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Prion-like proteins as epigenetic devices of stress adaptation

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Abstract

Epigenetic modifications allow cells to quickly alter their gene expression and adapt to different stresses. In addition to chromatin direct modifications, prion-like proteins have recently emerged as a system that can sense and adapt the cellular response to stressful conditions. Interestingly, such responses are maintained through prions' self-templating conformations and transmitted to the progeny of the cell that established a prion trait. Alternatively, mnemons are prion-like proteins which conformational switch encodes memories of past events and yet does not propagate to daughter cells. In this review, we explore the biology of the recently described prions found in *Saccharomyces cerevisiae* including [*ESI+*], [*SMAUG+*], [*GAR+*], [*MOT3+*], [*MOD+*], [*LSB+*] as well as the Whi3 mnemon. The reversibility of the phenotypes they encode allows cells to remove traits which are no longer adaptive under stress relief and chaperones play a fundamental role in all steps of prion-like proteins functions. Thus, the interplay between chaperones and prion-like proteins provides a framework to establish responses to challenging environments.

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1. Introduction

Cells, whether as single cells or colonies, exist in complex and stressful environments [1]. To alleviate the detrimental consequences of stress, cells have established response mechanisms to modulate their gene expression profiles [2]. Remarkably, single cells have the ability to transcriptionally respond quicker and stronger to a previously experienced stress. Such phenomenon often results from epigenetic modifications to periodically transcribed genes. This type of epigenetic transcriptional memory is a conserved mechanism reported in a range of organisms including *Arabidopsis*, Henrietta Lacks (HeLa) cells as well as *Saccharomyces cerevisiae* [3]. For example, budding yeast cells establish epigenetic transcriptional memories during alternative carbon source utilisation and inositol starvation. The *GAL1* and *INO1* genes involved in these processes are induced faster and more robustly if they have been previously activated [4,5], providing a fitness advantage to these cells.

An additional form of epigenetic memory involves prions and prion-like proteins. Prions are protein which are capable of adopting several conformations with at least one of them that is self-templating and is accompanied by a functional switch [6]. Known yeast prions include [*PSI+*] (prion form of the translation terminator Sup35), [*URE3*] (prion form of the nitrogen catabolite repression transcriptional regulator Ure2) and [*RNQ+*] (prion form of Rnq1) [7]. Even if these prion forms are associated with a loss of function [8], prions provide adaptational advantages in budding yeast [9,10]. Some proteins share sequence biases similarities to classical prions in their core prion-domain and are referred to as prion-like proteins [11]. The mRNA binding protein Whi3 is a prion-like protein that can switch conformation to a mnemon form in order to encode the memory of a mating pheromone refractory state [12,13]. The main difference to prions is that mnemons are not inherited by daughter cells during cell division while prions are, which lends the two mechanisms different properties in the consequences for the cell and the colony emanating from this cell. The presence of prions seems to be particularly prevalent in single-cell organisms including several species of fungi, which is likely due to the utilisation of low-probability and stochastic transitions on an individual cell basis in unpredictable ecological circumstances [14]. The stability and structural reversibility of many of these prions in wild strains is selected depending on the stability of their surroundings, where some strains may favour more reversible prions in more capricious living conditions [15]. This spatiotemporal regulation of prion formation and elimination therefore offers a selective advantage to cells by instilling a memory of their stress experiences across a number of generations. In this review, we explore how protein-based phenotypic switches are used to respond to stresses focusing on budding yeast and how they are regulated.

2. Prions in epigenetics, cell development and bet-hedging phenotypes

Epigenetic modifications entail gene expression changes without changes in the DNA sequence itself [16,17]. This is achieved through post-translational modifications of histones and DNA (e.g. methylation, acetylation, phosphorylation and ubiquitylation) [18,19]. Consequently, in lieu of chemically modifying phenotypes on a gene-by-gene basis, an entire gene expression landscape can be fashioned through more reversible and dynamic actions such as nucleosome positioning and

histone variation [20]. How can prions act as epigenetic switches and allow cells to select the phenotype they need?

