Lit Lunch – 6_12_15

Mary:

Histochem Cell Biol. 2015 May 8. [Epub ahead of print]

Chaperone molecules concentrate together with the ubiquitin-proteasome system inside particulate cytoplasmic structures: possible role in metabolism of misfolded proteins.

Vanoli A[1], Necchi V, Barozzi S, Manca R, Pecci A, Solcia E.

Abstract

Ubiquitin-proteasome system (UPS) proteins and proteolytic activity are localized in a recently identified cytoplasmic structure characterized by accumulation of barrel-like particles, which is known as the particulate cytoplasmic structure (PaCS). PaCSs have been detected in neoplastic, preneoplastic, chronically infected, and fetal cells, which produce high amounts of misfolded proteins to be degraded by the UPS. Chaperone molecules are crucial in the early stages of handling misfolded proteins; therefore, we searched for these molecules in PaCSs. Heat shock proteins (Hsp), Hsp90, Hsp70, Hsp40, and Bcl-2-associated athanogene (Bag)3 chaperones, although not Bag6, were selectively concentrated into PaCSs of several cell lines and ex vivo fetal or neoplastic cells. Present findings point to PaCSs as an integrated, active UPS center well equipped for metabolism of misfolded proteins, especially in cells under physiological (fetal development) or pathological (neoplasia or inflammation) stress.

Stephanie: Nature Plants

1) **Article:** Associations with rhizosphere bacteria can confer an adaptive advantage to plants

Cara H. Haney, Buck S. Samuel, Jenifer Bush & Frederick M. Ausubel

Abstract: Host-associated microbiomes influence host health. However, it is unclear whether genotypic variations in host organisms influence the microbiome in ways that have adaptive consequences for the host. Here, we show that wild accessions of *Arabidopsis thaliana* differ in their ability to associate with the root-associated bacterium *Pseudomonas fluorescens*, with consequences for plant fitness. In a screen of 196 naturally occurring *Arabidopsis* accessions we identified lines that actively suppress *Pseudomonas* growth under gnotobiotic conditions. We planted accessions that support disparate levels of fluorescent Pseudomonads in natural soils; 16S ribosomal RNA sequencing revealed that accession-specific differences in the microbial communities were largely limited to a subset of Pseudomonadaceae species. These accession-specific differences in*Pseudomonas* growth resulted in enhanced or impaired fitness that depended on the host's ability to support *Pseudomonas* growth, the specific *Pseudomonas* strains present in the soil and the nature of the stress. We suggest that small host-mediated changes in a microbiome can have large effects on host health.

Unraveling the functions of type II-prohibitins in *Arabidopsis* mitochondria

2) Janusz Piechota, Monika Bereza, Aleksandra Sokołowska, Kondrad Suszyński, Karolina Lech,Hanna Jańska
Plant Molecular Biology
June 2015, Volume 88, Issue 3, pp 249-267
Date: 21 Apr 2015

Abstract

In yeast and mammals, prohibitins (PHBs) are considered as structural proteins that form a scaffold-like structure for interacting with a set of proteins involved in various processes occurring in the mitochondria. The role of PHB in plant mitochondria is poorly understood. In the study, the model organism *Arabidopsis thaliana* was used to identify the possible roles of type-II PHBs (homologs of yeast Phb2p) in plant mitochondria. The obtained results suggest that the plant PHB complex participates in the assembly of multisubunit complexes; namely, respiratory complex I and enzymatic complexes carrying lipoic acid as a cofactor (pyruvate dehydrogenase, 2-oxoglutarate dehydrogenase and glycine decarboxylase). PHBs physically interact with subunits of these complexes. Knockout of two *Arabidopsis* type-II prohibitins (AtPHB2 and AtPHB6) results in a decreased abundance of these complexes along with a reduction in mitochondrial acyl carrier proteins. Also, the absence of AtPHB2 and AtPHB6 influences the expression of the mitochondrial genome and leads to the activation of alternative respiratory pathways, namely alternative oxidase and external NADH-dependent alternative dehydrogenases.

