Influence of [*PSI*$^+$] prion on the adaptability of yeast *Saccharomyces cerevisiae* cells

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Adaptation of microorganisms to the environment is regulated by genetic systems and epigenetic factors. Phenotypic suppression performed by the yeast *S. cerevisiae* epigenetic factor, prion [*PSI*$^+$], was investigated as a possible adaptive mechanism of the cells. Spontaneous [*PSI*$^+$] induction has been shown to proceed more efficiently in stressful conditions and to cause the formation of a heterogeneous population of [*PSI*$^+$] variants. Analysis of the growth and viability of isogenic [*PSI*$^+$] and [*psi*-] strains has shown that in a model system strong variants of [*PSI*$^+$] can suppress cell death and have a positive influence on the growth rate. It has been suggested that prion induction and propagation can be used to improve cell adaptability: strong [*PSI*$^+$] prions formed in the process of [*PSI*$^+$] induction can ensure a higher plasticity of part of cells in the population when adapted to the environmental conditions.

Key words: yeast, prion, [*PSI*$^+$], adaptability

INTRODUCTION

The adaptability of microorganisms to the environment is regulated by various genetic mechanisms. A possible participation of the epigenetic yeast factors, prions, in the adaptive processes of the cell, which gives phenotypic advantages to the whole population has been recently discussed (Chernoff, 2001; Uptain, Lindquist, 2002).

Prions are infectious proteins that cause mammalian neurodegenerative diseases (Aguzzi et al., 2001; Harris, 1999). They are also found in eucaryotic microorganisms, such as various yeast genera, e.g., *Saccharomyces*, *Candida*, *Pichia*, *Kluyveromyces*, and filamentous fungi *Podospora anserina* (Uptain, Lindquist, 2002). There are certain similarities between mammalian prions and prions of microorganisms, which are, infectivity, a species barrier that protects from the spreading of an infectious protein, the existence of different prion strains, and structural similarities of prion proteins determined by a prion domain responsible for prion properties (Bousset, Melki, 2002).

The best characterized epigenetic factors of the model microorganism *Saccharomyces cerevisiae* [*PSI*$^+$] and [URE3] are the respective prion forms of the proteins Sup35 and Ure2 (Derkatch et al., 1996; Serio and Lindquist, 1999; Uptain and Lindquist, 2002; Wickner, 1994). Sup35p is homologous to the translation termination factor eRF3 in higher eukaryotes (Serio, Lindquist, 1999; Stansfield et al., 1995; Zhouravleva et al., 1995). Ure2p is a product of the chromosome gene *URE2*, which participates in nitrogen metabolism regulation of the yeast cell (Uptain and Lindquist, 2002; Wickner, 1994). Prion isoforms of these proteins aggregate in yeast cell cytoplasm and propagate to turn a soluble form of the protein into its misfolded form (Patino et al., 1996; Paushkin et al., 1996; Thual et al., 1999). The purified Sup35p and Ure2p are capable of forming amyloid fibrils and thus allow suggesting the amyloid nature of the aggregates formed *in vivo* (Glover et al., 1997; Serio et al., 2000; Taylor et al., 1999). Overexpression of *SUP35* and *URE2* genes or overexpression of Sup35 and Ure2 proteins induce *de novo* appearance of the respective prions [*PSI*$^+$] and [*URE3*] (Derkatch et al., 1996; Wickner, 1994). Besides, overexpression of *SUP35* induces appearance of various [*PSI*$^+$] variants, which retain their properties in individual cell clones (Derkatch et al., 1996; Uptain et al., 2001). Sup35p aggregates of different [*PSI*$^+$] strains differ in their seeding efficiency *in vitro* (Uptain et al., 2001; Kochneva-Pervukhova et al., 2001).

Appearance of [*PSI*$^+$] in yeast cells is possible, if other prions, such as [*PIN*$^+$] – a product of the gene *RNQ1*, [*URE3*] are present, or it proceeds under an enhanced expression of the proteins possessing a certain number of repeats of polar amino acids characteristic of yeast prion proteins (Derkatch

et al., 2001; Osherovich and Weissman, 2001). Besides, the presence of [*PIN*$^+$] has been shown to predetermine a negative interaction of prions [*PSI*$^+$] and [*URE3*], when one prion represses the appearance and *de novo* propagation of the other (Bradley et al., 2002; Schwimmer and Masison, 2002). Appearance and *de novo* propagation of prions depend not only on their interaction, but also on the expression level of a series of factors encoded by a yeast genome (Uptain and Lindquist, 2002).