Prions acting on various epigenetic levels include [*ESI+*], [*LSB+*], [*SMAUG+*] and [*MOT3+*] which remodel gene expression either directly or indirectly [16, 25, 30-34, 36-37]. Some of their properties are summarised in Figure 1. Although the activity of these prions gives cells heritable phenotypes, they are implicated in different mechanisms. The [*ESI+*] prion is one example of a direct epigenetic modification, where chromosomal sub-telomeric domains are activated. Snt1 is the Set3C histone deacetylase scaffold in yeast and its conversion to the [*ESI+*] prion is induced by G2/M arrest-dependent phosphorylation [21]. Sub-telomeric domain activation is achieved by simultaneously recruiting RNA polymerase II and excluding Rap1, a functionally versatile repressor and activator [22]. Consequently, activation by [*ESI+*] mediates an upregulation of genes encoding for factors involved in meiosis, such as *IME1* and *SPO11*, as well as stress-responsive genes [22]. This emphasises the role of [*ESI+*] in aiding cells to adapt to stress, as [*ESI+*] cells grow more robustly in the presence of antifungal drugs than isogenic naïve cells [22]. Thus, [*ESI+*] provides a prion-based epigenetic mechanism by which active chromatin states can be inherited [22].

[*LSB+*], the prion form of the cytoskeletal protein Lsb2 which is induced by heat shock, diversifies phenotypes by promoting the formation of other prions [23–25]. While it is not a direct epigenetic modifier, [*LSB+*] itself is a heritable conformer of Lsb2 which mediates the maintenance of [*PSI+*] and, to a lesser extent, [*RNQ+*] (the prion form of Rnq1) [23–25]. Like [*ESI+*], this maintenance concomitantly alters downstream gene expression programs through [*PSI+*] and [*RNQ+*]. [*LSB+*] seem to be dynamically switching back to its non-prion form, displaying a metastable behaviour, which results in only a fraction of the daughters born from a mother cell that experienced a heat stress to be heat resistant [23,24]. This dichotomy in heat resistant phenotypes within the population could thus be explained by the disproportionate acquisition and maintenance of the [*PSI+*]/[*psi-*] in certain colonies by [*LSB+*], which is influenced by the duration of heat shock [30]. For both [*ESI+*] and [*LSB+*], cells are endowed with more robust phenotypes which are favoured in the majority of offspring, allowing them to survive in specific adversities such as heat stress and the presence of drugs or inhibitors.

[*SMAUG+*] is implicated in providing a mechanism by which cells can prepare themselves for starvation periods with similar durations as those previously experienced [15]. Vts1, the [*SMAUG+*]-forming protein, targets and represses the mRNA encoding Mum2 which is a positive determinant in meiotic progression [15,26,27]. Conversion to the [*SMAUG+*] prion is predominantly triggered in response to short starvation periods, while cells benefit from the [*smaug-*] trait during longer periods of nutrient limitation [26]. Changes in Mum2 expression account for varied sporulation efficiencies of yeast. By having these two forms of Vts1 at their disposal, cells can subsequently choose to either wait and improve proliferation stamina through suppression of Mum2 with [*SMAUG+*] or enter meiosis quickly with the [*smaug-*] conformation [15,26]. The former route is advantageous for shorter periods of nutrient deficiency, because cells can survive this without exit from mitosis and meiotic commitment, which halts growth and division. On the other hand, the latter route benefits cells during indefinite periods of starvation by swiftly introducing them into a protective sporulation mode and minimizing

energy expenditure used for growth and mitotic events. This selective advantage is propagated as an epigenetic memory of the history of starvation through [*SMAUG+*], as prion formation of Vts1 downregulates a Mum2-associated regulon involved in proliferation [27].

