Lit Lunch 4_24_15

Elizabeth:

April 20

Nature Chemical Biology

Mechanism of photoprotection in the cyanobacterial ancestor of plant antenna proteins - pp287 - 291
Hristina Staleva, Josef Komenda, Mahendra K Shukla, Václav Šlouf, Radek Kaňa, Tomáš Polívka & Roman Sobotka
Light-harvesting complexes (LHCs) manage energy flux into photosynthesis and dissipate excess light energy. The demonstration of dissipative energy transfer from chlorophyll-*a* to β-carotene in cyanobacterial high light–inducible proteins provides a mechanistic model for similar processes in LHCs.
See also: News and Views by Kirilovsky

Coordinated gripping of substrate by subunits of a AAA+ proteolytic machine - pp201 - 206
Ohad Iosefson, Andrew R Nager, Tania A Baker & Robert T Sauer
The construction of ClpX hexamers containing variable numbers and configurations of wild-type and grip-defective pore loops supports a model of concurrent loop movement that ensures substrate unfolding and translocation.

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
Noelia Foresi, Martín L. Mayta, Anabella F. Lodeyro, Denise Scuffi, Natalia Correa-Aragunde, Carlos García-Mata, Claudia Casalongué, Néstor Carrillo and Lorenzo Lamattina
Accepted manuscript online: 16 APR 2015 07:16AM EST | DOI: 10.1111/tpj.12852

Opposing effects of folding and assembly chaperones on evolvability of Rubisco - pp148 - 155
Paulo Durão, Harald Aigner, Péter Nagy, Oliver Mueller-Cajar, F Ulrich Hartl & Manajit Hayer-Hartl
doi:10.1038/nchembio.1715
Although nonspecific chaperones such as GroEL can increase evolvability by helping slightly destabilized mutants, a dedicated assembly chaperone decreases evolvability of the CO_2 fixation enzyme Rubisco, providing insights into Rubisco's poor catalytic power.

Nature Chemical Biology |

A proton relay enhances H_2O_2 sensitivity of GAPDH to facilitate metabolic adaptation
David Peralta, Agnieszka K Bronowska, Bruce Morgan, Éva Dóka, Koen Van Laer, Péter Nagy, Frauke Gräter & Tobias P Dick
Nature Chemical Biology 11,156–163 (2015) PDF
Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) is sensitive to reversible oxidative inactivation by hydrogen peroxide (H_2O_2). Here we show that H_2O_2 reactivity of the active site thiolate (C152) is catalyzed by a previously unrecognized mechanism based on a dedicated proton relay promoting leaving group departure. Disruption of the peroxidatic reaction mechanism does not affect the glycolytic activity of GAPDH. Therefore, specific and separate mechanisms mediate the reactivity of the same thiolate nucleophile toward H_2O_2 and glyceraldehyde 3-phosphate, respectively. The generation of mutants in which the glycolytic and peroxidatic activities of GAPDH are comprehensively uncoupled allowed for a direct assessment of the physiological relevance of GAPDH H_2O_2 sensitivity. Using yeast strains in which wild-type GAPDH was replaced with H_2O_2-insensitive mutants retaining full glycolytic activity, we demonstrate that H_2O_2 sensitivity of GAPDH is a key component of the cellular adaptive response to increased H_2O_2 levels.

Enzyme regulation: A thiol switch opens the gate - pp4 – 5
doi:10.1038/nchembio.1698
AAA+ proteases are quality control machineries consisting of substrate-binding ATPase modules for protein unfolding and a proteolytic chamber. New research now shows a redox switch in the *Escherichia coli* Lon protease that controls this process, widening the exit pore and activating proteolysis during transition from anaerobic to aerobic environments.
Full Text - Enzyme regulationA thiol switch opens the gate | PDF (552 KB) - Enzyme regulationA thiol switch opens the gate

See also: Article by Nishii et al.