The growth and viability of microorganisms are two related physiological processes, which reflect the capability of a cell population to adapt to the environmental conditions. The modeling of stress situations in laboratory conditions enables to evaluate the adaptive potential of epigenetic factors of the cell. We analyzed how induction of prion [*PSI*$^+$] and [*PSI*$^+$] itself can influence the growth and viability of cells.

MATERIALS AND METHODS

The yeast *Saccharomyces cerevisiae* strain 12A-DV201 – *MAT*α *leu2*^{UAA} *his7-1* [*PIN*$^+$] [*psi*$^-$], which displays a phenotype of reduced viability in minimal media was investigated. 12A-DV201 is a segregant of diploid DV201 (Rakauskaite and Citavicius, 2003). The wild type stain 15B-P4 *MAT*a was used for control. For [*PSI*$^+$] prion determination by expression of Sup35p and green fluorescent protein (GFP) fusion, plasmids SUP35G and pRS316CG (a gift from S. Lindquist) were modified as follows: for Sup35-GFP expression and GFP expression the *Nhe*I-*Xho*I-bordered P_{URE2} URE2N-GFP fragment from pVTG12 plasmid (Edskes et al., 1999) based on centromeric *LEU2* vector pRS315 was substituted by *Xho*I-*Pdi*I-bordered P_{CUP1} SUP35-GFP and P_{CUP1}GFP fragments from plasmids CSUP35G and pRS316CG, respectively. The yeast transformants were grown at 30 °C in a minimal (MD-Leu) medium (2% glucose, 0.5% $(NH_4)_2SO_4$, 0.05% $MgSO_4 \times 7H_2O$, 0.023% K_2HPO_4, 0.01% NaCl, 0.01% $CaCl_2$, 2% Bacto agar) saturated with 20 mg/l histidine and a 0.25 μM residual $CuSO_4$ concentration for Cu^{2+} ion induction of Sup35-GFP and GFP expression. Cells with Sup35-GFP aggregates were identified using a fluorescence microscopy system: Olympus Provis AX70TRF (Olympus, Japan); magnification ×1000. Cells were photographed with a Hamamatsu C4742-95-10NR digital camera.

The [*PSI*$^+$] prion was either induced spontaneously or the frequency of [*PSI*$^+$] induction was monitored by growing the 12A-DV201 strain on MD-Leu medium for 8 days at 30 °C. Cells were cured of prion by subculturing [*PSI*$^+$] clones on YPD medium (2% glucose, 2% peptone, 1% yeast extract, and 2% Bacto agar) with 5 mM guanidine hydrochloride three times every 24 hours at 30 °C. Strain growth specificity at 30 °C was determined in a liquid MD medium saturated with respective amino acids according to the genotype as indicated above and otherwise specified monitoring cells density every 24, 48, 72, and 97 hours. At the same time points the viability of the culture was determined as a percentage of colony-forming units on YPD medium from at least 800 cells.

RESULTS AND DISCUSSION

Prion [*PSI*$^+$] restores the gene function by phenotypic suppression of nonsense mutation without reversion of the mutation (Serio and Lindquist, 1999). Existence of [*PSI*$^+$] prion in yeast *S. cerevisiae* strain 12A-DV201 was confirmed by analysis of the phenotypic suppression of *leu2*^{UAA} mutation and satisfies the criteria of prion concept proposed by R. Wickner in 1994: 1. Prion [*PSI*$^+$] was spontaneously induced at low frequency (10^{-7}); 2. Prion [*PSI*$^+$] was cured by 5 mM guanidine hydrochloride; 3. In clones once cured of the prion, [*PSI*$^+$] reappeared spontaneously. When expressing the fusion protein Sup35-GFP, fluorescent aggregates of different shapes were formed in the cells bearing a [*PSI*$^+$] prion, while the protein was distributed evenly in the cytoplasm when expressing only GFP (Fig. 1). Since appearance of [*PSI*$^+$] prion is indispensable for prion [*PIN*$^+$], strain 12A-DV201 is of the [*PIN*$^+$][*psi*$^-$] phenotype.