Yeast cells overcome nutrient deficiency through the remodelling of homeostatic signalling pathways such as the TORC1 or Gpa2 pathways to mediate growth or arrest [28]. However, the list of prions which have been implicated in growth-associated stress responses is expanding. In addition to [*SMAUG+*], a number of other prions act as functional regulators of growth and development when changes in growth conditions occur (Fig. 1). A mechanism by which cells overcome a shift in metabolic settings is the development of multicellular phenotypes through the [*MOT3+*] prion [29]. Multicellularity profits organisms by providing protection against the environment, starvation and allows cells to differentiate and metabolically coordinate [29–31]. The [*MOT3+*] prion is induced by ethanol, a common metabolic stress, which is ultimately associated with biofilm formation under depletion of fermentable carbon sources [29]. [*MOT3+*] acts by upregulating *FLO11*, which encodes for GPI-anchored cell surface glycoproteins [32] and is implicated in differentiation of cells into diverse architectures such as chains and biofilms [29,30]. The interchange between [*MOT3+*] and [*mot3-*], which is dependent on a simple environmental stress, provides heritable changes in metabolic activity by way of a *FLO11*-dependent adhesion developmental program [29]. This prion-dependent activation of a downstream development regulon is similar to that of [*GAR+*], another prion that mediates yeast cells to switch from a metabolic “specialist” to a “generalist” fermentative lifestyle [33]. For yeast, glucose is the primary and favoured fermentable carbon source [34]. However, upon exposure to a chemical cue from bacteria, lactic acid [35], yeast cells select other carbon sources for fermentation, a phenotype that diverts them from glucose-repression given by the induction of [*GAR+*] [33]. Given the divergence of nutrient range and the increased metabolic availability of yeast induced by a bacterial signal, [*GAR+*] formation can be considered an adaptational mechanism; likewise, bacteria can also benefit from this switch due to a decrease in ethanol production from glucose metabolism [33]. A number of proteins such as Pma1 (Plasma membrane ATPase), Std1 (Suppressor of Tbp Deletion), Rgt2 (Restores Glucose Transport) and Hxt3 (Hexose Transporter) were identified to govern this phenotype which were shown to have different degrees of sequence conservation in other yeast species such as *Saccharomyces bayanus*, *Candida glabrata, Naumovozyma castellii* and *Dekkera bruxellensis* [33]. Thus, prion-based strategies as responses to starvation and metabolic stresses stretch across various yeast species [33].

Both [*GAR+*] and [*MOT3+*], as well as the other prions previously mentioned, provide a way for cells to diversify their phenotypes, some of which are exhibited in the majority of the population (Fig.1)[33]. While these phenotypes can be maintained over generations due to the self-templating properties and inheritance pattern of prions, they can also be reversible [29,33]. [*MOT3+*] can convert back to [*mot3-*] in hypoxic conditions [29]. A similar case is observed in [*MOD+*], the prion formed under selective pressures by the t-RNA isopentyl transferase Mod5 which confers resistance against ergosterol synthesis inhibitors, in which the [*mod-*] phenotype is gradually restored upon removal of antifungal agents [33,36]. Phenotypic diversification in unicellular organisms is often beneficial for survival as

this allows cells to sample their behaviour according to past environments [15]. This can be seen in the case of [*GAR*+], [*MOT3*+], [*PSI*+] and many other prions, where complex traits in cells are developed and bet hedge their available phenotypes in stressful environments [26,33]. Because prions such as [*PSI*+] often randomly appear in very few cells in a population (10^{-5} - 10^{-7}), different flavours (strains) of a prion may actually form as a way to select phenotypic traits that suit the current environment [10]. This bet hedging mechanism, based on conformational flexibility, could ensure that deleterious or toxic characteristics are eradicated while beneficial phenotypes are sustained and passed along to daughter cells ensuring survival under a constantly changing wild environmental condition [37–39]. Bet hedging could potentially save a population from extinction [37]. This idea is supported by the observation that switches to prion form increases when yeast cells undergo stress conditions [37,40–42]. Screening over 690 wild *Saccharomyces cerevisiae* strains obtained from different ecological environments revealed that a range of adaptive phenotypes were observed for [*PSI*+] and [*MOT3*+] prions [43]. However, these beneficial phenotypes also come at a cost since some strains harbouring prions grow poorly under standard conditions [37]. For example, the presence of [*MOD*+] causes poor growth in rich media [36,37]. Therefore, prions allow a fast and dynamic response to fluctuating growth conditions and they need to be reversible in order for cells to fit their expression programme with the environment they are experiencing [9,44].

[*PSI*+] is one of the most well-studied prions in biology. Sup35 acts as a translation termination factor which can sporadically switch between its [*PSI*+] and [*psi*-] states [45]. In its non-prion form, Sup35 targets the stop codon to trigger translation termination and upon conformational switch, the [*PSI*+] prion form is sequestered into amyloid fibers which results in stop codon read-through [10,46]. Interestingly, although [*PSI*+] infers a loss of function, deletion of *SUP35* is inviable; this suggests that not all of the Sup35 protein pool is sequestered to [*PSI*+] and it is likely that Sup35 prion acquisition has been selected to be incomplete. Given that regions downstream of stop codons are often associated with complex traits and functional protein domains such as nuclear localisation signals [9,10], by tailoring the extent of translation termination, a variety of genetic traits can be readily accessible for cells to adapt to different adversities. A canonical feature of stop codon read-through is used to prime cells for fixation of a temporary [*PSI*+]-dependent phenotype into a stable genetic change [9]. This phenomenon occurs through re-assortment during meiosis, generating heterogeneity in phenotypes in haploid progeny such that some cells exhibit the [*PSI*+] trait even after curing [9,43]. Therefore, in addition to short-lived phenotypic changes, [*PSI*+] also allows cells to acquire new complex traits that future generations can benefit from. In many cases, such prion-based strategies for cells to acquire different phenotypes present advantages over classical mutations, as genetic and phenotypic diversity generated by the latter often requires a large enough population [37]. Moreover, while phenotypes arising from prion acquisition are often comparable to loss-of-function mutations, reversal back to the functional phenotype rarely occurs in DNA mutations [33,37].