Transcription and processing of primary microRNAs are coupled by Elongator complex in*Arabidopsis*

Xiaofeng Fang, **Yuwei Cui**, **Yaoxi Li** & **Yijun QiAffiliationsContributionsCorresponding author**

Nature Plants **1**, Article number: 15075 (2015) doi:10.1038/nplants.2015.75

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MicroRNAs (miRNAs) are a class of small non-coding RNAs that play important regulatory roles in gene expression in plants and animals. The biogenesis of miRNAs involves the transcription of primary miRNAs (pri-miRNAs) by RNA polymerase II (RNAPII) and subsequent processing by Dicer or Dicer-like (DCL) proteins. Here we show that the Elongator complex is involved in miRNA biogenesis in *Arabidopsis*. Disruption of Elongator reduces RNAPII occupancy at miRNA loci and pri-miRNA transcription. We also show that Elongator interacts with the DCL1-containing Dicing complex and lack of Elongator impairs DCL1 localization in the nuclear Dicing body. Finally, we show that pri-miRNA transcripts as well as DCL1 associate with the chromatin of miRNA genes and the chromatin association

of DCL1 is compromised in the absence of Elongator. Our results suggest that Elongator functions in both transcription and processing of pri-miRNAs and probably couples these two processes.

Damian:

From Plant Physiology:

Haibin Lu,

- Balakumaran Chandrasekar,
- Julian Oeljeklaus,
- Johana C. Misas-Villamil,
- Zheming Wang,
- Takayuki Shindo,
- Matthew Bogyo,
- Markus Kaiser,
- and Renier A. L. van der Hoorn

Subfamily-specific Fluorescent Probes for Cys proteases Display Dynamic Protease Activities During Seed Germination Plant Physiol. pp.114.254466; First Published on June 5, 2015;doi:10.1104/pp.114.254466

Cys proteases are an important class of enzymes implicated in both developmental and defence-related programmed cell death and other biological processes in plants. Because there are dozens of Cys proteases that are post-translationally regulated by processing, environmental conditions and inhibitors, new methodologies are required to study these pivotal enzymes individually. Here, we introduce fluorescent activity-based probes that specifically target three distinct Cys protease subfamilies: aleurain-like proteases (ALPs), cathepsin B-like proteases (CTBs), and vacuolar processing enzymes (VPEs). We applied protease activity profiling with these new probes on Arabidopsis protease knock-out lines and agroinfiltrated leaves to identify the probe targets, and on other plant species to demonstrate their broad applicability. These probes revealed that most commercially available protease inhibitors target unexpected proteases in plants. When applied on germinating seeds, these probes reveal dynamic activities of ALPs, CTBs and VPEs, coinciding with the remobilization of seed storage proteins.

From the Plant Journal:

Expression of the tetrahydrofolate-dependent nitric oxide synthase from the green alga *Ostreococcus tauri* increases tolerance to abiotic stresses and influences stomatal development in Arabidopsis (pages 806–821)

Noelia Foresi, Martín L. Mayta, Anabella F. Lodeyro, Denise Scuffi, Natalia Correa-Aragunde, Carlos García-Mata, Claudia Casalongué, Néstor Carrillo and Lorenzo Lamattina

Article first published online: 27 MAY 2015 | DOI: 10.1111/tpj.12852

Significance Statement

Transgenic Arabidopsis plants expressing nitric oxide synthase from *Ostreococcus tauri* (OtNOS) accumulate high NO concentration and show increased tolerance to salt, drought and oxidative stress. Transgenic *OtNOS* lines exhibited increased stomatal index and survival rate to desiccation. OtNOS, unlike mammalian NOS, can efficiently

use tetrahydrofolate (THF) as cofactor in Arabidopsis plants. This finding identifies THF as the cofactor employed by the enzymatic system responsible for the arginine-dependent NO synthesis in higher plants.

NB: There is no homolog of this NOS in Arabidopsis thaliana. The closest relatives are P450 enzymes for which the C-terminal ferredoxin-nadph reductase-like domain is conserved, but the NOS domain at the N-terminus is not found in the Arabidopsis P450 proteins.