After spontaneous induction of prion [*PSI*$^+$], colonies of different size were formed (Fig. 2), showing that variants differing in growth rate were characteristic of phenotypic suppression of *leu2*^{UAA} mu-

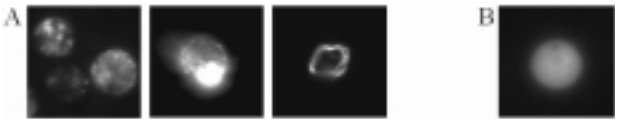

Fig. 1. *In vivo* detection of [*PSI*$^+$] prion state in yeast. (A) fluorescent aggregates of Sup35-GFP fusion protein indicate cells with [*PSI*$^+$] prion; (B) no aggregates are formed from GFP alone

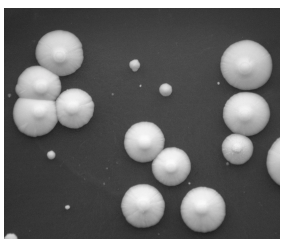

Fig. 2. Heterogeneity of spontaneous induction of [*PSI*$^+$] prion. [*PSI*$^+$] colonies differ in size: big and small colonies represent strong and weak [*PSI*$^+$] variants, respectively

tation present in 12A-DV201 strain. Big colonies corresponded to strong variants that grew faster because of a more effective nonsense suppression, which is known to be determined by a more optimal amount of prionized Sup35 protein in the cell (Uptain et al., 2001). Small colonies were weak variants. It is much harder to cure strong [*PSI*$^+$] variants by guanidine hydrochloride treatment (Derkatch et al., 1996). The examined case also led to this conclusion, because the subculturing of the colony for three times on guanidine hydrochloride showed no elimination of prion from big colonies, whereas small colonies were effectively cured in this way.

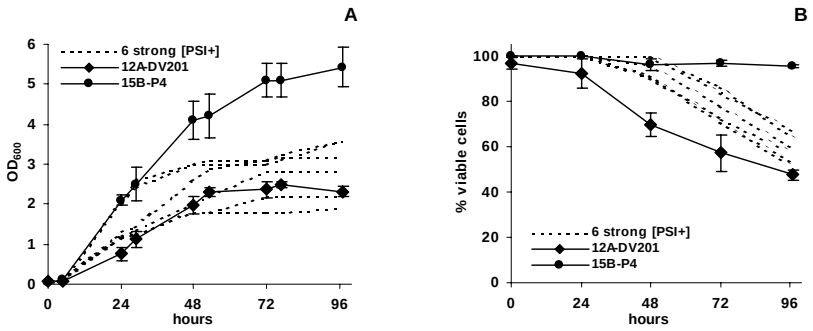

Fig. 3. Growth (A) and viability (B) of strong [*PSI*$^+$] variants in MD-Leu medium. 15B-P4 – wild type. 12A-DV201 strain was cultivated in optimal conditions (75 mg/l leucine in MD medium). Means of optical density and viability percentage obtained from three independent experiments are indicated. Bars represent standard deviations

In order to determine the rate of prion [*PSI*$^+$] spontaneous induction in response to environmental conditions, two conditions for 12A-DV201 strain culturing in minimal medium were created: simulating stress (leucine concentration was reduced to 15 mg/l) and growth optimal (75 mg/l of leucine). After 97 h of cultivation, the number of [*PSI*$^+$] clones that appeared in the population for 10^6 cells in stress conditions was higher by a factor of 5.4 ($P < 0.001$ according to the t (Student) criterion). It proved that stress of leucine deprivation more effectively induced appearance of [*PSI*$^+$] prion. The viability of strain 12A-DV201 in minimal medium was lowered: after 97 h of cultivation in stress and optimal conditions the viability decreased to ~30 and 40%, respectively, while the viability of the wild type strain remained high (~97%). The increased frequency of prion [*PSI*$^+$] appearance in stress conditions could show [*PSI*$^+$] to be beneficial for cells. Giving sense to *leu2*^{UAA} mutation and restoring the activity of the *LEU2* gene, the [*PSI*$^+$] prion produces clones of cells that are best adapted to the environment.