Therefore, prions are very common functional devices in budding yeast that cells can use to adapt to the many stresses they face. An advantage is that prions are inherited by the entire progeny of a single cell and this behaviour has facilitated their identification. However, this could be a disadvantage

if the adaptation is not beneficial for the progeny, thus a discrete inheritance pattern such as seen in mnemons or the use of very unstable prions are alternative patterns of protein-based phenotypes.

3. Mnemons

Although the list of prions is extending, only few have been identified in the pool of ±200 yeast proteins possessing prion-like domains. Many of these prion-like proteins do not characteristically fulfil all the conditions of classical prions including the formation of detergent resistant assemblies detected by semi-denaturating agarose gel electrophoresis and foci observed by fluorescence microscopy of the prion-like protein fused to a fluorophore, all generally done under over-expression conditions. This suggests that prion-like domains may help encoding more diverse functional switches than classical prions [11] such as the memory of deceptive mating attempts encoded by the Whi3 mnemon [12].

Haploid yeast cells communicate with a nearby mating partner by producing pheromones that bind to plasma membrane receptors (Ste2 and Ste3) setting up a cascade of events which results in cell cycle arrest in G1, formation of a mating projection (called a 'shmoo') and which culminates in the fusion of the mating partners to form a diploid cell [51–53]. However, in the presence of pheromone only, cells first shmoo and then exit this prospect of mating to resume their cell cycle through the establishment of a pheromone refractory state [54]. The cell that experienced this failed mating encounter remembers it, and does not shmoo again, whereas its daughter cells continue on this prospect of mating, shmooing immediately after birth. The Whi3 protein is a mnemon assuming a conformation which drives its super-assembly and thereby the development of the pheromone refractory state by releasing the inhibition Whi3 normally exert on translation of the G1 cyclin *CLN3* mRNA [12,13]. The striking difference of the Whi3 mnemon over prions is its mode of inheritance. Once super-assembled, Whi3 does not propagate to the daughter cells. This raises the question of how exactly the Whi3 mnemon form is established and maintained, yet this mode of inheritance has profound consequences for the population. Since only the cell in which Whi3 converted to its mnemon form contains the super-assemblies, the phenotype it encodes is lost very quickly in the population. Therefore, there is probably no need to evolve a mechanism to revert this conversion. If this was the case, one could imagine that either mnemons have co-evolved with asymmetric cell division and lost their reversibility or that the mechanisms confining the mnemon form to the mother cell have been selected to work as an eraser in the progeny. This type of behaviour works well in dividing cells, in which only one of the two daughter cells can inherit the phenotype, however, there are potential similarities within non-dividing cells. Indeed, the cytoplasmic polyadenylation element binding proteins (CPEBs) switch their conformation to a prion-like conformation to encode long-term potentiation in *Aplysia*, *Drosophila* and mice [55–59]. In this case, what would make these proteins behave as mnemon is their confinement, not in one of the two daughter cells, but in one cellular appendage. CPEBs work at the dendritic spine such that their prion or mnemon form could well be confined to this region. We suspect that many other prion-like proteins could work through a confined self-templating conformation to encode cellular memories of past adaptation.

4. Role of chaperones in epigenetic memory inheritance and maintenance

Environmental stress can cause protein unfolding and accumulation of a diverse range of misfolded proteins which rely on chaperones for restoration to a functional state. Heat shock in particular, results in a plethora of protein structures, some of which condensate together into disordered masses while others, like prions form ordered protein conformations [60,61].