Cell, Volume 159, Issue 5, 20 November 2014, Pages 1188-1199
A Widespread Glutamine-Sensing Mechanism in the Plant Kingdom

The Plant Journal Content Alert (New Articles)
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
Noelia Foresi, Martín L. Mayta, Anabella F. Lodeyro, Denise Scuffi, Natalia Correa-Aragunde, Carlos García-Mata, Claudia Casalongué, Néstor Carrillo and Lorenzo Lamattina
Accepted manuscript online: 16 APR 2015 07:16AM EST | DOI: 10.1111/tpj.12852

Journal of Evolutionary Biology Content Alert (New Articles)
***E. coli* populations in unpredictably fluctuating environments evolve to face novel stresses through enhanced efflux activity** Shraddha Madhav Karve, Sachit Daniel, Yashraj Deepak Chavhan, Abhishek Anand, Somendra Singh Kharola and Sutirth Dey

There is considerable understanding about how laboratory populations respond to predictable (constant or deteriorating-environment) selection for single environmental variables like temperature or pH. However, such insights may not apply when selection environments comprise multiple variables that fluctuate unpredictably, as is common in nature. To address this issue, we grew replicate laboratory populations of *E. coli* in nutrient broth whose pH and concentrations of salt (NaCl) and hydrogen peroxide (H_2O_2) were randomly changed daily. After ~170 generations, the fitness of the selected populations had not increased in any of the three selection environments. However, these selected populations had significantly greater fitness in four novel environments which have no known fitness-correlation with tolerance to pH, NaCl or H_2O_2. Interestingly, contrary to expectations, hypermutators did not evolve. Instead, the selected populations evolved an increased ability for energy dependent efflux activity that might enable them to throw out toxins, including antibiotics, from the cell at a faster rate. This provides an alternate mechanism for how evolvability can evolve in bacteria and potentially lead to broad-spectrum antibiotic resistance, even in the absence of prior antibiotic exposure. Given that environmental variability is increasing in nature, this might have serious consequences for public-health.

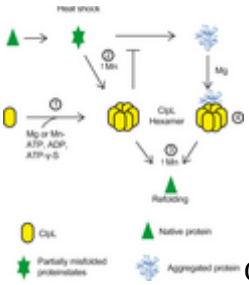
Analytical Biochemistry: Alert 10 April-16 April
Using photosystem I as a reporter protein for 13C analysis in a coculture containing cyanobacterium and a heterotrophic bacterium *Pages 86-88* Le You, Haijun Liu, Robert E. Blankenship, Yinjie J. Tang

Nature Reveiws in Microbiology - May
Microbiome: Taking advantage of quorum sensing p252 | doi:10.1038/nrmicro3477
A new study shows how altering the levels of quorum sensing signals can modulate the composition of the antibiotic-treated gut microbiota. **PDF**

Antimicrobials: Targeting of *C. difficile* made easy p250 | doi:10.1038/nrmicro3481
A new study describes the development of a modified bacteriocin that specifically targets and kills the major nosocomial pathogen *Clostridium difficile*. **PDF**

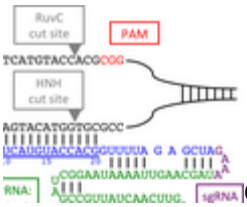
Recent functional insights into the role of (p)ppGpp in bacterial physiology
Vasili Hauryliuk et al. p298 | doi:10.1038/nrmicro3448
In this Review, Gerdes and colleagues discuss the multifaceted alarmones guanosine tetraphosphate and guanosine pentaphosphate (collectively referred to as (p)ppGpp) and their functions in the regulation of bacterial physiology, including their synthesis and degradation, as well as their role in transcriptional regulation, in GTP biosynthesis and in the formation of bacterial persisters. Abstract | Full Text | **PDF**

FEBS Journal Content Alert: 282, 8 (April 2015)
ClpL is a chaperone without auxiliary factors (pages 1352–1367)
Sang-Sang Park, Hyog-Young Kwon, Thao Dang-Hien Tran, Moo-Hyun Choi, Seung-Ha Jung, Sangho Lee, David E. Briles and Dong-Kwon Rhee
Article first published online: 27 FEB 2015 | DOI: 10.1111/febs.13228



Chaperones are pivotal players in cellular protein homeostasis. Caseinolytic protease L (ClpL) from the opportunistic pathogenic bacterium *Streptococcus mutans* is member of the heat shock protein 100 (HSP100) family. ClpL homologues were known to require a co-chaperone such as DnaK or Hsp70. Park *et al*. have shown in their recent paper that ATP-dependent refolding, holdase and disaggregation activity of *Streptococcus* ClpL is independent of co-chaperone presence. Mn^{2+} ions enhance activity relative to Mg^{2+}, which could be significant for respiratory tract colonization and virulence because Mn^{2+} ions are abundant in salvia.
This article is accompanied by a podcast, listen now. Or listen in iTunes.

