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YEAST PRION PROTEIN Ure2p – A USEFUL MODEL FOR HUMAN PRION DISEASES

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SUMMARY

Mammalian transmissible spongiform encephalopathies are uncommon and irreversible diseases caused by prions. Prions lack nucleic acid and can self-propagate by converting normal cell protein to isomeric prion form. In the pathogenesis of these diseases a long variable incubation period occurs, followed by progressive appearance of severe clinical symptoms and death.

A major knowledge in the field of prions comes from studies on a functionally unrelated protein of yeast *Saccharomyces cerevisiae* – [*URE3*], which in normal state (Ure2p) possesses a variety of regulatory and enzymatic functions. Ure2p is a cytoplasmic homodimeric protein with structural homology to glutathione S-transferases and crucial role in nitrogen metabolism, oxidant protection and heavy metal resistance in yeast.

In this work, we discuss the role of Ure2p to provide valuable information about protein infectivity, prion structure and functions.

Key words: Transmissible Spongiform Encephalopathies, Prion-Induced Disorders, Yeast Prions, Ure2p,

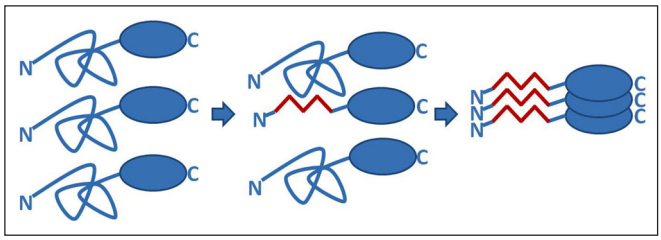
Prion diseases in humans – a brief summary

In humans transmissible spongiform encephalopathies are present as sporadic (Creutzfeldt-Jakob disease), inhered (fatal familial insomnia and Gerstmann-Sträussler-Scheinker syndrome) and transmissible disorders (new variant of Creutzfeldt-Jakob disease and kuru). In contrast to other neurodegenerative disorders they meet (at least the transmissible ones) the microbiological criteria for infectious disease. All forms despite their miscellaneous origin provoke typical spongiform damage of brain due to vacuolization of cells and formation of extracellular amyloid aggregates [1].

For many years, attempts to isolate any nucleic acid-containing agent such as virus or bacterium responsible for brain structural changes were unsuccessful. The putative infectious particle displayed some strange and atypical features - smaller than any known viral size and extreme resistance to UV, ionizing radiation, formalin, heat, nucleases and proteases [1]. To explain this, in the 80^{s} of 20th century, *Prusiner* formulated a controversial and revolutionary idea – proteins could be infective. Thus, the 'protein-only concept' was born and the infectious agent was named 'prion', a term derived from proteinaceous and **in**fectious.

The actual, prevalent concept assumes that a conformational change of normal cell protein generates beta-sheet enriched form, which polimerizes in insoluble amyloid fibrils (Fig. 1). The protein molecule present in healthy individuals converts to prion protein through an unknown post-translational process and misses any nucleotide determinant other than the normal gene. After initial single conformational change, the resulted altered protein serves as a template for fast, irreversible and fatal propagation of amyloid state. Hence, the deleterious phenotype can be a result either from loss of normal protein function or from toxicity gain due to amyloid formation.

Fig. 1. Schematic model for prion amyloid formation of Ure2p. A normal protein molecule (in blue) undergoes conformational change (in red) and promotes same conformational abnormality in neighbor molecules till formation of amyloid fibrils.



Ure2p – a yeast nitrogen repression regulator 'of no importance'

A decade before the appearance of 'anti-dogma' protein-only theory, a totally unrelated event occurred in the yeast microbiology. *Lacroute* had reported the existence of one non-Mendelian genetic element in *Saccharomyces cerevisiae*, associated with nitrogen metabolism regulation [2, 3]. At that time nobody realized that after twenty years this genetic element would become the major milestone of all prion studies and the strongest proof for protein infectivity.

These early works reported the isolation of recessive (*ure2*) and dominant (*URE3*) mutations both determining the ability to overcome the effect of nitrogen catabolite repression (NCR), a regulatory mechanism involved in the cell response to different nitrogen sources. In brief, when *S. cerevisiae* grows on a preferred nitrogen source, the good nitrogen (ammonia) strongly represses the expression of genes required for the utilization of alternative nitrogen sources (proline or glutamate) (for reviews see [4, 5]). Depleting of preferred nitrogen source induces high level expression of required genes to ensure the assimilation of less preferred nitrogen sources available in the medium.