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HSP33 in eukaryotes – an evolutionary tale of a chaperone adapted to photosynthetic organisms (pages 850–860)

Na'ama Segal and Michal Shapira

Article first published online: 27 MAY 2015 | DOI: 10.1111/tpj.12855

Significance Statement

Hsp33 is the only known chaperone which is activated under oxidizing conditions, and was well characterized in bacteria. Since the natural physiology of photosynthetic organisms involves light-induced oxidative stress, we were interested to see whether the algal ortholog, HSP33, is expressed in the chloroplast and if it possesses a similar activation mode. Our results highlight a significant evolutionary variability of the algal protein and we also discuss its biotechnological value.

Sugars as hydroxyl radical scavengers: proof-of-concept by studying the fate of sucralose in Arabidopsis (pages 822–839)

Andrea Matros, Darin Peshev, Manuela Peukert, Hans-Peter Mock and Wim Van den Ende

Article first published online: 27 MAY 2015 | DOI: 10.1111/tpj.12853

Significance Statement

Plant sugars represent an integral part of antioxidant mechanisms contributing to cellular ROS homeostasis. In this study we showed the *in vivo* formation of recombination and oxidation products by non-enzymatic reactions with hydroxyl radicals using sucralose, an artificial analogue of sucrose. Oxidation products of endogenous sugars have also been elucidated *in planta* for Arabidopsis and barley.

Molecular Cell: Alert 1 November-7 November

Glutamine Oxidation Maintains the TCA Cycle and Cell Survival during Impaired Mitochondrial Pyruvate Transport Original Research Article

Pages 414-424

Chendong Yang, Bookyung Ko, Christopher T. Hensley, Lei Jiang, Ajla T. Wasti, Jiyeon Kim, Jessica Sudderth, Maria Antonietta Calvaruso, Lloyd Lumata, Matthew Mitsche, Jared Rutter, Matthew E. Merritt, Ralph J. DeBerardinis

A Novel Therapeutic Target In Asthma: Translational Evidence For Inhibition Of S-Nitrosoglutathione Reductase L. G. Que , M. Kraft , N. Lugogo , R. Katial , S. A. Shoemaker , J. M. Troha , 1 1 2 3 4 4 5 Duke University Medical Center, Durham, NC, Duke University Medical Center Division of Pulmonary and

Critical Care Med., Durham, NC, 1 2 National Jewish Health, Denver, CO, N30 Pharmaceuticals, Inc., Boulder, CO, 3 4 5 S-nitrosoglutathione (GSNO) is an endogenous bronchodilator that is deficient in the airways of asthmatics. Preservation of GSNO through inhibition of its primary catabolizing enzyme S-nitrosoglutathione reductase (GSNOR) may provide a novel therapeutic strategy in asthma. We have previously shown that airway SNOs are decreased and that expression and activity of GSNOR are increased in human asthma. Furthermore, ablation of GSNOR protected allergic mice from airway hyperresponsivity (AHR). Novel, small molecule inhibitors of GSNOR have also been found to protect wild type, ovalbumin sensitized and challenged mice from Methacholine-induced AHR while significantly decreasing eosinophilic infiltration and inflammatory biomarkers in the bronchoalveolar lavage (BAL) compared with controls. This translational evidence from GSNOR mice and experimental allergic asthma models to man supports the potential utility of GSNOR -/- inhibition in the treatment of asthma. Two small molecule inhibitors of GSNOR (N6022 for intravenous/inhaled administration and N91115 for oral administration), developed by N30 Pharmaceuticals, have recently been assessed in Phase 1 clinical studies. To date, no dose limiting toxicities have been identified over the projected therapeutic dose range. Adverse events were generally mild and no serious adverse events or significant changes in laboratory parameters, including methemoglobin, ECGs, or vital signs (heart rate and blood pressure) were reported. The effect of N6022 on AHR was also studied in 14 subjects with mild asthma in an exploratory, double blind, randomized, placebo-controlled crossover study. At baseline, subjects were not receiving controllers, had a pre-bronchodilator FEV > 75% predicted, 1 and had a baseline provocative concentration of methacholine causing a 20% fall in FEV of < 8 mg/mL (MPC). N6022 produced a 1 20 significant increase in the percentage of 2 doubling dose increases in the MPC during the study (21% vs. 6%, $p < 0.05$). Additionally, 20 N6022 produced a significant increase in MPC from baseline over the 7-day study period compared with placebo (+ 61% on N6022 vs. – 20 13% on placebo, $p = 0.026$). Subjects with a dose doubling in the MPC on N6022 showed a trend toward a higher baseline serum 20 eosinophil cationic protein (ECP), while those with a greater than 50% increase in the MPC on N6022 had a significantly elevated ECP at 20 baseline compared to those with no response to N6022. The consistent data from the GSNOR mouse to the clinic provide a strong rationale for the future development of GSNOR inhibitors in -/- the treatment of asthma.

