

Review

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Review

How to Survive without Water? A Short Lesson from Desiccation Tolerance of the Budding Yeast

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Abstract: Water is essential for all life on earth. It is a major component that makes up living organisms and plays a vital role in multiple biological processes. It provides a medium for chemical and enzymatic reactions in the cell and is a major player for osmoregulation and maintenance of cell turgidity. Despite this, many organisms, called anhydrobiotes, are capable of surviving under extremely dehydrated conditions. Less is known about how anhydrobiotes adapt and survive under the desiccation stress. Studies have shown that morphological and physiological changes occur in anhydrobiotes in response to desiccation stress. Certain disaccharides and proteins, including heat shock proteins, intrinsically disordered proteins, and hydrophilins, play important roles in the desiccation tolerance of the anhydrobiotes. In this review, we summarize the recent findings of the desiccation tolerance in the budding yeasts *Saccharomyces cerevisiae*. We also propose that the yeast under desiccation could be used as a model to study neurodegenerative disorders.

Keywords: anhydrobiotes; desiccation stress; desiccation tolerance; *saccharomyces cerevisiae*; survival

1. Introduction

Water is the most abundant, yet essential molecule in all living organisms on earth, making up about 60-90% of the total mass in living organisms [1]. It is essential not only for life on earth but even in the search for life on other planets; it serves as an important biotic indicator [2]. Water functions as a solvent and is required for many biological processes. When organisms do not have water, the consequences are detrimental. Certain organisms, however, can survive with minimal water for long periods of time. These organisms are commonly called anhydrobiotes, which are a group of unique organisms that can survive anhydrobiosis, or, life without water [3]. Understanding how anhydrobiotes respond and mitigate the stress caused by desiccation could help us better understand stress biology. It is particularly important as today's climate change occurs more dramatically, and water resources become scarcer.

The capacity of resistance to desiccation is not limited to one species. Anhydrobiotes have been identified in bacteria, yeast, plants, and small animals, such as tardigrades, which can survive for years without water [3,4]. Plant seeds, for example, lose up to 95% of water during maturation and maintain their viability under harsh environmental conditions [5]. Tardigrades can not only survive near complete desiccation, but also other environmental extremes, such as high vacuum, high/low temperature and UV radiation [6]. The budding yeast *Saccharomyces cerevisiae* can also survive desiccation and has been widely used in the industry of bakery and brewing and other biotech fields [7].

Desiccation imposes a variety of stresses to the organism, such as osmotic stress, oxidative stress, and DNA damage stress. These stresses are likely interconnected and provide cross-protections between different stresses. Transient heat shock, for example, significantly increases desiccation tolerance of the desiccation-sensitive yeast cells [8]. Other stresses, such as osmotic or oxidative stress have less of an impact on desiccation tolerance, suggesting the cross-protection is not equal among different stresses. A similar gene expression profile is observed when budding yeast is imposed with different environmental stresses [9], further suggesting the interconnections among different stresses.

Anhydrobiotes, such as yeast, go through many preconditioning steps to acquire desiccation tolerance. During these preconditioning steps, they undergo a range of morphological and physiological changes such as thickened cell walls and accumulation of stress proteins to prepare themselves for desiccation tolerance [10,11]. In addition, cells have shown metabolic changes to promote survival, using food reservoirs and reducing metabolic activities. Certain metabolic pathways, such as the fatty acid oxidation pathway, become more apparent during the desiccation process [12]. Some metabolic processes could be halted during desiccation [13].

In this review, we briefly discuss recent findings of the desiccation stress and stress response of anhydrobiotes, specifically of the budding yeast *Saccharomyces cerevisiae*. We attempt to address two major questions: how do anhydrobiotes acquire desiccation tolerance; and how do anhydrobiotes maintain life during the desiccated state. In addition, we briefly discuss the feasibility of using desiccated yeast as a model to study prion diseases, which share certain common features with desiccated yeast, like protein misfolding [14].