Chaperones of the heat shock protein (Hsp) family are proteins which assist in maintaining proteostasis by remodelling altered protein conformations. One of the most important chaperones required for the formation and maintenance of many prions is Hsp104, an AAA+ ATPase protein that forms a ring-shaped hexameric structure [62]. Hsp104 fragments large prion aggregates into seeds or propagons which can diffuse to daughter cells during cell division [11,60,62]. For prions to be maintained, newly made and already existing soluble non-prion proteins have to undergo conformational change by conversion to the prion form [44]. This process is aided by propagons which provide fibril ends for the incorporation of new monomers; the fibrils which are constantly fragmented by chaperones and transmitted to daughter cells in order to maintain the prion state [44,63]. Do all prions require the same chaperones and are there prions which do not require chaperones? While Hsp104 forms the core chaperone involved in prion regulation and propagation, it does this in association with other chaperones such as Hsp70 and Hsp40, which act upstream to deliver substrates to Hsp104 [64]. The Hsp70 family contains four members (Ssa1-Ssa4) which work with cochaperones of the J-protein family and guanine exchange factors [65]. Hsp70 relies on Hsp40 for substrates transfer as well as its activation [66]. Chaperones are regulated at transcriptional, translational and post-translational level (by phosphorylation and acetylation) [67,68].

Changes in the level of chaperones, by inhibition or overexpression, can remove prion traits; a process which is termed curing [22,69]. How do chaperones work together in prion curing or propagation? The relationship between chaperones regarding prion regulation appears to be quite complicated. For example, low levels of Hsp104 promote [*PSI+*] prion formation *in vitro* while high amounts of Hsp104 cures only [*PSI+*] prions by converting the prion protein to monomeric Sup35 and this effect can be counteracted by excess Hsp70 [69–71]. On the other hand, elevated amounts of Hsp70 cure some [*PSI+*] variants formed from excess Hsp104, while co-chaperones Stl1 and Cpr7 which modulate Hsp90 ATPase activity increase the efficiency of [*PSI+*] curing by overexpression of Hsp104 [72,73]. Similarly, Hsp70 prevents formation of Whi3 super-assemblies while Hsp104 slightly promotes their formation [12]. Therefore, a complex choreography of Hsp104 with Hsp70 and Hsp40 seems to propagate most yeast prions [8] and the Whi3 mnemon. There are yet exceptions to this and many recently identified prions are able to transmit their epigenetic state without Hsp104 (Table 1). For example, the [*ESI+*] prion relies on Hsp90, [*GAR+*] and [*SMAUG+*] prions both rely on Hsp70 and the chaperone governing the [*ISP+*] prion is yet to be identified [22,27,47]. If most prion formation and propagation is controlled by chaperones, a question is how do chaperones enable variability of prion phenotypes?

Amyloid formed from the same prion protein can be structurally polymorphic. Plasticity of the same prion protein results in distinct conformers with varying degrees of phenotypic characteristics which are called variants or strains [39]. Prion variants have been identified in the most extensively investigated prions, [*PSI+*], [*PIN+*] and [*URE3*]. Chaperones are also responsible for formation of

prion variants. For example variation in the extent at which prion polymers are fragmented by Hsp104 is responsible for the differences in phenotype between weak and strong [*PSI+*] variants [66]. The amyloid core length generated from the prion forming region of Sup35 determines to a great extent the effectiveness of [*PSI+*] prion propagation; strong [*PSI+*] variants have shorter core length and are more effectively fragmented by Hsp104 compared to weak [*PSI+*] [74]. In contrast to [*PSI+*] variants, the formation of [*PIN+*] variants was shown to depend on non-prion forming regions of Rnq1 and that differential interaction with Sis1 was responsible for phenotypic variability observed in the [*PIN+*] variants [66,75].