Physiology – New Insights into the Physiology and Pathophysiology of Diving and Hyperbaric Environments:

- Heath Gasier,
- Lynn Tatro,
- Ivan Demchenko,
- Hager Suliman,
- and Claude Piantadosi

S-Nitrosoglutathione Reductase Null Mice Display Increased Brain Glutamic Acid Decarboxylase Activity and Seizure Resistance in Hyperbaric OxygenFASEB J April 2015 29:678.14

An imbalance between glutamatergic and g-aminobutyric acid (GABA)ergic synaptic transmission is associated with hyperbaric oxygen (HBO_2) induced seizures. Here we explored the impact of S-nitrosylation in preventing oxygen toxicity in S-nitrosoglutathione reductase (GSNOR) null mice and tested whether S-nitrosylation of brain glutamic acid decarboxylase (GAD) may alter its activity, thus the synthesis of inhibitory GABA. Wild type (WT) and GSNOR -/- mice were exposed to HBO_2 at 4

ATA for up to 100 min and seizure latency was recorded. The medulla, cerebellum and forebrain were harvested from HBO_2 exposed and control mice for determination of GAD activity (fluorometrically) and S-nitrosylated GAD-65 (Biotin-switch). The mean (± SE) seizure latency was significantly delayed in the GSNOR -/- (63 ± 7 min) compared to WT (34 ± 6 min) mice, and the proportion of GSNOR -/- mice that experienced seizures (56%) was significantly less than WT mice (87%). Relative to controls, GAD activity in the medulla and cerebellum was significantly increased in the GSNOR -/- compared to a reduction in WT mice: medulla (GSNOR -/-: +22% and WT: -13%) and cerebellum (GSNOR-/-: +23% and WT: -12%). A significant fall in the degree of GAD-65 S-nitrosylation was observed in GSNOR -/- (-63%) compared to WT (-17%) mice suggesting augmented denitrosylation after GSNOR deletion. Dysregulated S-nitrosylation increased seizure latency and reduced the percentage of mice that developed seizures. The protection afforded by reduced S-nitrosylation may be explained in part by increased GAD activity that would favor GABA synthesis, thus inhibit neuronal excitation and seizures.

Cao, Y., S.A. Gomes, E.B. Rangel, E.C. Paulino, T.L. Fonseca, J. Li, . . . J.M. Hare, *S-nitrosoglutathione reductase–dependent PPARγ denitrosylation participates in MSC-derived adipogenesis and osteogenesis.* The Journal of Clinical Investigation, 2015. **125**(4): p. 1679-1691.

Bone marrow–derived mesenchymal stem cells (MSCs) are a common precursor of both adipocytes and osteoblasts. While it is appreciated that PPARγ regulates the balance between adipogenesis and osteogenesis, the roles of additional regulators of this process remain controversial. Here, we show that MSCs isolated from mice lacking S-nitrosoglutathione reductase, a denitrosylase that regulates protein S-nitrosylation, exhibited decreased adipogenesis and increased osteoblastogenesis compared with WT MSCs. Consistent with this cellular phenotype, S-nitrosoglutathione reductase–deficient mice were smaller, with reduced fat mass and increased bone formation that was accompanied by elevated bone resorption. WT and S-nitrosoglutathione reductase–deficient MSCs exhibited equivalent PPARγ expression; however, S-nitrosylation of PPARγ was elevated in S-nitrosoglutathione reductase–deficient MSCs, diminishing binding to its downstream target fatty acid–binding protein 4 (FABP4). We further identified Cys 139 of PPARγ as an S-nitrosylation site and demonstrated that S-nitrosylation of PPARγ inhibits its transcriptional activity, suggesting a feedback regulation of PPARγ transcriptional activity by NO-mediated S-nitrosylation. Together, these results reveal that S-nitrosoglutathione reductase–dependent modification of PPARγ alters the balance between adipocyte and osteoblast differentiation and provides checkpoint regulation of the lineage bifurcation of these 2 lineages. Moreover, these findings provide pathophysiological and therapeutic insights regarding MSC participation in adipogenesis and osteogenesis.