2. How Anhydrobiotes Acquire Desiccation Tolerance

2.1. No Pain, No Gain—Low Stress Produces More Tolerance

Tolerance to oxidative stress is significantly enhanced when yeast cells are first exposed to low levels of oxidative stress [15]. Similarly, the desiccation tolerance for anhydrobiotes is not innate. They must go through a 'painful' process, i.e., experiencing a low level of stress in order to gain desiccation tolerance - the capacity of surviving with severe water loss. This stress may or may not be directly related to desiccation. In plants, for example, acquisition of desiccation tolerance is triggered by gradual dehydration and an increase in the production of abscisic acid [16,17]. Nematodes (*Caenorhabditis elegans*) gain their desiccation tolerance by going through starvation to induce dauer larvae, followed by initial dehydration at high relative humidity (pre-conditioning) [18,19]. Preconditioning is also required for tardigrades to gain desiccation tolerance by initial slow drying [20,21]. Desiccation tolerance in yeast is commonly induced via starvation by growing cells into stationary phase when cells significantly reduce their metabolic level [22]. Under starvation, diploid yeast cells undergo meiosis and form spores, which are resistant to a wide range of harsh environmental stresses, such as UV radiation, varying temperature, and desiccation [23].

Compared to stationary (starved) cells, dividing yeast cells growing in a rich medium (log-phase) have minimal tolerance to desiccation with a survival rate ranging from 0.0001% to 10%, depending on the desiccation method [12,22]. One intriguing question is: who are these 'lucky' surviving cells and why they are so 'lucky'? Our recent study revealed that these 'lucky' cells share a few unique characteristics, including: 1). They are all replicative young cells; 2). They are all in the G1 phase of the cell cycle; 3). They all have condensed chromosomes. The condensed chromosome suggests that genes are more silenced, which is confirmed by the low metabolic activities of these cells [24] (Figure 1). One possibility is this could be a feature developed through evolution, in which a small portion of cells is always prepared to encounter the unpredicted and sudden changes of their environment.

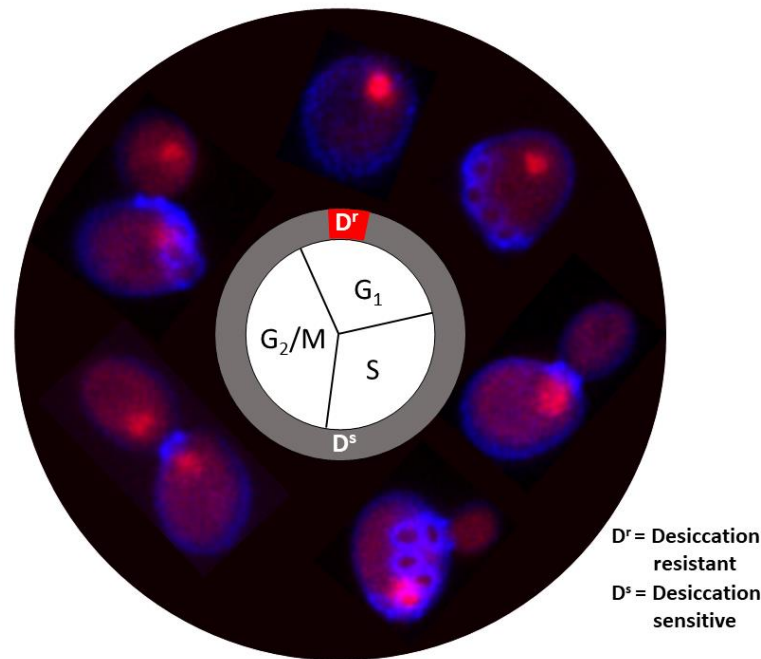


Figure 1. Cell cycle and desiccation tolerance in *S. cerevisiae*. Red: DRAQ5 staining of nuclei. Blue: Fluorescence brightener 28 staining of cell wall and bud scars, which indicate the replicative age of yeast cells. The desiccation resistant cells (D') are in G1 but have higher fluorescence intensity (Redraw based on [24]).

Cell cycle arrest has also been reported in both plants [25,26] and algae during desiccation [27]. DNA synthesis is repressed, and the new cycle of cell division is halted upon desiccation stress. Down-regulation of cell cycle associated transcripts is observed in the desiccation-tolerant microalgae, *Klebsormidium*. Under desiccated conditions, cells arrest at the G1 checkpoint, preventing entry into S phase where DNA replication occurs [27]. Desiccation causes DNA damage due to the formation of reactive oxygen species (ROS) and other stressors, so the cell cycle arrest helps with coordinating DNA repair mechanisms [28]. Failure of the cell cycle arrest results in cell death [29,30]. These studies suggest that cell cycle and stress response pathways are interconnected, with many stress response genes being regulated in a cell cycle-dependent manner. For example, certain transcription factors involved in the stress response, like Msn2/4, are regulated by cell cycle-dependent mechanisms. These factors can activate the expression of genes encoding protective proteins, such as chaperones and antioxidants, which help cells cope with desiccation stress [31].