While *ure2* mutation is recessive and shows ordinary Mendelian inheritence, [*URE3*] manifests dominant inherit-

ance and does not have any known genetic distribution in the offspring. In sporulation experiments it displays a 4/0 segregation – all formed spores are [*URE3*]. First, as it can be transmitted via cytoduction, it was thought to be part of the mitochondrial genome [2]. However, its behavior is quite different from the inheritance of a mitochondrial or plasmid gene. In addition, [*URE3*] does not propagate in *ure2*Δ mutant: the corresponding gene was found to be located in the nucleus of yeast cells and to be identical to that of the recessive mutation *ure2* [3]. This strange and very unusual behavior was finally and somewhat surprisingly explained by *Wickner* in 1994 [6] who extended the prion concept to yeast proteins.

Is Ure2p/[*URE3*] a real prion?

Wickner has proposed several genetic criteria to identify a protein as a prion [6, 7]. First, there would be a reversible curability: prions, as well viruses and plasmids can be cured or eliminated from the infected cells after some treatment; while other infectious elements cannot appear *de novo* in the same cell after curing, prions can arise again, as the normal protein is still there. In fact, 5 mM guanidine added to the culture medium could efficiently cure [*URE3*] phenotype and the same cured cells could generate *de novo* [*URE3*] [6]. Second, overexpression of the corresponding protein would increase the frequency of prion appearance, as a result of increased protein content. When, in *ure2*Δ strain, a plasmid overproducing Ure2p was introduced, a frequent "spontaneous generation" of [*URE3*], with properties identical to the original [*URE3*] appeared [8]. The overproduction of Ure2p elevated the frequency of [*URE3*] by 20- to 200-fold. Third, the prion would confer a phenotype identical to that of the deletion mutant. As shown in all classical work based on [*URE3*], it displays a phenotype similar to that of recessive *ure2*Δ mutant strains.

Ure2p/[*URE3*] meets these rigorous criteria and extracts of [*URE3*] cells are protease-resistant [9], which represents the first biochemical evidence for real existence of prions in yeast. In addition, Ure2p/[*URE3*] forms aggregates in [*URE3*] cells [10] and can generate amyloid filaments *in vitro* [11].

Ure2p/[*URE3*] retains real prion features, but an important difference with human prions exists – yeast ones are not lethal. While mammalian prions provoke invariably fatal disease, yeast [*URE3*] simply drives new phenotype (concurrent utilization of good and poor nitrogen source) to cell. Thus, in yeast despite the 'infection', 'prion disease' or death does not occur. The conformational change may represent a mechanism for fast switch between different phenotypic characteristics in response to environmental change [12]. Prion inheritance allows flexible regulation, as it can be very fast transmitted between mating cells and to offspring without nucleic acid mutation – a kind of 'cytoplasmic' or 'protein' mutation, where different prion strains can be considered as mutant alleles of the normal protein. When aggregated in the cytoplasm of infected cell, prion molecule may sequester other cellular factors, causing a multigene-knockdown phenotype [13]. The fact that most of the yeast prions are transcriptional regulators of finely tuned physiological processes supports this theory. But to claim that yeast prions are fully harmless for cell means to underestimate their pathogenicity. If [*URE3*] is an adaptive response to a definite environmental change then such a change could be easily determined in experimental conditions. Until now, an environmental change that triggers prion formation is not found and the nature of initial conformational switch is not elucidated. Moreover, *S. cerevisiae* possesses a significant prion-curing system [14] – at least the cured prions are not beneficial to the cell. Indeed, many [*URE3*] variants decrease growth of infected cells [14].

Is amino acid composition of Ure2p in the origin of its unusual properties?

An one-copy nuclear gene without introns – *URE2* – encodes for Ure2p/[*URE3*]. It lies on chromosome 14 (ORF YNL229C) and occupies location 220201 to 219137 [15]. Prion strains [*URE3*] show same level of transcription rates as the wild type and prion protein misses additional post-translational modifications. Ure2p and its prion state [*URE3*] differ only in their conformation and cell toxicity.

BLAST search in available databases [16] denies a significant sequence similarity between Ure2p (as well as any other yeast prion) and human prion.

Human prion protein is a 253 amino acid protein with glycosylphosphatidyl-inositol (GPI) anchor to translocate into the plasma membrane [17]. The yeast protein Ure2p is cytosolic and consists of 354 amino acids divided in two well-defined regions – unstructured, flexible and protease-sensitive N-terminal domain of around 90 amino acids and globular, functional C-domain [18]. The N-terminal domain contains up to 45% polar uncharged amino acids (asparagine and glutamine) (Fig. 2) and suffices for induction of [*URE3*] phenotype *in vivo* [9] and for amyloid forming *in vitro* [11, 19]. Glutamine repeats excess is associated with a number of neurodegenerative diseases, including Huntington's disease [20], but is not present in human prion protein. Deletion of asparagine/glutamine repeats in the prion domain of Ure2p reduces the prion generation and propagation [21] and inhibits *in vitro* amyloid formation [19].

