Lit Lunch - April 4th, 2014

INDU

1. Science. 2014 Feb 14;343(6172):795-8. doi: 10.1126/science.1247407.

An antifreeze protein folds with an interior network of more than 400 semi-clathrate waters.

Sun T(1), Lin FH, Campbell RL, Allingham JS, Davies PL.

Author information:
(1)Department of Biomedical and Molecular Sciences, Queen's University, Kingston, ON K7L 3N6, Canada.

Erratum in
Science. 2014 Feb 28;343(6174):969.

Comment in
Science. 2014 Feb 14;343(6172):743-4.

When polypeptide chains fold into a protein, hydrophobic groups are compacted in the center with exclusion of water. We report the crystal structure of an alanine-rich antifreeze protein that retains ~400 waters in its core. The putative ice-binding residues of this dimeric, four-helix bundle protein point inwards and coordinate the interior waters into two intersecting polypentagonal networks. The bundle makes minimal protein contacts between helices, but is stabilized by anchoring to the semi-clathrate water monolayers through backbone carbonyl groups in the protein interior. The ordered waters extend outwards to the protein surface and likely are involved in ice binding. This protein fold supports both the anchored-clathrate water mechanism of antifreeze protein adsorption to ice and the water-expulsion mechanism of protein folding.

PMID: 24531972 [PubMed - indexed for MEDLINE]

DAMIAN

1)
Carolina Pereira Tavares, Javier Vernal, Ricardo Alexandre Delena, Lorenzo Lamattina, Raul Cassia, Hernán Terenzi. S-nitrosylation influences the structure and DNA binding activity of AtMYB30 transcription factor from Arabidopsis thaliana.
(2014). BBA Proteomics. 1844 (2): 810

MYB proteins are a family of transcription factors that play an important role in plant development and regulatory defense processes. *Arabidopsis thaliana* MYB30 (AtMYB30), a member of this protein family, is involved in cell death processes during the hypersensitive response (HR) of plants. HR is characterized by a vast production of reactive oxygen species (ROS) and nitric oxide (NO). NO may thus influence the binding of AtMYB30 to DNA. In this work we evaluated the effect of NO on AtMYB30 DNA binding activity, and also in the protein structural properties. A fully active minimal DNA-binding domain (DBD) of AtMYB30 (residues 11–116) containing two cysteine residues (C49 and C53) was overexpressed and purified. Site-directed mutagenesis was used to obtain AtMYB30 DBD mutants C49A and C53A. The DNA binding activity of AtMYB30 DBD, and Cys single mutants is clearly inhibited upon incubation with a NO donor, and S-nitrosylation was confirmed by the biotin switch assay. Finally, in order to understand the mechanism of NO effect on AtMYB30 DNA binding activity we performed circular dichroism analysis, to correlate the observed protein function inhibition and a potential structural impairment on AtMYB30 DBD. Indeed, NO modification of C49 and C53 residues promotes a subtle modification on the secondary structure of this transcription factor. We thus

demonstrated, using various techniques, the *in vitro* effect of NO on AtMYB30 DBD, and thus the potential consequences of NO activity on plant metabolism influenced by this transcription factor.

2)
Juan C. Begara-Morales, Beatriz Sanchez-Calvo, Francisco Luque, Maria O Leyva- Perez, Marina Leterrier, Francisco J. Corpas*, Juan B. Barroso. Differential transcriptomic analysis by RNA-seq of GSNO-responsive genes between Arabidopsis roots and leaves.
(2014) Plant Cell Physiol doi: 10.1093/pcp/pcu044

S-nitrosoglutathione (GSNO) is a nitric oxide-derived molecule that can regulate protein function by a post-translational modification designated *S*-nitrosylation. GSNO has also been detected in different plant organs under physiological and stress conditions and it can also modulate gene expression. Arabidopsis plants 30 days old were grown under hydroponic conditions, and exogenous 1 mM GSNO was applied to the root systems for 3 h. Differential gene-expression analyses were made both in roots and in leaves by RNA sequencing (RNA-seq). A total of 3,263 genes were identified as being modulated by GSNO. Most of the genes identified were associated with the protection mechanism against stress situations, many of these having previously been identified as target genesof GSNO by array-based methods. However, new genes were identified, such as methionine sulfoxide reductase (MSR) in leaves or different miscellaneous RNA (*miscRNA*) in Arabidopsis roots. As a result, 1,945 GSNO-responsive genes expressed differently in leaves and roots were identified, and 114 of these corresponded exclusively to one of these organs. In summary, it is demonstrated that RNA-seq extends our knowledge of GSNO as a signalling molecule which differentially modulates gene expression in roots and leaves under non-stress conditions.