2.2. Morphological and Physiological Changes in Response to Desiccation Stress

2.2.1. Morphological Changes

In response to stress, anhydrobiotes make significant morphological and physiological changes to prepare themselves for harsher conditions. In yeast, starvation stress leads to a thickened cell wall that is more thermotolerant and more resistant to enzymatic digestion [32]. Their metabolic level is also significantly reduced [33]. Stationary cells have more mitochondria because they have to use ethanol as their carbon source since glucose is being depleted. Most of the stationary cells also accumulate more lipid droplets, which consists primarily of the neutral lipids, triacylglycerols and steryl esters, as a reservoir for energy [34]. When they are re-introduced into fresh nutrients, the lipids are quickly consumed before cells use external nutrients for cellular growth [35].

Desiccation stress to stationary yeast cells causes further structural changes [36-38]. These changes include altered cell walls, altered cellular and nuclear membranes and a reduction in cell size. Desiccation also induces oxidative stress, which in turn causes DNA and membrane damages [39]. Using transmission electron microscopy (TEM), we recently showed that desiccation in yeast

triggers endoplasmic reticulum (ER) stress and unfolded protein response [12]. The ER is misfolded and the nuclear membrane is ruptured (Figure 2). Vacuoles are not readily observed in desiccated yeast cells. In *C. elegans*, structural damage, including damage to the cell and mitochondrial membrane, is observed in desiccation-sensitive dauers, or desiccation-tolerant dauers without proper preconditioning [19].



Figure 2. TEM image of a stationary yeast cell desiccated for 14 days, showing a whorl-like structure (boxed and inset) caused by ER stress (Adopted from reference [12]).

2.2.2. Physiological Changes

Like structural changes in anhydrobiotes, many physiological changes occur during the preconditioning, or the initial low stress stage. Starvation stress leads to a significant decrease of metabolism within the cells and an increased accumulation of proteins and non-reducing disaccharides that function as stress effectors, including hydrophilins, heat shock proteins and trehalose. These proteins and non-reducing disaccharides help to preserve both membrane and protein structure as well as prevent protein misfolding [10,11].

Stress proteins: Stress proteins are composed of three intertwined protein families: heat shock proteins (HSPs), intrinsically disordered proteins (IDPs) and hydrophilins. HSPs are molecular chaperones that contribute to the maintenance of cellular homeostasis by facilitating the refolding of misfolded proteins. They are broadly categorized based on their molecular weights, including: Hsp40 (~40 kDa), Hsp60 (57-65 kDa), Hsp70 (68–80 kDa), Hsp90 (83–99 kDa), and small HSPs (15–40 kDa) [40]. HSPs also play crucial roles in stress response. Many HSPs are induced upon stresses including heat, osmotic, oxidative and desiccation stress [41-43]. The yeast small heat shock protein Hsp12p, for example, protects against desiccation stress by interacting with the plasma membrane and protecting the membrane structure during desiccation [44]. The disaggregase Hsp104p also enhances yeast desiccation tolerance. Interestingly, this enhancement is accomplished only in cooperation with the disaccharide trehalose [45]. Hsp70p levels are increased upon stress, but no correlation was observed between Hsp70p increase and desiccation tolerance in yeast [46]. It would be interesting to see if Hsp70p requires other stress effectors to function. Correlation of Hsp70p level and desiccation has also been reported in other organisms. In the green algae *Klebsormidium*, Hsp70 gene was

upregulated in desiccation-tolerant strains upon desiccation stress [27]. In the brine shrimp *Artemia*, knockdown of the Hsp70 gene reduces the viability of desiccated cysts [47].

Intrinsically disordered proteins (IDPs) are a large and functionally important family of proteins characterized by their lack of stable three-dimensional structures yet existent in multiple interconverting conformational states. Many IDPs can change to a fixed tertiary structure after binding to other proteins or RNA [48]. IDPs play important roles in many biological processes, including cell organization, development, and stress tolerance [10,49]. The tardigrade-specific IDPs are essential and sufficient for desiccation tolerance [10]. The late embryogenesis abundant (LEA) proteins are plant specific IDPs and facilitate the stabilization of membranes during desiccation, which enhances the desiccation tolerance of plant seeds [50]. In yeast, the IDP Hsp12p interacts with the plasma membrane and protects membrane structures against desiccation stress [44]. Hsp12p also synergizes with trehalose to mitigate protein aggregation and desiccation stress [11].