When analyzing the influence of [*PSI*$^+$] factor on the adaptability of 12A-DV201 strain in stress conditions, examined were the growth and viability of isogenic derivatives:

1. [*PIN*$^+$][*PSI*$^+$] clones, obtained after induction of strong [*PSI*$^+$].

2. [*PIN*$^+$][*psi*-] and [*pin*-][*psi*-] derivatives, obtained by removing [*PSI*$^+$] and [*PIN*$^+$][*PSI*$^+$] respectively from [*PIN*$^+$][*PSI*$^+$] by guanidine hydrochloride treatment.

Six strong [*PSI*$^+$] variants were selected and their growth and viability monitored in conditions selective for [*PSI*$^+$] prion (MD-Leu medium) (Fig. 3). Existence of strong [*PSI*$^+$] had a different effect on cells growth. It restored the biosynthesis of leucine, and the growth rate of cultures became close to or even exceeded the growth rate of strain 12A-DV201 in optimal conditions. It should be noted that the exponential growth of two best growing [*PSI*$^+$] variants was identical to that of the wild type strain 15B-P4.

The profile of viability curves of all strong [*PSI*$^+$] variants was similar, but the [*PSI*$^+$] variants were more viable when compared to the isogenic strain 12A-DV201 cultivated in optimal growth conditions (Fig. 3B). Compared to strain 12A-DV201, strong isogenic [*PSI*$^+$] variants also retained their viability for a longer period of time. Their viability of exponential growth and post-diauxic shift (48 h of cultivation) corresponded to the viability of the wild type strain, showing that strong [*PSI*$^+$] variants can sustain the viability of yeast culture.

The analyzed strong [*PSI*$^+$] variants were induced spontaneously and selected according to the size of colonies. More detailed investigations of indiviadual [*PSI*$^+$] clones revealed physiological differences that confirmed the heterogeneity of the cell population, determined by the activity of [*PSI*$^+$] factor. [*PSI*$^+$] variants could temporarily adapt the cell and sustain its viability in critic conditions. Eventually, in the process of cell division, selection of [*PSI*$^+$] variants optimal for growth and viability can take place. This statement was confirmed by the results obtained by analyzing the frequency of [*PSI*$^+$] appearance in stress conditions. Cells from the exponential phase and post-diauxic shift formed [*PSI*$^+$] colonies of various sizes, whereas cells from deep stationary phase culture formed only big colonies resembling strong [*PSI*$^+$] variants. Differences in growth and especially in viability that developed in stationary phase between strong [*PSI*$^+$] variants and wild type strain could show toxicity of the [*PSI*$^+$] aggregates that accumulated inside the cells during

prolonged cultivation. This explanation is consistent with the facts of [*PSI*$^+$] prion toxicity reported in stationary phase cultures (Chernoff et al., 1998; Derkatch et al., 2001).

The adaptive value of [*PSI*$^+$] phenotypic suppression could be confirmed by the situation when the loss of prion could influence the viability of yeast culture. To test this hypothesis, the best-growing [*PSI*$^+$] variants were cured of prions by guanidine hydrochloride treatment, and 12A-DV201 isogenic strains [*PIN*$^+$][*psi*-], [*pin*-][*psi*-], and [*PIN*$^+$][*PSI*$^+$], were subjected to further investigations.

[*PIN*$^+$][*psi*-] was selected as a variant that could not grow in selective conditions for [*PSI*$^+$] prion but spontaneous induction of [*PSI*$^+$] took place in it. [*pin*-][*psi*-] did not grow in selective conditions and could not induce prion [*PSI*$^+$]. These strains allowed to evaluate separately the impact of [*PSI*$^+$] and [*PIN*$^+$] prions on the growth and viability of cells.

Isogenic [*psi*-] variants obtained from [*PSI*$^+$] were cultivated in stress conditions (Fig. 4A). Both [*psi*-] variants displayed a slow growth phenotype

