Mary

Ectopic Expression of Plant RNA Chaperone Offering Multiple Stress Tolerance in E. coli.

Mol Biotechnol. 2017 Jan 30;.

Jabeen B, Naqvi SM, Mahmood T, Sultana T, Arif M, Khan F.

Members of the plant glycine-rich RNA-binding proteins (GR-RBPs) family have been reported in flowering, development, circadian rhythms, biotic and abiotic stresses. Particularly, GR-RBPs are reported to function as RNA chaperones, promoting growth and acclimation during cold shock. It is indispensable to further question the efficacy and mechanism of GR-RBPs under various environmental strains. Monitoring the expression of stress-regulated proteins under stress conditions has been a beneficial strategy to study their functional roles. In an effort to elucidate the *Nt*GR-RBP1 function, stress markers such as salinity, drought, low temperature and heat stresses were studied. The *NtGR-RBP1* gene was expressed in *E. coli* followed by the exposure to stress conditions. Recombinant *E. coli*expressing *Nt*GR-RBP1 were more tolerant to stresses, e.g., salinity, drought, cold and heat shock. Recombinants exhibited higher growth rates compared to control in spot assays. The tolerance was further confirmed by monitoring the growth in liquid culture assays. Cells expressing *Nt*GR-RBP1 under salt (500 mM NaCl), drought (20% PEG), cold (4 and 20 °C) and heat stresses (50 °C) had enhanced growing ability and better endurance. Our study supports the notion that the protective role of *Nt*GR-RBP1 may contribute to growth and survival during diverse environmental stresses.

Role of sHsps in organizing cytosolic protein aggregation and disaggregation.

Cell Stress Chaperones. 2017 Jan 24;. [Epub ahead of print]

Mogk A, Bukau B.

Abstract Small heat shock proteins (sHsps) exhibit an ATP- independent chaperone activity to prevent the aggregation of misfolded proteins in vitro. The seemingly conflicting pres- ence of sHsps in insoluble protein aggregates in cells obstructs a precise definition of sHsp function in proteostasis networks. Recent findings specify sHsp activities in protein quality con- trol systems. The sHsps of yeast, Hsp42 and Hsp26, interact with early unfolding intermediates of substrates, keeping them in a ready-to-refold conformation close to the native state. This activity facilitates substrate refolding by ATP- dependent Hsp70-Hsp100 disaggregating chaperones. Hsp42 can actively sequester misfolded proteins and promote their deposition at specific cellular sites. This aggregase activity represents a cytoprotective protein quality control strategy. The aggregase function of Hsp42 controls the formation of cytosolic aggregates (CytoQs) under diverse stress regimes and can be reconstituted in vitro, demonstrating that Hsp42 is necessary

and sufficient to promote protein aggregation. Substrates sequestered at CytoQs can be dissociated by Hsp70-Hsp100 disaggregases for subsequent triage between refolding and degradation pathways or are targeted for de- struction by selective autophagy termed proteophagy.

Alyssa

Structural Basis for the Interaction of a Human Small Heat Shock Protein with the 14-3-3 Universal Signaling Regulator

By interacting with hundreds of protein partners, 14-3-3 proteins coordinate vital cellular processes. Phosphorylation of the small heat shock protein, HSPB6, within its intrinsically disordered N-terminal domain activates its interaction with 14-3-3, ultimately triggering smooth muscle relaxation. After analyzing the binding of an HSPB6-derived phosphopeptide to 14-3-3 using isothermal calorimetry and X-ray crystallography, we have determined the crystal structure of the complete assembly consisting of the 14-3-3 dimer and full-length HSPB6 dimer and further characterized this complex in solution using fluorescence spectroscopy, small-angle X-ray scattering, and limited proteolysis. We show that selected intrinsically disordered regions of HSPB6 are transformed into well-defined conformations upon the interaction, whereby an unexpectedly asymmetric structure is formed. This structure provides the first atomic resolution snapshot of a human small HSP in functional state, explains how 14-3-3 proteins sequester their regulatory partners, and can inform the design of small-molecule interaction modifiers to be used as myorelaxants.

Minsoo

1. Plant Cell Environ. 2016 Dec 16. doi: 10.1111/pce.12884. [Epub ahead of print]

The occurrence and control of nitric oxide generation by the plant mitochondrial electron transport chain.