Hydrophilins are a group of proteins characterized with high glycine content (> 6%) and high hydrophilicity index (> 1.0) [51,52]. Hydrophilins often include intrinsically disordered proteins (IDPs) partially due to their high content of glycine, a disorder-promoting residue [11]. Genes encoding hydrophilins are induced by osmotic stress, suggesting that these proteins play a role in response to water loss, or desiccation stress. Twelve hydrophilin proteins have been identified in *Saccharomyces cerevisiae*. Their possible involvement in desiccation stress is listed in Table 1. While the molecular mechanism in stress protection of many hydrophilins is not well studied, it is believed that they act to stabilize proteins and membranes during desiccation [53]. Studies have shown that both Sip18p [52] and Stf2p [53] enhance desiccation tolerance by reducing the ROS level during desiccation stress.

Proteins that are not HSPs, IDPs or hydrophilins may also be involved in membrane stability. The cortical ER protein Ist2p, for example, connects ER to plasma membrane and stabilizes the membrane during desiccation stress. Ist2p also plays a key role in sustaining or restoring the plasma membrane structure during rehydration [54].

Table 1. Yeast hydrophilins and their possible roles in desiccation stress.

GENE ID	GENE NAME	POSSIBLE ROLE IN (DESICCICATION) RESISTANCE	REFERE NCES
YJL184W	GON7	Involved in cell wall mannoprotein biosynthesis and osmotic stress response.	[55]
YMR175W	SIP18	Involved in osmotic and desiccation stress response.	[56,57]
YMR260C	TIF11	Localizes to cytoplasmic stress granule; desiccation resistance increases in mutant.	[8,58]
YFL014W	HSP12	Plant LEA-like protein, involved in plasma membrane organization and response to multiple stresses, including desiccation stress.	[44]
YDL213C	NOP6	Required for desiccation-rehydration process.	[53]
YGR008C	STF2	Involved in cellular response to desiccation, oxidation, and DNA replication stress.	[53]
YBR016W	CPP1	Involved in the adaptive response to hyperosmotic stress. Detailed biological function unknown.	[59]
YPL223C	GRE1	Paralog to SIP18. Involved in response to multiple stresses, including osmotic, oxidative, heat shock and desiccation.	[60]
YFL010C	WWM1	Biological function unknown. Interacts with the caspase-related protease Mca1p.	[61]
YJL144W	ROQ1	Regulator of the Ubr1p E3 ubiquitin ligase; Involved in osmotic, DNA replication and desiccation stress.	[61,62]
YNL162W	RPL42A	Subunit of the large ribosomal 60S subunit. Function in desiccation stress unknown.	[53,63]
YNL190W		Cell wall protein; essential for desiccation stress response.	[53]

Trehalose: Trehalose is one of the most well-studied stress effectors in desiccation biology. A study showed that both the structure and the dynamics of the dehydrated matrices differ significantly between trehalose (a non-reducing disaccharide) and sucrose (a reducing disaccharide). The dehydrated trehalose matrix is homogeneous whereas the dehydrated sucrose forms a heterogeneous matrix. This unique structure makes trehalose a more effective stabilizer for proteins under stress [64,65].

High concentration of trehalose is found in many anhydrobiotes [66]. In budding yeast, elevated levels of trehalose are found only in stationary cells, which are desiccation tolerant. The trehalose concentration is very low in exponentially growing cells, and these cells are very sensitive to desiccation [22,24]. Stationary yeast cells have a metabolic mode distinct from the exponentially growing cells. Cells growing exponentially use fermentative glycolysis to meet their energetic and biosynthetic needs. When glucose is depleted, cells are transitioned to respiratory metabolism, primarily using ethanol as their energy source [67].

In yeast, both glycolytic and respiratory activities are very low during the stationary phase, when trehalose has accumulated [68]. The glyoxylate shunt, or glyoxylate cycle, plays an essential role in trehalose synthesis in both stationary yeast cells and dauer larva of the *C. elegans* [69]. The glyoxylate shunt works by bypassing the steps in the citric acid cycle to produce trehalose using ethanol or acetate as its carbon source. Fatty acids, which are abundant in stationary yeast, could also be used as a carbon source of the glyoxylate cycle [69,70].

Trehalose often cooperates with other stress proteins to establish desiccation tolerance. In yeast, for example, trehalose works together with Hsp12p to promote both short-term and long-term desiccation tolerance [11]. It has also been shown that trehalose cooperates with Hsp104p to promote short-term desiccation tolerance while trehalose is responsible for long-term survival [45]. In tardigrade, while trehalose levels are relatively low, the effector still plays a crucial role in promoting desiccation tolerance by working synergistically with the tardigrade-specific disordered protein CAHS D [21].