Genetic screens and functional genomics using CRISPR/Cas9 technology (pages 1383–1393)
Ella Hartenian and John G. Doench
Article first published online: 16 MAR 2015 | DOI: 10.1111/febs.13248



CRISPR/Cas9 technology represents the newest tool for genetic screens, allowing unprecedented flexibility, speed, and accuracy for functionally characterizing the genomes of a wide-variety of organisms. This review focuses on the latest developments and current challenges of this exciting new technology, with an emphasis on its practical application to discover gene function.

Physiologia Plantarum Content Alert: 154, 1 (May 2015)
Phi-class glutathione-*S*-transferase is involved in *Dn1*-mediated resistance (pages 1–12)
Thia Schultz, Leon van Eck and Anna-Maria Botha
Article first published online: 28 OCT 2014 | DOI: 10.1111/ppl.12284

A proteomic analysis of rice seed germination as affected by high temperature and ABA treatment (pages 142–161)
Shu-Jun Liu, Heng-Heng Xu, Wei-Qing Wang, Ni Li, Wei-Ping Wang, Ian Max Møller and Song-Quan Song
Article first published online: 5 NOV 2014 | DOI: 10.1111/ppl.12292

Journal of Agronomy and Crop Scienc... Content Alert: 201, 3 (June 2015)
Impact of High Night-Time and High Daytime Temperature Stress on Winter Wheat (pages 206–218)
S. Narayanan, P. V. V. Prasad, A. K. Fritz, D. L. Boyle and B. S. Gill
Article first published online: 29 AUG 2014 | DOI: 10.1111/jac.12101

Reddy PS, Sharma KK, Vadez V, Reddy MK.
Molecular Cloning and Differential Expression of Cytosolic Class I Small Hsp Gene Family in Pennisetum glaucum (L.).
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Redox-dependent chaperone/peroxidase function of 2-Cys-Prx from the cyanobacterium Anabaena PCC7120: role in oxidative stress tolerance.
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Acta Crystallogr D Biol Crystallogr. 2015 Apr;71(Pt 4):800-8. PMID: 25849391 [PubMed - in process]

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Individual and Collective Contributions of Chaperoning and Degradation to Protein Homeostasis in E.Â coli.
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Overexpression of Small Heat Shock Protein Enhances Heat- and Salt-Stress Tolerance of Bifidobacterium longum NCC2705.
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Chemistry & Biology: Alert 18 April-24 April
Molecular Networking and Pattern-Based Genome Mining Improves Discovery of Biosynthetic Gene Clusters and their Products from *Salinispora* Species Original Research Article *Pages 460-471*
Katherine R. Duncan, Max Crusemann, Anna Lechner, Anindita Sarkar, Jie Li, Nadine Ziemert, Mingxun Wang, Nuno Bandeira, Bradley S. Moore, Pieter C. Dorrestein, Paul R. Jensen
•Pattern-based genome mining was applied to 35 *Salinispora* strains
•Molecular networking facilitated new compound discovery
•The quinomycin-type depsipeptide retimycin A was characterized

Genome sequencing has revealed that bacteria contain many more biosynthetic gene clusters than predicted based on the number of secondary metabolites discovered to date. While this biosynthetic reservoir has fostered interest in new tools for natural product discovery, there remains a gap between gene cluster detection and compound discovery. Here we apply molecular networking and the new concept of pattern-based genome mining to 35 *Salinispora* strains, including 30 for which draft genome sequences were either available or obtained for this study. The results provide a method to simultaneously compare large numbers of complex microbial extracts, which facilitated the identification of media components, known compounds and their derivatives, and new compounds that could be prioritized for structure elucidation. These efforts revealed considerable metabolite diversity and led to several molecular family-gene cluster pairings, of which the quinomycin-type depsipeptide retimycin A was characterized and linked to gene cluster NRPS40 using pattern-based bioinformatic approaches.

Cell: Alert 18 April-24 April

A Primer to Single-Particle Cryo-Electron Microscopy Review Article *Pages 438-449*
Yifan Cheng, Nikolaus Grigorieff, Pawel A. Penczek, Thomas Walz

Single-Particle Cryo-EM at Crystallographic Resolution Review Article *Pages 450-457*
Yifan Cheng

Andreas Mayer, Julia di Iulio, Seth Maleri, Umut Eser, Jeff Vierstra, Alex Reynolds, Richard Sandstrom, John A. Stamatoyannopoulos, L. Stirling Churchman
Native Elongating Transcript Sequencing Reveals Human Transcriptional Activity at Nucleotide Resolution *Cell, Volume 161, Issue 3, 23 April 2015, Pages 541-554* **PDF (3669 K)**