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The plant mitochondrial electron transport chain (ETC) is bifurcated such that electrons from ubiquinol are passed to oxygen via the usual cytochrome path or through alternative oxidase (AOX). We previously showed that knockdown of AOX in transgenic tobacco increased leaf concentrations of nitric oxide (NO), implying that an activity capable of generating NO had been effected. Here we identify the

potential source of this NO. Treatment of leaves with antimycin A (AA, Qi -site inhibitor of Complex III) increased NO amount more than treatment with myxothiazol (Myxo, Qo -site inhibitor) despite both being equally effective at inhibiting respiration. Comparison of nitrate-grown wild-type to AOX knockdown and overexpression plants showed a negative correlation between AOX amount and NO amount following AA. Further, Myxo fully negated the ability of AA to increase NO amount. With ammonium-grown plants, neither AA nor Myxo strongly increased NO amount in any plant line. When these leaves were supplied with nitrite alongside the AA or Myxo, then the inhibitor effects across lines mirrored that of nitrate-grown plants. Hence the ETC, likely the Q-cycle of Complex III generates NO from nitrite, and AOX reduces this activity by acting as a non-energy-conserving electron sink upstream of Complex III.

2. Nature. 2017 Feb 16;542(7641):367-371. doi: 10.1038/nature21362. Epub 2017 Feb 8.

C. elegans neurons jettison protein aggregates and mitochondria under neurotoxic stress.

Melentijevic I(1), Toth ML(1), Arnold ML(1), Guasp RJ(1), Harinath G(1), Nguyen KC(2), Taub D(3,)(4), Parker JA(5), Neri C(6), Gabel CV(3,)(4), Hall DH(2), Driscoll M(1).

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The toxicity of misfolded proteins and mitochondrial dysfunction are pivotal factors that promote age-associated functional neuronal decline and neurodegenerative disease. Accordingly, neurons invest considerable cellular resources in chaperones, protein degradation, autophagy and mitophagy to maintain proteostasis and mitochondrial quality. Complicating the challenges of neuroprotection, misfolded human disease proteins and mitochondria can move into neighbouring cells via unknown mechanisms, which may promote pathological spread. Here we show that adult neurons from Caenorhabditis elegans extrude large (approximately 4 μm) membrane-surrounded vesicles called exophers that can contain protein aggregates and organelles. Inhibition of chaperone expression, autophagy or the proteasome, in addition to compromising mitochondrial quality, enhances the production of exophers. Proteotoxically stressed neurons that generate exophers subsequently function better than similarly stressed neurons

that did not produce exophers. The extruded exopher transits through surrounding tissue in which some contents appear degraded, but some non-degradable materials can subsequently be found in more remote cells, suggesting secondary release. Our observations suggest that exopher-genesis is a potential response to rid cells of neurotoxic components when proteostasis and organelle function are challenged. We propose that exophers are components of a conserved mechanism that constitutes a fundamental, but formerly unrecognized, branch of neuronal proteostasis and mitochondrial quality control, which, when dysfunctional or diminished with age, might actively contribute to pathogenesis in human neurodegenerative disease and brain ageing.

Keith

Mechanistic basis for the recognition of a misfolded protein by the molecular chaperone Hsp90.

Nat Struct Mol Biol. 2017 Feb 20.

Oroz J1, Kim JH1, Chang BJ2, Zweckstetter M1,2,3.

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3Department of Neurology, University Medical Center Göttingen, University of Göttingen, Göttingen, Germany.

The critical toxic species in over 40 human diseases are misfolded proteins. Their interaction with molecular chaperones such as Hsp90, which preferentially interacts with metastable proteins, is essential for the blocking of disease progression. Here we used nuclear magnetic resonance (NMR) spectroscopy to determine the three-dimensional structure of the misfolded cytotoxic monomer of the amyloidogenic human protein transthyretin, which is characterized by the release of the C-terminal β-strand and perturbations of the A-B loop. The misfolded transthyretin monomer, but not the wild-type protein, binds to human Hsp90. In the bound state, the Hsp90 dimer predominantly populates an open conformation, and transthyretin retains its globular structure. The interaction surface for the transthyretin monomer comprises the N-terminal and middle domains of Hsp90 and overlaps with that of the Alzheimer's-disease-related protein tau. Taken together, the data suggest that Hsp90 uses a mechanism for the recognition of aggregation-prone proteins that is largely distinct from those of other Hsp90 clients.