Hsp90 is a central chaperone because most of its client proteins are specifically involved in key signalling and cell cycle regulatory pathways necessary for cell survival under stress conditions [76]. Hsp90 possesses an N terminal ATPase domain necessary for client folding, a middle region which is also necessary for client interaction and a C terminal domain required for dimerization [77]. Unlike Hsp90, other chaperones such as Hsp70 are generalists with regards to the client they bind [77]. In bacteria Hsp90 is non-essential whereas it is essential for cell viability in all eukaryotes that have been investigated [77,78]. The involvement in major cellular processes has made Hsp90 a key target in anticancer drug development [76]. Interestingly, Hsp90 connects both phenotypic and genetic interaction networks and therefore plays a key evolutionary role in adaptation [79]. Most of its client proteins tend to remain in an unfolded or aggregated state until the proper environmental cue is available for them to become activated [80]. Remarkably, Hsp90 is expressed at a higher rate than other chaperones even under non-stress conditions suggesting that it is well capable of buffering both genetic variation and epigenetic variation under moderate stress conditions. Because, its client proteins unfold easily when affected by environmental challenges, there is an opportunity for a wider phenotypic variation [81]. Although Hsp90 is abundant, its function may become compromised when stress elevates the levels of client proteins, causing destabilisation and binding of some proteins more effectively by Hsp90 therefore reducing availability of the chaperone for other clients. Also because Hsp90 client proteins in their metastable state are hypersensitive, the ability of Hsp90 to retain such proteins in a state poised for activation could be overwhelmed resulting in aggregation or conformations with rare phenotypes [81]. Novel phenotypes arise when the buffering capacity of Hsp90 is compromised by different factors in *Drosophila*, *Arabidopsis* and fungi [79–82]. Therefore, chaperones represent both a system to manage the accumulation of unfolded proteins that accumulate during a stress and a system that is permissive enough to allow the emergence of many prion-like behaviour for cells to explore the best conformational landscape fitting a specific stress. Because prion-like proteins can adopt self-templating conformations that may be perpetuated by the chaperone system, these combinations allow for the emergence of powerful mechanisms to establish not only adaptations to stress but the maintenance of these adaptations as cellular memories.

5. Conclusion

In metazoans such as in humans, the pathogenic role of prions has been the discovery driver of our understanding of prion-based biology. However, as many functional prions continue to be identified in

yeast, we begin to understand the ability of organisms to recruit non-genetic mechanisms in coping with immediate environmental stress. After many generations, these traits may become canalised, in which case the traits are expressed without the original inducing factor. Reversibility of these prion states allow for removal of traits thus avoiding a situation of 'lock-in' of traits should the trait become no more adaptive under the prevailing conditions [77]. We suspect that many more prions will be discovered. But more than that, the case of the non-amyloid prion [*SMAUG+*] and of the Whi3 mnemon should push us to consider prion like elements as they are and that they may not necessarily fulfil all the classical properties of canonical prions.

Figure Legends

Figure 1: Schematic of epigenetic mechanism of prion and mnemon adaptation to environmental stress.

Table 1: A summary of the properties of some prions and mnemon.

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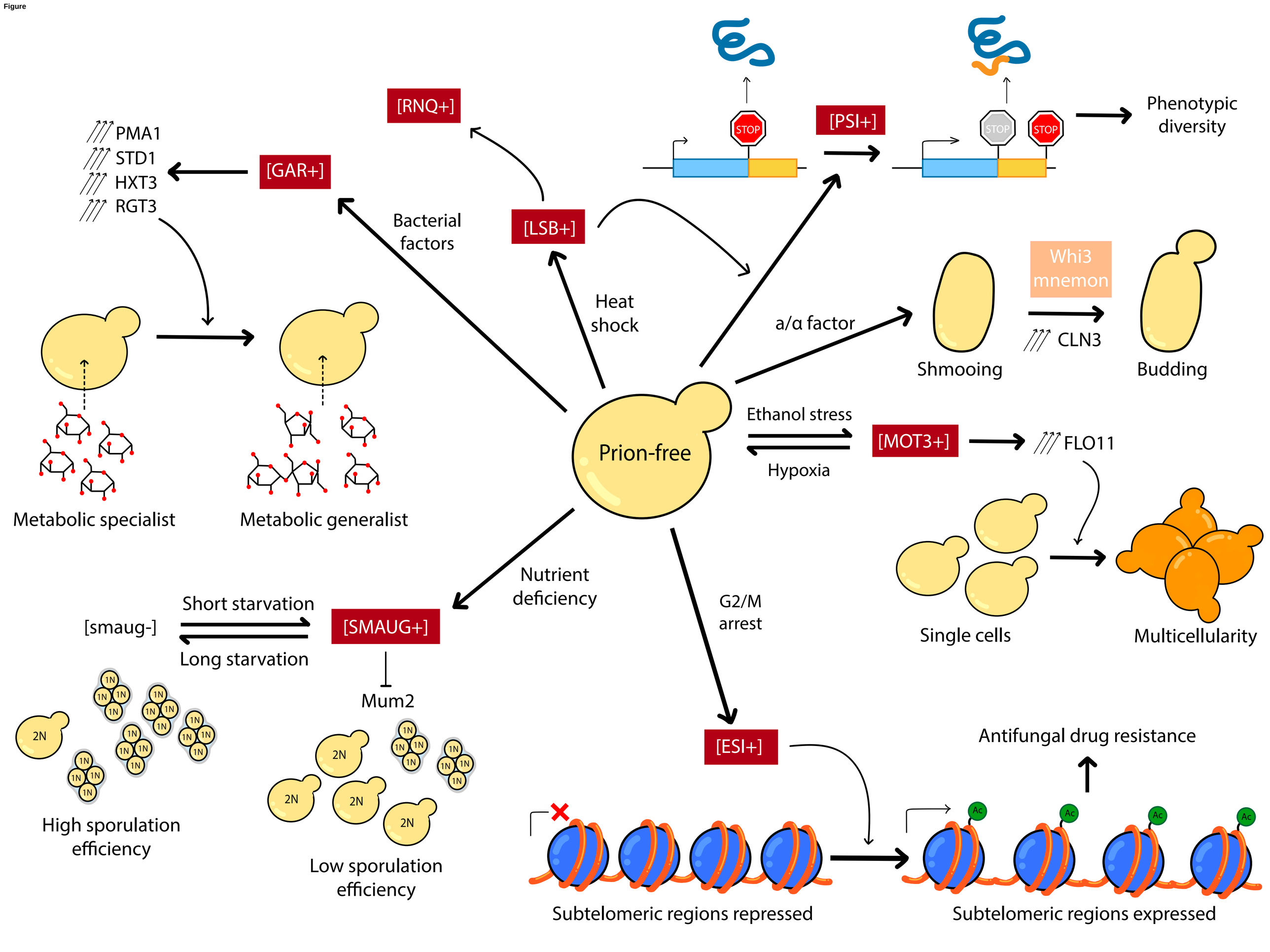
Figure