Glycerol: Loss of water alters the osmolarity of cells and therefore induces osmotic stress. The high osmolarity glycerol (HOG) pathway is activated upon osmotic stress and increases the production of glycerol, which is the main osmolyte in yeast [71]. However, studies have shown that glycerol does not affect desiccation tolerance [22,72]. Our preliminary data showed that the addition of glycerol to culture medium prior to desiccation does enhance the desiccation tolerance (Zhang, unpublished data). More studies are needed in elucidating possible roles of glycerol in the desiccation stress response.

Proline: Proline is an amino acid that is unique among the standard amino acids in which it does not have a free α -amino group. In bacteria or plants, proline accumulates in response to osmotic stress and functions as an osmoprotectant [73]. In yeast, increasing proline level by either deleting the proline-oxidase (PUT1) or externally adding proline enhances both freezing and desiccation resistance [74]. However, in yeast, no proline increase was observed upon stress, unlike in bacteria or plants [73]. Like glycerol, the involvement of proline in desiccation stress warrants further investigations.

3. How do Anhydrobiotes Survive in Desiccated State

3.1. Minimal Metabolism but Not Ametabolism

One pressing question is: how do anhydrobiotes survive during desiccation stress and within the desiccated state? When transitioned from starvation to desiccation stage, yeast cells lose the two most important ingredients for life: food and water. To counter this problem, cells utilize two strategies –reduce their metabolic activities and use their own food “reservoirs”. When starved, yeast cells accumulate lipid droplets and trehalose to use as an energy reservoir [34]. When they are re-introduced to fresh nutrients, both lipids and trehalose are quickly consumed before cells use external nutrients for cellular growth [35,45]. If stress continues, or becomes more severe (starvation plus

desiccation), cells may use this reserved energy to further prepare themselves for the anhydrobiotic stage.

The anhydrobiotic state is sometimes considered as the anhydrobiotic organisms being in a state of ametabolism or suspended metabolism due to desiccation [75]. In anhydrobiotic nematodes, metabolism cannot be detected using radiolabeled glucose [3]. However, molecular mobility and enzyme activities, although minimal, have been detected in desiccated lichens [76]. Enzyme activity was also observed in desiccated yeast for up to half a year [45]. Trehalose was slowly digested by trehalases while yeast was in its desiccated state. The consumption of trehalose likely provides energy to maintain life. However, knockout of trehalase genes (ATH1 and NTH1) extends the viability after desiccation [45]. It is possible that in the absence of trehalases, other forms of energy are used, while trehalose is used to preserve the protein and membrane structure. In our recent study, we observed that vacuoles, serving as the primary site for protein degradation and recycling, are mostly diminished 14 days after desiccation [12], suggesting that yeast cells likely use resources recycled from vacuoles to prepare/sustain them for the anhydrobiotic state. We also observed dynamic changes of lipid bodies. The circular membrane structure, induced by desiccation, is merged and releases the lipid into the lipid body (Figure 3); and the lipid body steadily decreases, likely consumed by cells as an energy source. Defects in lipid droplet synthesis significantly reduce desiccation tolerance, further suggesting that lipid consumption is important for survival of desiccation.