Proteomic analysis of exported chaperone/co-chaperone complexes of *P. falciparum* reveals an array of complex protein-protein interactions

Sci Rep. 2017 Feb 20;7:42188.

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Malaria parasites modify their human host cell, the mature erythrocyte. This modification is mediated by a large number of parasite proteins that are exported to the host cell, and is also the underlying cause for the pathology caused by malaria infection. Amongst these proteins are many Hsp40 co-chaperones, and a single Hsp70. These proteins have been implicated in several processes in the host cell, including a potential role in protein transport, however the further molecular players in this process remain obscure. To address this, we have utilized chemical cross-linking followed by mass spectrometry and immunoblotting to isolate and characterize proteins complexes containing an exported Hsp40 (PFE55), and the only known exported Hsp70 (PfHsp70x). Our data reveal that both of these proteins are contained in high molecular weight protein complexes. These complexes are found both in the infected erythrocyte, and within the parasite-derived compartment referred to as the parasitophorous vacuole. Surprisingly, our data also reveal an association of PfHsp70x with components of PTEX, a putative protein translocon within the membrane of the parasitophorous vacuole. Our results suggest that the P. falciparum- infected human erythrocyte contains numerous high molecular weight protein complexes, which may potentially be involved in host cell modification.

Elizabeth

February 28
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Lysine acetyltransferase NuA4 and acetyl-CoA regulate glucose-deprived stress granule formation in Saccharomyces cerevisiae.
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Systematic deletion of the ER lectin chaperone genes reveals their roles in vegetative growth and male gametophyte development in Arabidopsis (pages 972–983)

Kien Van Vu, Ngoc Trinh Nguyen, Chan Young Jeong, Yong-Hwa Lee, Hojoung Lee and Suk-Whan Hong
Version of Record online: 8 FEB 2017 | DOI: 10.1111/tpj.13435
Significance Statement
Calnexin (CNX) and calreticulin (CRT) are homologous lectin chaperones in the endoplasmic reticulum (ER) that facilitate glycoprotein folding and retain folding intermediates to prevent their transit via the secretory pathway. The role of the CNX/CRT cycle in growth and development under normal growth conditions is not well understood. Here we show that CNX and CRT play essential and overlapping roles during vegetative growth and male gametophyte development in *Arabidopsis*.

Untangling the genetics from the epigenetics in pancreatic cancer metastasis - pp323 - 324
Christopher R Vakoc & David A Tuveson doi:10.1038/ng.3798
Comparative genomic analyses of primary tumors and metastases within individuals with pancreatic cancer have exposed the complex clonal dynamics that underlie the dissemination of cancer cells to distant sites. Recent studies implicate non-genetic mechanisms in this process, particularly fluctuations in chromatin states and metabolism, which can endow rare cells within a primary tumor with metastatic potential.
Full Text - Untangling the genetics from the epigenetics in pancreatic cancer metastasis | PDF (1,598 KB) - Untangling the genetics from the epigenetics in pancreatic cancer metastasis
See also: Article by Makohon-Moore et al. | Article by McDonald et al.

Nature Reviews Molecular Cell Biology contents March 2017 Volume 18 Number 3 pp 137-210
Organelle dynamics: Connections, connections, connections
p139 | doi:10.1038/nrm.2017.14
Three independent studies in human cell lines reveal new functions of membrane contact sites between the endoplasmic reticulum (ER) and mitochondria and between the ER and peroxisomes.
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March 2017 Vol 18 No 3
RNA modifications and structures cooperate to guide RNA–protein interactions
Cole J.T. Lewis, Tao Pan & Auinash Kalsotra Abstract Full text PDF (658KB)

February 2017 Vol 18 No 2
The roles of RNA processing in translating genotype to phenotype
Kassie S. Manning & Thomas A. Cooper Abstract Full text PDF (820KB)

January 2017 Vol 18 No 1
Post-transcriptional gene regulation by mRNA modifications
Boxuan Simen Zhao, Ian A. Roundtree & Chuan He Abstract Full text PDF (575KB)

January 2017 Vol 18 No 1
Alternative polyadenylation of mRNA precursors
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