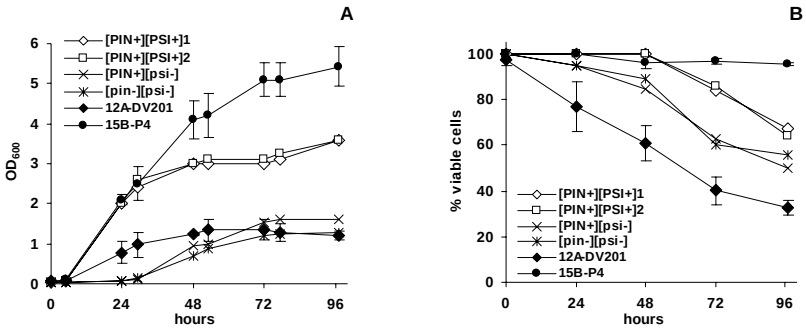

Fig. 4. Comparison of growth (A) and viability (B) of isogenic [*PSI*$^+$] and [*psi*-] variants. [*psi*-] variants and 12A-DV201 strain were grown in stress conditions (15 mg/l leucine in MD medium). 15B-P4 – wild type. Means of optical density and viability percentage obtained from three independent experiments are indicated. Bars represent standard deviations

as compared to isogenic [*PSI*$^+$] variants. Besides, differently from 12A-DV201 strain, the lag phase of both analyzed [*psi*-] variants was prolonged and lasted 24 h. Compared to [*PSI*$^+$], the viability of [*psi*-] variants was lower (Fig. 4B). In spite of that, both cured [*psi*-] variants retained an increased viability as compared to 12A-DV201 strain even in stress conditions. The obtained results showed that:

1. Removal of [*PSI*$^+$] caused prolongation of lag phase dispensable of [*PIN*$^+$] presence.

2. Removal of strong [*PSI*$^+$] had a negative influence on the viability of cells, therefore [*PSI*$^+$] could provide adaptive advantages to a population of the cells when their growth is limited.

3. Prion [*PIN*$^+$] had no influence on the growth and viability of cells, because the loss of [*PSI*$^+$] alone as well as of both prions from the [*PIN*$^+$][*PSI*$^+$] variant caused the same effect on the growth and viability of the cultures.

The obtained data showed that in stress conditions limiting leucine, an essential nutrient in the growth medium strong variants of [*PSI*$^+$] prion could in part compensate the deprivation of leucine by suppressing *leu2*^{UAA} mutation. The operation of such adaptive mechanism is likely to be time-limited, because [*PSI*$^+$] aggregates can accumulate and become toxic in stationary phase cells (Derkatch et al., 2001; Chernoff et al., 1998). On the other hand, there is a possibility of [*PSI*$^+$] prion interaction with other protein, which can be advantageous to the cell; also, it is possible that prion can cause phenotypic suppression of other "silent" mutations present in the genome. Increased viability characteristic of the isogenic [*PSI*$^+$] variants studied can be a consequence not only of leucine biosynthesis restoration, but also of phenotypic suppression of nonsense mutation/-s in other gene/-s, which lowers viability of the cells. Although until present prions have not been found in natural and industrial yeast isolates (Chernoff, 2001; Chernoff et al., 1998), our data have shown that prionization can serve as the adaptive mechanism.

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MIELIŲ *SACCHAROMYCES CEREVISIAE* [*PSI*$^+$] PRIONO ĮTAKA LĄSTELIŲ ADAPTYVUMUI

S a n t r a u k a

Mikroorganizmų prisitaikymą aplinkoje reguliuoja genetinės sistemos ir epigenetiniai veiksniai. Epigenetinio veiksnio – mielių *S. cerevisiae* [*PSI*$^+$] priono – fenotipinė supresija nagrinėta kaip galimas ląstelių adaptacinis mechanizmas. Parodyta, kad stresinėmis sąlygomis spontaninė [*PSI*$^+$] priono indukcija vyksta efektyviau ir dėl jos susidaro heterogeniška [*PSI*$^+$] variantų populiacija. Atlikta izogeninių [*PSI*$^+$] ir [*psi*-] kamienų augimo ir gyvybingumo palyginamoji analizė parodė, kad modelinėje sistemoje stiprūs [*PSI*$^+$] variantai gali slopinti ląstelių žūtį bei turi teigiamos įtakos augimo greičiui. Iškelta prielaida, kad mielių ląstelėse prionizacija gali būti panaudojama adaptaciniams tikslams: [*PSI*$^+$] indukcijos metu susidarantys stiprūs [*PSI*$^+$] prionai gali suteikti daliai populiacijos ląstelių didesnį plastiškumą prisitaikant prie aplinkos sąlygų.

Raktažodžiai: mielės, prionas, [*PSI*$^+$], adaptyvumas