Fig. 2. Primary sequence of Ure2p. Prion domain is underlined and bold. Glutamine and aspargine residues are in red.

MMNNNGNQVSNLSNALRQVNIGNRNSNTTTDQSNINFEFSTGVNNNNNNNSSS
NNNNVQNNNSGRNGSQNNDNENNIKNTLEQHRQQQQAFSDMSHVEYSRITKFF
QEQPLEGYTLFSHRSAPNGFKVAIVLSELGFHYNTIFLDFNLGEHRAPEFVSVNPNARV
PALIDHGMDNLSIWESGAILLHLVNKYYKETGNPLLWSDDLADQSQINAWLFFQTSG
HAPMIGQALHFRYFHSQKIASAVERYTDEVRRVYGVVEMALAERREALVMELDTENA
AAYSAGTTPMSQSRFFDYPVWLVGDKLTIADLAFVPWNNVVDRIGINIKIEFPEVYKW
TKHMMRRPAVIKALRGE

The amino acid composition of N-terminal prion region itself and not the exact sequence determines the ability of Ure2p to change in a prion state. Different *URE2* variants, each of them with shuffled nucleotides, but unchanged amino acid content and codon use were generated and introduced on the place of normal gene. All of these variants were able to form [*URE3*] amyloids *in vitro* [22].

Tertiary structure of Ure2p – two in one phenomenon

To understand the way prions arise and propagate, we need to know the structure of normal and prion states of the protein. Unfortunately, all traditional approaches (X-ray crystallography and solution NMR) are not applicable in the case of prions, as they could not crystallized because of their filamentous nature. Ure2p was the first prion protein to enlighten the structural issue, because of its combined structure. While N-terminal part of Ure2p molecule is necessary and sufficient for prion properties of Ure2p [9], the C-terminal part represents the functional part of the molecule and displays a structural similarity to a class of detoxifying enzymes – glutathione S-transferases (GST) [23]. The two regions are not overlapping and have negligible effects each other. This gives an easier approach to understand prion structure – by dividing the molecule to its functionally separated parts and studying each part independently. Thus, the first prion structure (in fact the non-prion region of a prion protein) appeared in 2001 [24, 25]. Recently, solid-state NMR has addressed the atomic-resolution structure of full-length Ure2p to confirm a very well ordered globular domain with a conserved GST fold, and a partially ordered prion domain [26].

Purification experiments (after overexpression in *Escherichia coli* cells) demonstrate that recombinant Ure2p is a soluble monomeric protein which can form dimers, tetramers, as well as insoluble high molecular weight fibrillar oligomers able to bind Congo Red as do amyloid fibers [18].

The finding that shuffling the amino acid sequence of Ure2p prion domain does not destroy its prion capacity [22] let to the proposition that the prion structures are parallel in-register beta-sheets. According to this model, the beta-sheets in the N-terminal end of each molecule aligne with identical residues stacked on top of each other. This forms an amyloid core with globular non-prion domains hanging off the core [reviewed in 27].

The functional diversity of Ure2p – a unique feature

Ure2p (in its normal state) retains a broad spectrum of physiological roles in yeast cell – regulates nitrogen catabolite repression (NCR), salt stress and glutathione (GSH) degradation, and participates in various oxidant and heavy metal detoxifications (Fig. 3).

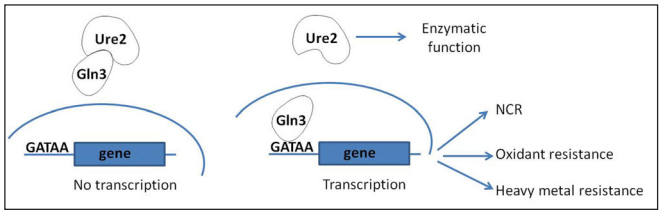


Fig. 3. Functions of Ure2p in *Saccharomyces cerevisiae*. Left panel – Ure2p inhibits GATA regulation factor (Gln3) when no external stimuli are present; no transcription of regulated genes occurs. Right panel – Ure2p liberates Gln3 to enter the nucleus and to enhance the expression of required genes when appropriated external stimuli are present. In both conditions Ure2p may display its enzymatic function.