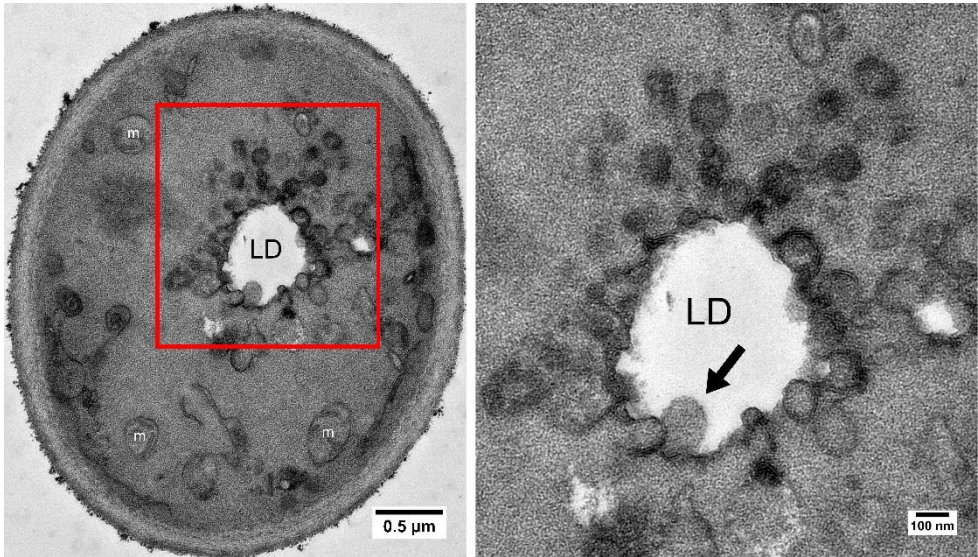


Figure 3. TEM image of a stationary yeast cell desiccated for 14 days, showing the lipid droplet surrounded by circular ER structures. Some of the circular structure appears to have no membrane (arrow in enlarged box area) (Adopted from reference [12]).

We compared the gene expression profiles between non-desiccated and 7-day desiccated stationary yeast cells. Among the up-regulated genes, the only enriched pathway was the fatty acid oxidation pathway, where six genes were identified (Table 2; Zhang, unpublished data). These data strongly suggest that fatty acid oxidation (β -oxidation) plays a significant role in the desiccation response.

Table 2. Desiccation-induced upregulated genes enriched in the fatty acid oxidation pathway in budding yeast.

Gene ID	Gene Name	Description
YER015W	LPX1	Peroxisomal matrix-localized lipase; required for normal peroxisomal morphology.
YGL205W	POX1	Fatty-acyl coenzyme A oxidase; involved in the fatty acid β -oxidation pathway.

YIL160C	POT1	3-ketoacyl-CoA thiolase with broad chain length specificity; cleaves 3-ketoacyl-CoA into acyl-CoA and acetyl-CoA during beta-oxidation of fatty acids.
YKR009C	FOX2	3-hydroxyacyl-CoA dehydrogenase and enoyl-CoA hydratase; multifunctional enzyme of the peroxisomal fatty acid beta-oxidation pathway.
YLR284C	ECI1	Peroxisomal delta3, delta2-enoyl-CoA isomerase; essential for the beta-oxidation of unsaturated fatty acids.
YOR180C	DCI1	Peroxisomal protein involved in fatty acid metabolism.

β-oxidation of fatty acids provides not only necessary energy to cells, but also metabolic water. Oxidation of fat produces about 110 g of metabolic water per 100 g of fat, which is far more than oxidation of carbohydrates or proteins produces [77,78]. This metabolic water could potentially be crucial to the survival of the desiccated yeast and essential for enzymatic activities [45]. Similarly, metabolic water provides an important water source for animals living in desert landscapes or for migrating birds [79,80].

4. Desiccated Yeast as a Model to Study Prion and Other Neurodegenerative Disorders

Desiccation induces protein misfolding, which is a major cause of many neurodegenerative disorders [81]. This could make desiccated yeast good models to study neurodegenerative disorders, such as prion diseases.

Prion diseases are rare, yet fatal infections caused by the misfolding and aggregation of proteins, known as prions. These protein aggregates cluster within the body, specifically in the brain, and can cause degeneration and damage of brain tissue [82] often resulting in hinderance of thinking and reasoning. One of the most common prion diseases in humans is Creutzfeldt-Jakob disease (CJD) [82]. CJD causes deterioration of brain tissue from the aggregation of prions, inhibiting the normal function of the brain. Currently, there is no known cause for CJD but there is speculation that the cause is wide ranging [83].

The budding yeast possesses several prion proteins. They are not homologous to mammal prions but share significant similarities of the amino acid composition and transmission of phenotype [14,84]. The most studied yeast prion is [PSI⁺], a misfolded aggregate of the Sup35 protein. Sup35 is a translation termination factor from the eRF3 family [85]. An easy way to identify [PSI⁺] formation is using an ADE2 mutant strain that contains a pre-mature stop codon. In the absence of [PSI⁺], i.e., [psi⁻], the colony of this strain becomes red in rich medium that lacks additional adenine. When the yeast cells contain [PSI⁺] positive proteins, the colonies become white due to the misfolded, non-functional Sup35 skipping the pre-mature stop codon, producing a full length of Ade2 protein [86]. Using this strategy, we isolated and examined the [PSI⁺] strain with and without desiccation stress using TEM. Our preliminary results showed that heavy [PSI⁺] aggregates were formed under desiccation, suggesting the feasibility of using desiccation stress to study prion biology.

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