S-nitrosoglutathione reductase plays opposite roles in SH-SY5Y models of Parkinson's disease and amyotrophic lateral sclerosis.

Salvatore Rizza, Claudia Cirotti, Costanza Montagna, Simone Cardaci, Claudia Consales, Mauro Cozzolino, M. T. Carri, Francesco Cecconi, and Giuseppe Filomeni

Mediators of Inflammation. Accepted article.

Oxidative and nitrosative stresses have been reported as detrimental phenomena concurring to the onset of several neurodegenerative diseases. Here we reported that the ectopic modulation of the denitrosylating enzyme S-nitrosoglutathione reductase (GSNOR) differently impinges on the phenotype of two SH-SY5Y-based in vitro models of neurodegeneration, namely Parkinson's disease (PD) and familial amyotrophic lateral sclerosis (fALS). In particular, we provide evidence that GSNORknocking down protects SH-SY5Y against PD toxins, while, by contrast, its upregulation is required for G93A-SOD1 expressing cells resistance to NO-releasing drugs. Although completely opposite, both conditions are characterized by Nrf2 localization in the nuclear compartment: in the first case induced by GSNOR silencing, while in the second one underlying the anti-nitrosative response. Overall, our results demonstrate that GSNOR expression have different effect on neuronal viability in dependence of the stimulus applied, and suggest that GSNOR could be a responsive gene downstream of Nrf2 activation.

Keith:

Cell

Widespread Proteome Remodeling and Aggregation in Aging C. elegans

Cell*161*, 919–932, May 7, 2015

Dirk M. Walther,[1,5] Prasad Kasturi,[2,5] Min Zheng,[2] Stefan Pinkert,[2,7] Giulia Vecchi,[3] Prajwal Ciryam,[3,4]
Richard I. Morimoto,[4] Christopher M. Dobson,[3] Michele Vendruscolo,[3] Matthias Mann,[1,6] and F. Ulrich Hartl[2,6,*]

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Aging has been associated with a progressive decline of proteostasis, but how this process affects proteome composition remains largely unexplored. Here, we profiled more than 5,000 proteins along the lifespan of the nematode C. elegans. We find that one-third of proteins change in abundance at least 2-fold during aging, resulting in a severe prote- ome imbalance. These changes are reduced in the long-lived daf-2 mutant but are enhanced in the short-lived daf-16 mutant. While ribosomal proteins decline and lose normal stoichiometry, proteasome complexes increase. Proteome imbalance is accom- panied by widespread protein aggregation, with abundant proteins that exceed solubility contributing most to aggregate load. Notably, the

properties by which proteins are selected for aggregation differ in the daf-2 mutant, and an increased formation of aggregates associated with small heat-shock proteins is observed. We suggest that sequestering proteins into chaperone-enriched aggregates is a protective strategy to slow proteostasis decline during nematode aging.

Nature Structural and Molecular Biology

Aβ(1–42) fibril structure illuminates self-recognition and replication of amyloid in Alzheimer's disease

Nature Structural & Molecular Biology **22**, 499–505 (2015)

Department of Chemistry, University of Illinois at Chicago, Chicago, Illinois, USA. Yiling Xiao, Dan McElheny, Sudhakar Parthasarathy, Fei Long & Yoshitaka Ishii

Cancer and Inflammation Program, Leidos Biomedical Research, National Cancer Institute at Frederick, Frederick, Maryland, USA. Buyong Ma & Ruth Nussinov **Institute of Biomedical Research and Innovation, Kobe, Japan.** Minako Hoshi **Department of Anatomy and Developmental Biology, Graduate School of Medicine, Kyoto University, Kyoto, Japan.** Minako Hoshi **Sackler Institute of Molecular Medicine, Department of Human Genetics and Molecular Medicine, Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel.** Ruth Nussinov **Center for Structural Biology, University of Illinois at Chicago, Chicago, Illinois, USA.** Yoshitaka Ishii