Ure2p is a regulator in NCR, a mechanism which prevents unnecessary production of permeases and other proteins for the utilisation of non-preferred compounds, when a preferred nitrogen source is available. It is the major negative regulator of GATA family of transcription factors in *S. cerevisiae* cell [4]. Ure2p binds to two of GATA factors Gln3p and Gat1p preventing their nucleus localization and therefore inhibiting the transcription of GATA regulated genes. In response to external stimuli (for example, nitrogen limitation), Gln3p and Gat1p discharge from Ure2p and enter the nucleus to activate transcription of needed genes (Fig. 3). Beyond the nitrogen regulation, *ure2*Δ mutant exhibits a pleiotropic phenotype determined by transcriptional GATA repression of other genes involved in cell response to salt stress [28] and in the degradation of glutathione [29].

Ure2p completely loses its NCR regulatory function during conformational change in [*URE3*] prion state [3] and this is likely to be a steric effect rather than loss of native structure.

When the sequence similarity of Ure2p to GSTs [23] was found [24, 25] an intriguing question arose "Whether or not Ure2p is a glutathione *S*-transferase?" This family of enzymes catalyzes a wide variety of reactions [30], mainly in the detoxification of electrophilic chemicals and lipid peroxidation products, but also includes isomerisation reactions and glutathione peroxidase activities by conjugation to the tripeptide GSH. Thus, GSTs show overlapping functions with other glutathione binding enzymes in yeast, such as glutathione peroxidases (GPxs) and glutaredoxins.

Although Ure2p has GPx activity *in vitro* with inorganic and organic peroxides in both native and prion-aggregated form [31], as well as glutaredoxin activity [32], attempts to demonstrate activity of Ure2p with canonical GST model substrates such as 1-chloro-2,4-dinitrobenzene, have been unsuccessful [33]. However, disruption of the *URE2* gene renders *S. cerevisiae* sensitive to possible alternative GST substrates such as Al, Ag, As, Cd, Co, Cr, Cu, Fe, Hg, Ni, Se, diamide, hydrogen peroxide, cumene and *t*-butyl hydroperoxides [34, 35, 36, 37, 38]. The identification of these new *ure2*Δ phenotypes prompts the question whether the detoxication of heavy metals and peroxides derives from an enzymatic activity as a GST enzyme, or is a result of direct/indirect GATA regulation of one or more genes whose products are involved in cellular defense against oxidative stress. To solve this question is important as the Ure2p regulatory activity associates with a stoichiometric reaction between a GATA factor and itself. Since Ure2p in its prion form is a fibrillar polymer, it is evident that it cannot keep this interaction. In contrast a GST activity may not be adversely affected by prion formation because this is catalytic rather than stoichiometric reaction.

In fact both possibilities may happen *in vivo*. Despite

the GPx activity *in vitro* [31], the disruption *ure2*Δ mutant displays unchanged GPx activity *in vivo*. Its inability to grow in presence of hydrogen peroxide is related to diminishing levels of GSH as a result from increased GSH degradation due to deregulated localization of the gamma-glutamyl transpeptidase activating GATA factors [37].

Experimental data rejects a direct enzymatic role of Ure2p in arsenic detoxication [38]. As for peroxides sensitivity, Ure2p is likely to control arsenic transport via GATA regulatory function rather than to conjugate arsenic ions. In contrast, Ure2p seems to participate directly in nickel and cadmium detoxification and [*URE3*] prion formation does not affect this function [35].

The well-characterized functional diversity of Ure2p is a unique feature while more of the known mammalian prions are of yet unspecified functions. However, many reports show similar protective role of mammalian prions against oxidative damage and participation in metal metabolism [39]. Prion neurotoxicity in mammals may derive from imbalance of metal homeostasis and oxidative redox state in brain tissues (reviewed in [40]). Two ways of actions are considered: (1) a functional role in metal metabolism (Cu, Fe, Zn, Mg and Ni) and loss of this function when protein molecules aggregate; and (2) gain of toxic function when metals are included in redox-active aggregates, able to generate oxidative stress. Studies on cell and animal model support in same degree both hypotheses but neither the physiological role of metal binding nor the pathogenicity of metal-prion complexes is elucidated.

The coincidence in anti-oxidative functions of lower and higher eukaryotic prions is a pertinent question deserving more experiments, as it can be in the basis of profound understanding of the role of human prion proteins.

CONCLUSION

Yeast prions including Ure2p provide an excellent model for studying mechanisms of prion formation and propagation. An essential issue is the biological role of prions, which in human yet has to be discovered. Understanding in more details how Ure2p functions and in what conditions it loses the variety of its functions (or only some of them) and becomes infectious will help our understanding of a range of severe neurodegenerative diseases in human.

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