UMARU

1) Protein aggregation can inhibit clathrin-mediated endocytosis by chaperone competition

Anan Yua, Yoko Shibataa, Bijal Shahb, Barbara Calaminib, Donald C. Lob, and Richard I. Morimoto

Abstract

Protein conformational diseases exhibit complex pathologies linked to numerous molecular defects. Aggregation of a disease-associated protein causes the misfolding and aggregation of other proteins, but how this interferes with diverse cellular pathways is unclear. Here, we show that aggregation of neurodegenerative disease-related proteins (polyglutamine, huntingtin, ataxin-1, and superoxide dismutase-1) inhibits clathrin-mediated endocytosis (CME) in mammalian cells by aggregate-driven sequestration of the major molecular chaperone heat shock cognate protein 70 (HSC70), which is required to drive multiple steps of CME. CME suppression was also phenocopied by HSC70 RNAi depletion and could be restored by conditionally increasing HSC70 abundance. Aggregation caused dysregulated AMPA receptor internalization and also inhibited CME in primary neurons expressing mutant huntingtin, showing direct relevance of our findings to the pathology in neurodegenerative diseases. We propose that aggregate-associated chaperone competition leads to both gain-of-function and loss-of-function phenotypes as chaperones become functionally depleted from multiple clients, leading to the decline of multiple cellular processes. The inherent properties of chaperones place them at risk, contributing to the complex pathologies of protein conformational diseases

STEPHANIE

1) Int J Mol Sci. 2014 Mar 21;15(3):5063-78. doi: 10.3390/ijms15035063.

A chrysanthemum heat shock protein confers tolerance to abiotic stress.

Song A[1], Zhu X[2], Chen F[3], Gao H[4], Jiang J[5], Chen S[6].
Author information

Abstract

Heat shock proteins are associated with protection against various abiotic stresses. Here, the isolation of a chrysanthemum cDNA belonging to the HSP70 family is reported. The cDNA, designated CgHSP70, encodes a 647-residue polypeptide, of estimated molecular mass 70.90 kDa and pI 5.12. A sub-cellular localization assay indicated that the cDNA product is deposited in the cytoplasm and nucleus. The performance of Arabidopsis thaliana plants constitutively expressing CgHSP70 demonstrated that the gene enhances tolerance to heat, drought and salinity. When CgHSP70 was stably over-expressed in chrysanthemum, the plants showed an increased peroxidase (POD) activity, higher proline content and inhibited malondialdehyde (MDA) content. After heat stress, drought or salinity the transgenic plants were better able to recover, demonstrating CgHSP70 positive effect.

ELIZABETH

March 9

Molecular Cell: Alert 1 March-7 March

Polyphosphate Is a Primordial Chaperone Original Research Article

Pages 689-699

Michael J. Gray, Wei-Yun Wholey, Nico O. Wagner, Claudia M. Cremers, Antje Mueller-Schickert, Nathaniel T. Hock, Adam G. Krieger, Erica M. Smith, Robert A. Bender, James C.A. Bardwell, Ursula Jakob

Sjogren LL, Tanabe N, Lymperopoulos P, Khan NZ, Rodermel SR, Aronsson H, Clarke AK.
Quantitative analysis of the chloroplast molecular chaperone ClpC/Hsp93 in Arabidopsis reveals new insights into its localization, interaction with the Clp proteolytic core and functional importance.
J Biol Chem. 2014 Mar 5;. [Epub ahead of print]
PMID: 24599948 [PubMed - as supplied by publisher]

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ATP Requirement for Chloroplast Protein Import Is Set by the Km for ATP Hydrolysis of Stromal Hsp70 in Physcomitrella patens.
Plant Cell. 2014 Mar 4;. [Epub ahead of print]
PMID: 24596240 [PubMed - as supplied by publisher]

Reddy PS, Kavi Kishor PB, Seiler C, Kuhlmann M, Eschen-Lippold L, Lee J, Reddy MK, Sreenivasulu N.
Unraveling Regulation of the Small Heat Shock Proteins by the Heat Shock Factor HvHsfB2c in Barley: Its Implications in Drought Stress Response and Seed Development.
PLoS One. 2014;9(3):e89125.
PMID: 24594978 [PubMed - in process]

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Co-overexpression of two Heat Shock Factors results in enhanced seed longevity and in synergistic effects on seedling tolerance to severe dehydration and oxidative stress.
BMC Plant Biol. 2014 Mar 4;14(1):56. [Epub ahead of print]