Increasing evidence has suggested that formation and propagation of misfolded aggregates of 42-residue human amyloid β (Aβ(1–42)), rather than of the more abundant Aβ(1–40), provokes the Alzheimer's disease cascade. However, structural details of misfolded Aβ(1–42) have remained elusive. Here we present the atomic model of an Aβ(1–42) amyloid fibril, from solid-state NMR (ssNMR) data. It displays triple parallel-β-sheet segments that differ from reported structures of Aβ(1–40) fibrils. Remarkably, Aβ(1–40) is incompatible with the triple-β-motif, because seeding with Aβ(1–42) fibrils does not promote conversion of monomeric Aβ(1–40) into fibrils via cross-replication. ssNMR experiments suggest that C-terminal Ala42, absent in Aβ(1–40), forms a salt bridge with Lys28 to create a self-recognition molecular switch that excludes Aβ(1–40). The results provide insight into the Aβ(1–42)-selective self-replicating amyloid-propagation machinery in early-stage Alzheimer's disease.

Structural basis for amyloidogenic peptide recognition by sorLA

Nature Structural & Molecular Biology **22**, 199–206 (2015)

Institute for Protein Research, Osaka University, Suita, Japan. Yu Kitago, Masamichi Nagae, Zenzaburo Nakata, Shizuka Takagi-Niidome, Emiko Mihara & Junichi Takagi**Okazaki Institute for Integrative Bioscience, National Institutes of Natural Sciences, Okazaki, Japan.**Maho Yagi-Utsumi & Koichi

Kato**Graduate School of Pharmaceutical Sciences, Nagoya City University, Nagoya, Japan.**Maho Yagi-Utsumi & Koichi Kato **Graduate School of Medical Life Science, Yokohama City University, Yokohama, Japan.**

Terukazu Nogi

SorLA is a neuronal sorting receptor considered to be a major risk factor for Alzheimer's disease. We have recently reported that it directs lysosomal targeting of nascent neurotoxic amyloid-β (Aβ) peptides by directly binding Aβ. Here, we determined the crystal structure of the human sorLA domain responsible for Aβ capture, Vps10p, in an unbound state and in complex with two ligands. Vps10p assumes a ten-bladed β-propeller fold with a large tunnel at the center. An internal ligand derived from the sorLA propeptide bound inside the tunnel to extend the β-sheet of one of the propeller blades. The structure of the sorLA Vps10p– Aβ complex revealed that the same site is used. Peptides are recognized by sorLA Vps10p in redundant modes without strict dependence on a particular amino acid sequence, thus suggesting a broad specificity toward peptides with a propensity for β-sheet formation.

Indu:

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Nathen:

Understanding the mechanism of thermotolerance distinct from heat shock response through proteomic analysis of industrial strains of Saccharomyces cerevisiae.

Shui W[1], Xiong Y[2], Xiao W[3], Qi X[2], Zhang Y[3], Lin Y[2], Guo Y[2], Zhang Z[2], Wang Q[2], Ma Y[2].

Author information

Abstract

Saccharomyces cerevisiae has been intensively studied in responses to different environmental stresses such as heat shock through global omic analysis. However, the S. cerevisiae industrial strains with superior thermotolerance have not been explored in any proteomic studies for elucidating the tolerance mechanism. Recently a new diploid strain was obtained through evolutionary engineering of a parental industrial strain, and it exhibited even higher resistance to prolonged thermal stress. Herein, we performed iTRAQ-based quantitative proteomic analysis on both the parental and evolved industrial strains to further understand the mechanism of thermotolerant adaptation. Out of ~2600 quantifiable proteins from biological quadruplicates, 193 and 204 proteins were differentially regulated in the parental and evolved strains respectively during heat-stressed growth. The proteomic response of the industrial strains cultivated under prolonged thermal stress turned out to be substantially different from that of the laboratory strain exposed to sudden heat shock. Further analysis of transcription factors underlying the proteomic perturbation also indicated the distinct regulatory mechanism of thermotolerance. Finally, a co-chaperone Mdj1 and a metabolic enzyme Adh1 were selected to investigate their roles in mediating heat-stressed growth and ethanol production of yeasts. Our proteomic characterization of the industrial strain led to comprehensive understanding of the molecular basis of thermotolerance, which would facilitate future improvement in the industrially important trait of S. cerevisiae by rational engineering.