Andreas Mayer, Julia di Iulio, Seth Maleri, Umut Eser, Jeff Vierstra, Alex Reynolds, Richard Sandstrom, John A. Stamatoyannopoulos, L. Stirling Churchman
Native Elongating Transcript Sequencing Reveals Human Transcriptional Activity at Nucleotide Resolution
Cell, Volume 161, Issue 3, 23 April 2015, Pages 541-554 PDF (3669 K)

The Plant Journal Content Alert (New Articles)
Two *Chlamydomonas* OPR proteins stabilize chloroplast mRNAs encoding small subunits of photosystem II and cytochrome b_6f Fei Wang, Xenie Johnson, Marina Cavaiuolo, Alexandra-Viola Bohne, Joerg Nickelsen and Olivier Vallon Accepted manuscript online: 21 APR 2015 08:11AM EST | DOI: 10.1111/tpj.12858

HSP33 in eukaryotes – an evolutionary tale of a chaperone adapted to photosynthetic organisms
Na'ama Segal and Michal Shapira
Accepted manuscript online: 20 APR 2015 12:54AM EST | DOI: 10.1111/tpj.12855

Chromatin remodelling during male gametophyte development
Michael Borg and Frédéric Berger
Accepted manuscript online: 20 APR 2015 12:53AM EST | DOI: 10.1111/tpj.12856

Physiologia Plantarum Content Alert (New Articles)
Stress memory induced transcriptional and metabolic changes of perennial ryegrass (*Lolium perenne*) in response to salt stress Tao Hu, Yupei Jin, Huiying Li, Erick Amombo and Jinmin Fu
Accepted manuscript online: 23 APR 2015 01:42AM EST | DOI: 10.1111/ppl.12342

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Small heat shock protein 20 (Hsp20) facilitates nuclear import of protein kinase D 1 (PKD1) during cardiac hypertrophy.
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Cytoplasmic Dynein Is Required for the Spatial Organization of Protein Aggregates in Filamentous Fungi.
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Foresi N, Mayta ML, Lodeyro AF, Scuffi D, Correa-Aragunde N, GarcÃa-Mata C, CasalonguÃ© C, Carrillo N, Lamattina L.
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.
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MonzÃ³n GC, Regente M, Pinedo M, Lamattina L, de la Canal L.
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Subunit asymmetry and roles of conformational switching in the hexameric AAA+ ring of ClpX.
Nat Struct Mol Biol. 2015 Apr 13;. PMID: 25866879 [PubMed - as supplied by publisher]

Damian:

Nitric oxide synthase in innate and adaptive immunity: an update

Christian Bogdan

Trends in Immunology

Volume 36, Issue 3, March 2015, Pages 161–178

Stephanie:

TIBS:

Folding upon phosphorylation: translational regulation by a disorder-to-order transition

Lauren Ann Metskas[1, 2],

Elizabeth Rhoades[1, 2]

Show moredoi:10.1016/j.tibs.2015.02.007 Get rights and content

4E binding proteins (4E-BPs) play an important role in the regulation of translation by binding to eukaryotic translation initiation factor 4E (eIF4E) and inhibiting assembly of the eIF4F complex. While phosphorylation of 4E-BPs is known to disrupt their binding to eIF4E, the mechanism by which this occurs has been unclear. In a recent study, Forman-Kay and coworkers demonstrate that this mechanism is primarily structure-based: phosphorylation of 4E-BPs results in a disorder-to-order transition, bringing them from their binding-competent disordered state to a folded state incompatible with eIF4E binding.

➔ For Damian: From Molecular Plant: Nitric Oxide: A multi-tasked Signaling Gas in Plants – Domingos et. Al

Indu:

1: Halstead JM, Lionnet T, Wilbertz JH, Wippich F, Ephrussi A, Singer RH, Chao JA. Translation. An RNA biosensor for imaging the first round of translation from single cells to living animals. Science. 2015 Mar 20;347(6228):1367-671. doi: 10.1126/science.aaa3380. PubMed PMID: 25792328.

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Minsoo:

1. Plant Cell Physiol. 2015 Apr;56(4):790-802.

S-Nitrosoglutathione Reductase-Modulated Redox Signaling Controls Sodic Alkaline Stress Responses in Solanum lycopersicum L.

Gong B(1), Wen D(1), Wang X(1), Wei M(1), Yang F(1), Li Y(1), Shi Q(2).

