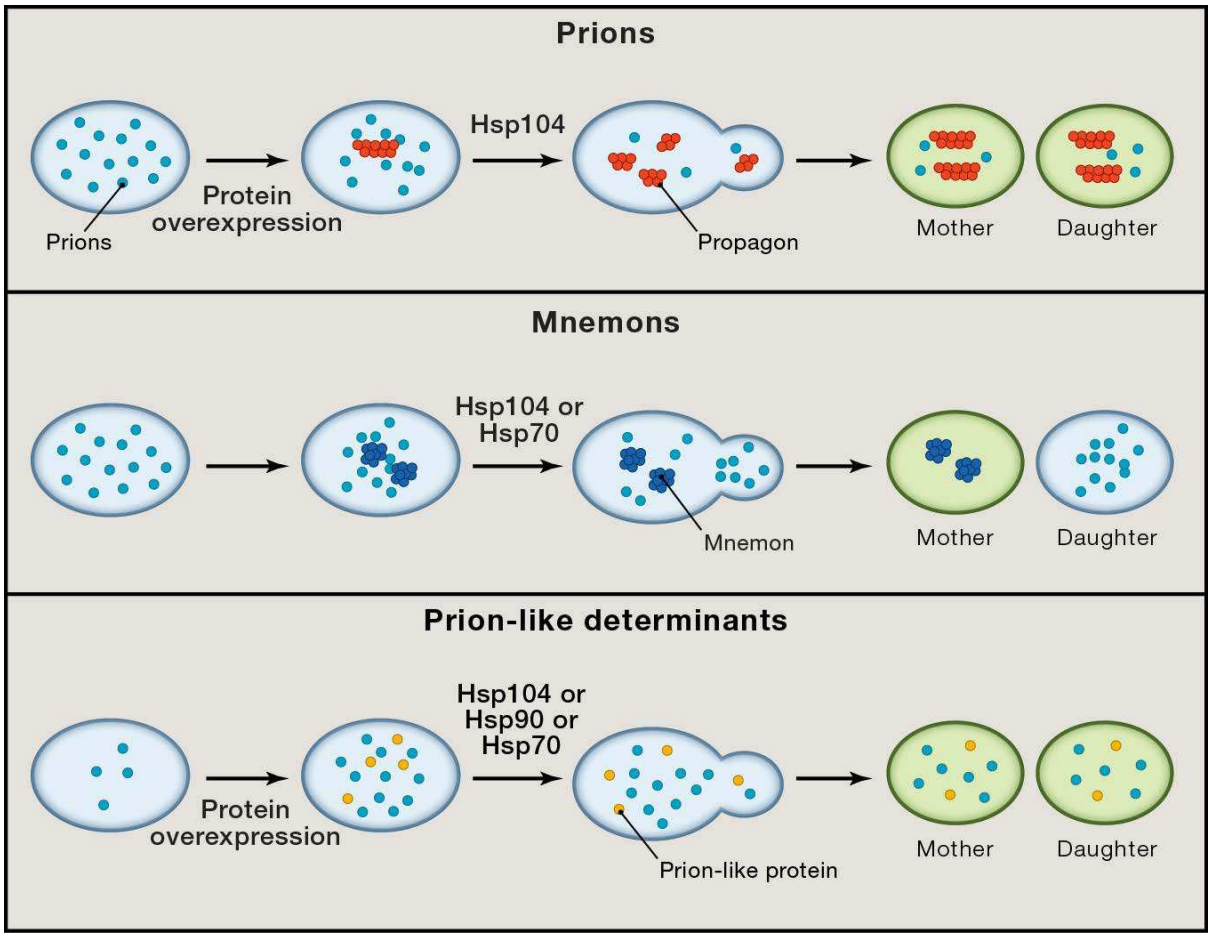
FIGURE



Three types of protein-based inheritance described in the yeast *Saccharomyces cerevisiae.* **Upper panel:** prions that can be generated *de novo* by overexpression of the prion-forming protein. The resulting amyloid fibrils (red) are fragmented by Hsp104 into smaller elements called propagons that can be transferred to daughter cells at mitosis. **Middle panel:** mnemons are generated in cells in response to a chemical signal. The only example so far described is the Whi3-based mnemons (Caudron et al 2014), high molecular weight forms of the protein (in dark blue) that are retained by the mother cell and not passed on to daughter cells. These forms are not amyloid but require Hsp70 or Hsp104 for their maintenance. **Lower panel:** the prion-like proteins described by Chakrabortee et al (2016) which are induced *de novo* by overexpression of a typically low abundance protein although the nature of the resulting altered forms of the protein (yellow) remain to be defined but are not amyloid in nature. Depending on the protein, they either require Hsp104, Hsp90 or Hsp70 to maintain the associated phenotype. In all three cases the cells in green show the altered phenotype.