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Small molecule probes to quantify the functional fraction of a specific protein in a cell with minimal folding equilibrium shifts.
Proc Natl Acad Sci U S A. 2014 Mar 3;. [Epub ahead of print]
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Differential transcriptomic analysis by RNA-seq of GSNO-responsive genes between Arabidopsis roots and leaves.
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Molecular Cell: Alert 3 March-9 March
Modulation of the Hsp90 Chaperone Cycle by a Stringent Client Protein Original Research Article
Oliver Robin Lorenz, Lee Freiburger, Daniel Andreas Rutz, Maike Krause, Bettina Karolina Zierer, Sara Alvira, Jorge Cuéllar, José María Valpuesta, Tobias Madl, Michael Sattler, Johannes Buchner

Journal of Photochemistry and Photobiology B: Biology: Alert 18 March-24 March
Photosynthesis: Limitations in Response to High Temperature Stress Original Research Article
Sonal Mathur, Anjana Jajoo

Journal of Plant Physiology: Alert 18 March-24 March
Potassium (K+) in plants
Ingo Dreyer

A Two-Step Process for Epigenetic Inheritance in *Arabidopsis* Original Research Article

Todd Blevins, Frédéric Pontvianne, Ross Cocklin, Ram Podicheti, Chinmayi Chandrasekhara, Satwica Yerneni, Chris Braun, Brandon Lee, Doug Rusch, Keithanne Mockaitis, Haixu Tang, Craig S. Pikaard

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High-throughput screen of natural product extracts in a yeast model of polyglutamine proteotoxicity.
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Global transcript and phenotypic analysis of yeast cells expressing Ssa1, Ssa2, Ssa3 or Ssa4 as sole source of cytosolic Hsp70-Ssa chaperone activity.

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Current Opinion in Biotechnology: Alert 20 March-26 March
Novel perspectives for the engineering of abiotic stress tolerance in plants Review Article
Julieta V Cabello, Anabella F Lodeyro, Matias D Zurbriggen

Cell: Alert 22 March-28 March
Differential Scales of Protein Quality Control Review Article
Suzanne Wolff, Jonathan S. Weissman, Andrew Dillin
Archives of Biochemistry and Biophysics
Chaperone-like activity of monomeric human 14-3-3ζ on different protein substrates Original Research Article
Nikolai N. Sluchanko, Svetlana G. Roman, Natalia A. Chebotareva, Nikolai B. Gusev

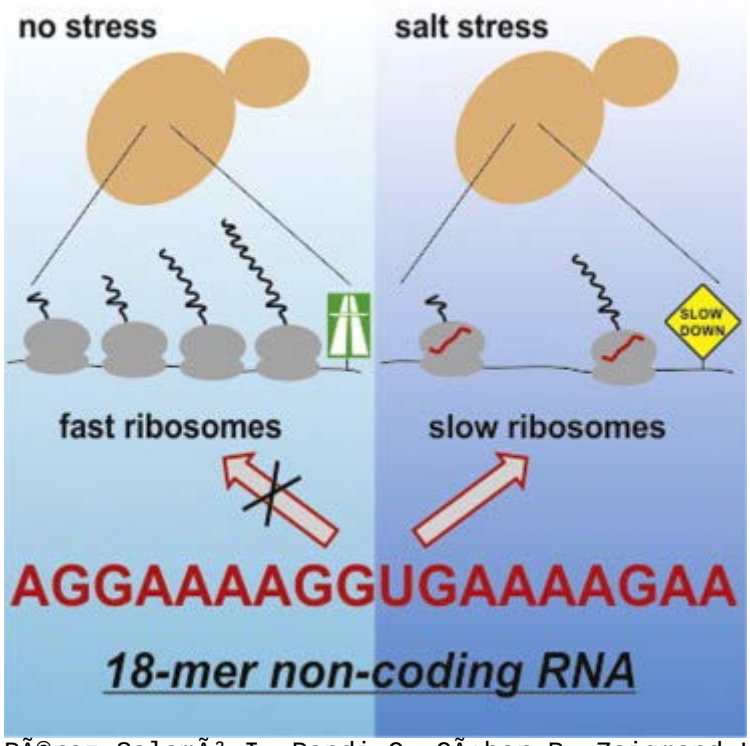
Molecular Cell: Alert 24 March-30 March

An mRNA-Derived Noncoding RNA Targets and Regulates the Ribosome

This study reveals the yeast ribosome as direct target for small regulatory ncRNAs
An 18-nt-long exon-derived RNA fragment from the *TRM10* locus binds to ribosomes
This 18-mer ncRNA inhibits global protein biosynthesis in vivo and in vitro
This translation attenuation is crucial for adaption under hyperosmotic stress