PMA1
STD1
HXT3
RGT3
[GAR+]
[RNQ+]
[LSB+]
[PSI+]
STOP
STOP
STOP
Phenotypic diversity
Bacterial factors
Heat shock
a/α factor
Whi3 mnemon
CLN3
Shmooing
Budding
Prion-free
Ethanol stress
Hypoxia
[MOT3+]
FLO11
Single cells
Multicellularity
Metabolic specialist
Metabolic generalist
Nutrient deficiency
G2/M arrest
[smaug-]
Short starvation
Long starvation
[SMAUG+]
Mum2
2N
1N
High sporulation efficiency
Low sporulation efficiency
[ESI+]
Antifungal drug resistance
Ac
Subtelomeric regions repressed
Subtelomeric regions expressed

Table

Prion	Protein	Cell growth & development	Structural reversibility	Epigenetic memory	Stress resistance	Chaperone	References
[*PSI+*]	Sup35				Some variants show advantages under various stress conditions	Hsp104	[41]
[*SMAUG+*]	Vts1	Regulation of sporulation efficiency	Transition between [*SMAUG+*] and [smaug-] based on starvation mode; stability based on environment predictability	Heritable starvation adaptation gene expression program		Hsp70	[27,47]
[*ESI+*]	Snt1	Upregulates genes involved in meiosis (e.g. IME1, SPO11)		Directly acts on histone modifications (H4), mediates active chromatin inheritance	[*ESI+*] confers zinc and antifungal drug resistance	Hsp90	[22]
[*MOT3+*]	Mot3	Upregulates *FLO11* promoting biofilm formation	[*MOT3+*] cured to [*mot3-*] in fermentable carbon source media	Multicellularity inherited over a few generations	[*MOT3+*] confers ethanol resistance	Hsp104	[11,29]
[*MOD+*]	Mod5		[*MOD+*] cured to [*mod-*] upon removal of ergosterol inhibitors		[*MOD+*] confers ergosterol inhibitor resistance	Hsp104	[48]
[*LSB+*]	Lsb2			Retained prions in a fraction of daughter generations	Fraction of future generations retain heat resistance	Hsp104	[23,24]
[*GAR+*]	Std1/Pma1		Cured by desiccation	Enables alternative carbon utilisation		Hsp70	[49,50]
Whi3 (prion-like protein)	Whi3			Non-heritable Memory of mating pheromone refractory state		Ssa1	[12,13]

***Credit Author Statement**

HPO: Writing- Original draft preparation. YL: Writing - Original draft preparation. FC: Writing - Reviewing and Editing.