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Yeast prions: paramutation at the protein level?

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Abstract

Prions are proteins that have the potential to refold into a novel conformation that templates the conversion of like molecules to the altered infectious form. In the yeast *Saccharomyces cerevisiae, trans*-generational epigenetic inheritance can be mediated by a number of structurally and functionally diverse prions. Prionogenesis can confer both loss-of-function and gain-of-function properties to the prion protein and this in turn can have a major impact on host phenotype, short-term adaptation and evolution of new traits. Prionogenesis shares a number of properties in common with paramutation and can be considered as a mitotically and meiotically heritable change in protein conformation induced by *trans*-interactions between homologous proteins.

Paramutation is a *trans*-acting genetic mechanism in plants and mammals that transfers inherited information from one allele of a nuclear gene to a second allele of the same gene. The net outcome of this information 'transfer' is that the expression of the receiving 'paramutable' allele is reconfigured, fixed and inherited through subsequent generations (Figure 1A). Because the primary DNA sequence of the paramutable allele is not altered by the paramutagenic event, paramutation can be considered a *trans*-generational epigenetic mechanism. Data are now emerging that suggest that the inherited changes most likely occur via an RNAi-mediated mechanism leading to chromatin modification and/or DNA methylation [1] [2] [3]. Paramutation is therefore an example of a non-Mendelian inheritance mechanism that can lead to phenotypic changes to the host organism without fixing heritable changes in the genome.

Paramutation is not the only means of achieving trans-generational epigenetic inheritance. In fungi, a new form of such non-Mendelian inheritance has emerged based on prions; self-perpetuating altered conformational forms of a protein that are able to impose their new conformation on other molecules of the same protein without the need for underlying changes in the encoded polypeptide sequence [4-6]. Transmission of, or *de novo* appearance of, prions can therefore lead to heritable changes based on templating alternative protein structures rather than introducing changes in DNA sequence. This epigenetic mechanism can be considered a form of paramutation in which the information that is transferred to the 'paramutable allele' (the authentically folded [*prion*$^-$] protein form) is achieved *via* a direct interaction between the protein product of the inducing 'paramutagenic allele' (the alternative [*PRION*$^+$] prion conformation) and that of the 'paramutable allele' via protein:protein interaction (Figure 1B).