The structural and functional repertoire of small non-protein-coding RNAs (ncRNAs) is central for establishing gene regulation networks in cells and organisms. Here, we show that an mRNA-derived 18-nucleotide-long ncRNA is capable of downregulating translation in *Saccharomyces cerevisiae* by targeting the ribosome. This 18-mer ncRNA binds to polysomes upon salt stress and is crucial for efficient growth under hyperosmotic conditions. Although the 18-mer RNA originates from the *TRM10* locus, which encodes a tRNA methyltransferase, genetic analyses revealed the 18-mer RNA nucleotide sequence, rather than the mRNA-encoded enzyme, as the translation regulator. Our data reveal the

ribosome as a target for a small regulatory ncRNA and demonstrate the existence of a yet unkown mechanism of translation regulation. Ribosome-targeted small ncRNAs are found in all domains of life and represent a prevalent but so far largely unexplored class of regulatory molecules.



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Dynamical structure of Î±B-crystallin.
Prog Biophys Mol Biol. 2014 Mar 24;. [Epub ahead of print]

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Hierarchical Functional Specificity of Cytosolic Heat Shock Protein 70 (Hsp70) Nucleotide Exchange Factors in Yeast.
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J Biotechnol. 2014 Mar 22;. [Epub ahead of print]

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Proc Natl Acad Sci U S A. 2014 Jan 14;111(2):585-92.

Chemistry & Biology
New Articles in Press, 24 March-30 March 2014 rts

1. **Lassomycin, a Ribosomally Synthesized Cyclic Peptide, Kills *Mycobacterium tuberculosis* by Targeting the ATP-Dependent Protease ClpC1P1P2**

Phosphorylation of Heat Shock Protein 27 Antagonizes TNF-α induced HeLa cell apoptosis via Regulating TAK1 ubiquitination and activation of p38 and ERK signaling Original Research Article
Zhilin Qi, Lei Shen, Huiting Zhou, Yi Jiang, Lei Lan, Lan Luo, Zhimin Yin
The Plant Journal Content Alert (New Articles)
Trehalose metabolism in plants

John Edward Lunn, Ines Delorge, Carlos María Figueroa, Patrick Van Dijck and Mark Stitt
Physiologia Plantarum Content Alert (New Articles)
Advances in identification and validation of plant microRNAs and their target genes
Xin Sun, Yanping Zhang, Xudong Zhu, Nicholas Kibet Korir, Ran Tao, Chen Wang and Jinggui Fang
Plant, Cell & Environment Content Alert (New Articles)
Global reprogramming of transcription and metabolism in *Medicago truncatula* during progressive drought and after re-watering
JI-YI ZHANG, MARIA H. CRUZ DE CARVALHO, IVONE TORRES-JEREZ, YUN KANG, STACY N. ALLEN, DAVID V. HUHMAN, YUHONG TANG, JEREMY MURRAY, LLOYD W. SUMNER and MICHAEL K. UDVARDI
Journal of Agronomy and Crop Sci... Content Alert (New Articles)
Predicting Crop Yields with the Agricultural Reference Index for Drought
P. Woli, J. W. Jones, K. T. Ingram and G. Hoogenboom
Hofmann H.
Single-molecule spectroscopy of unfolded proteins and chaperonin action.
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Abscisic acid-induced nitric oxide and proline accumulation in independent pathways under water-deficit stress during seedling establishment in Medicago truncatula.
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Liu D, Sheng C, Gao S, Jiang W, Li J, Yao C, Chen H, Wu J, Chen S, Huang W.
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GarcÃa-GÃ³mez JJ, FernÃ¡ndez-Pevida A, Lebaron S, Rosado IV, Tollervey D, Kressler D, de la Cruz J.
Final Pre-40S Maturation Depends on the Functional Integrity of the 60S Subunit Ribosomal Protein L3.
PLoS Genet. 2014 Mar;10(3):e1004205.

KEITH

1) Lens Crystallin Modifications and Cataract in Transgenic Mice Overexpressing Acylpeptide Hydrolase*

THEJOURNALOFBIOLOGICALCHEMISTRY VOL.289,NO.13,pp.9039–9052,March28,2014

Puttur Santhoshkumar‡, Leike Xie‡, Murugesan Raju‡, Lixing Reneker‡, and K. Krishna Sharma‡§1

Departments of ‡Ophthalmology and §Biochemistry, University of Missouri, Columbia, Missouri 65212

The accumulation of crystallin fragments *in vivo* and their subsequent interaction with crystallins are responsible, in part, for protein aggregation in cataracts. Transgenic mice overex- pressing acylpeptide hydrolase (APH) specifically in the lens were prepared to test the role of protease in the generation and accumulation of peptides. Cataract development was seen at various postnatal days in the majority of mice expressing active APH (wt-APH). Cataract onset and severity of the cataracts cor- related with the APH protein levels. Lens opacity occurred when APH protein levels were >2.6% of the total lens protein and the specific activity, assayed using Ac-Ala-*p*-nitroanilide substrate, was >1 unit. Transgenic mice carrying inactive APH (mt-APH) did not develop cataract. Cataract development also correlated with N-terminal cleavage of the APH to generate a 57-kDa pro- tein, along with an increased accumulation of low molecular weight (LMW) peptides, similar to those found in aging human and cataract lenses. Nontransgenic mouse lens proteins incu- bated with purified wt-APH *in vitro* resulted in a >20% increase in LMW peptides. Crystallin modifications and cleavage were quite dramatic in transgenic mouse lenses with mature cataract. Affected lenses showed capsule rupture at the posterior pole, with expulsion of the lens nucleus and degenerating fiber cells. Our study suggests that the cleaved APH fragment might exert catalytic activity against crystallins, resulting in the accumula- tion of distinct LMW peptides that promote protein

aggregation in lenses expressing wt-APH. The APH transgenic model we developed will enable *in vivo* testing of the roles of crystallin fragments in protein aggregation.

2) Structure of the Rpn11–Rpn8 dimer reveals mechanisms of substrate deubiquitination during proteasomal degradation

Nature Structural & Molecular Biology **21**, 220–227 (2014)

Evan J Worden, Chris Padovani & Andreas Martin

California Institute for Quantitative Biosciences, University of California, Berkeley, Berkeley, California, USA.
Department of Molecular and Cell Biology, University of California, Berkeley, Berkeley, California, USA.

Polyubiquitin chains target protein substrates to the 26s proteasome, where they are removed by the deubiquitinase rpn11 to allow efficient substrate degradation. Despite rpn11's essential function during substrate processing, its detailed structural and biochemical characterization has been hindered by difficulties in purifying the isolated enzyme. Here
we report the 2.0-Å crystal structures of Zn^{2+}-free and Zn^{2+}-bound *Saccharomyces cerevisiae* rpn11 in an mPn-domain heterodimer with rpn8. the rpn11-rpn8 interaction occurs via two distinct interfaces that may be conserved in related mPn-domain complexes. our structural and mutational studies reveal that rpn11 lacks a conserved surface to bind the ubiquitin ile44 patch, does not interact with the moiety on the proximal side of the scissile isopeptide bond and exhibits no linkage specificity for ubiquitin cleavage. these findings explain how rpn11 functions as a promiscuous deubiquitinase for cotranslocational substrate deubiquitination during proteasomal degradation.

Yichen:

Proc Natl Acad Sci U S A. 2014 Mar 3. [Epub ahead of print]
Small molecule probes to quantify the functional fraction of a specific protein in a cell with minimal folding equilibrium shifts.

Liu Y1, Tan YL, Zhang X, Bhabha G, Ekiert DC, Genereux JC, Cho Y, Kipnis Y, Bjelic S, Baker D, Kelly JW.
Author information

Abstract

Although much is known about protein folding in buffers, it remains unclear how the cellular protein homeostasis network functions as a system to partition client proteins between folded and functional, soluble and misfolded, and aggregated conformations. Herein, we develop small molecule folding probes that specifically react with the folded and functional fraction of the protein of interest, enabling fluorescence-based quantification of this fraction in cell lysate at a time point of interest. Importantly, these probes minimally perturb a protein's folding equilibria within cells during and after cell lysis, because sufficient cellular chaperone/chaperonin holdase activity is created by rapid ATP depletion during cell lysis. The folding probe strategy and the faithful quantification of a particular protein's functional fraction are exemplified with retroaldolase, a de novo designed enzyme, and transthyretin, a nonenzyme protein. Our findings challenge the often invoked assumption that the soluble fraction of a client protein is fully folded in the cell. Moreover, our results reveal that the partitioning of destabilized retroaldolase and transthyretin mutants between the aforementioned conformational states is strongly influenced by cytosolic proteostasis network perturbations. Overall, our results suggest that applying a chemical folding probe strategy to other client proteins offers opportunities to reveal how the proteostasis network functions as a system to regulate the folding and function of individual client proteins in vivo.