Author information:

(1)State Key Laboratory of Crop Biology, Scientific Observing and Experimental Station of Environment Controlled Agricultural Engineering in Huang-Huai-Hai Region, Ministry of Agriculture, PR China; College of Horticulture Science and Engineering, Shandong Agricultural University, Tai'an, 271018, PR China. (2)State Key Laboratory of Crop Biology, Scientific Observing and Experimental Station of Environment Controlled Agricultural Engineering in Huang-Huai-Hai Region, Ministry of Agriculture, PR China; College of Horticulture Science and Engineering, Shandong Agricultural University, Tai'an, 271018, PR China

qhshi@sdau.edu.cn.

S-Nitrosoglutathione reductase (GSNOR) plays an important role in regulating nitric oxide (NO) and S-nitrosothiol (SNO) homeostasis, and is therefore involved in the modulation of processes mediated by reactive nitrogen species (RNS).

Although RNS have emerged as a key component in plant response to abiotic stress, knowledge of their regulation by GSNOR under alkaline stress was lacking. In this study, **metabolic regulation of NO and SNOs was investigated in tomato plants of the wild type (WT), GSNOR overexpression lines (OE-1/2) and GSNOR suppression lines (AS-1/2) grown under either control conditions or sodic alkaline stress.** Phenotype, photosynthesis, reactive oxygen species (ROS) metabolism, Na(+)-K(+) homeostasis and expression of genes encoding ROS scavenging, Na(+) detoxification and programmed cell death (PCD) were also analyzed. Compared with WT lines, **OE-1/2 lines were alkaline tolerant, while AS-1/2 lines were alkaline sensitive**. In **AS-1/2 lines**, although genetic expression of Na(+) detoxification was activated by GSNOR-regulated NO and ROS signaling, **excess RNS and ROS accumulation also led to serious oxidative stress and induced PCD**. In contrast, **overexpression of GSNOR significantly increased ROS scavenging efficiency.** Thus, it seemed that increasing alkaline tolerance via GSNOR overexpression in tomato was attributed to the regulation of redox signaling including RNS and ROS.

2. Proc Natl Acad Sci U S A. 2015 Mar 17;112(11)

Thioredoxin, a master regulator of the tricarboxylic acid cycle in plant mitochondria.

Daloso DM(1), Müller K(2), Obata T(2), Florian A(2), Tohge T(2), Bottcher A(2),

Riondet C(3), Bariat L(3), Carrari F(4), Nunes-Nesi A(5), Buchanan BB(6),

Reichheld JP(7), Araújo WL(8), Fernie AR(9).

Author information:

(1)Max-Planck-Institut für Molekulare Pflanzenphysiologie,14476 Potsdam-Golm,

Germany; Max Planck Partner Group at the Departamento de Biologia Vegetal,

Universidade Federal de Viçosa, 36570-900 Viçosa, MG, Brazil;

(9)Max-Planck-Institut für Molekulare Pflanzenphysiologie,14476 Potsdam-Golm, Germany; view@berkeley.edu

jpr@univ-perp.fr wlaraujo@ufv.br fernie@mpimp-golm.mpg.de.

Plant mitochondria have a fully operational tricarboxylic acid (TCA) cycle that plays a central role in generating ATP and providing carbon skeletons for a range of biosynthetic processes in both heterotrophic and photosynthetic tissues. The cycle enzyme-encoding genes have been well characterized in terms of transcriptional and effector-mediated regulation and have also been subjected to reverse genetic analysis. However, despite this wealth of attention, a central question remains unanswered: "**What regulates flux through this pathway in vivo**?" Previous proteomic experiments with Arabidopsis discussed below have revealed that **a number of mitochondrial enzymes, including members of the TCA cycle and affiliated pathways, harbor thioredoxin (TRX)-binding sites and are potentially redox-regulated**. We have followed up on this possibility and found TRX to be a redox-sensitive mediator of TCA cycle flux. In this investigation, we first **characterized, at the enzyme and metabolite levels, mutants of the mitochondrial TRX pathway in Arabidopsis: the NADP-TRX reductase a and b double mutant (ntra ntrb) and the mitochondrially located thioredoxin o1 (trxo1) mutant.** These studies were followed by a comparative evaluation of the redistribution of isotopes when (13)C-glucose, (13)C-malate, or (13)C-pyruvate was provided as a substrate to leaves of mutant or WT plants. In a complementary approach, we evaluated the in vitro activities of a range of TCA cycle and associated enzymes under varying redox states. The combined dataset suggests that **TRX may deactivate both mitochondrial succinate dehydrogenase and fumarase and activate the cytosolic ATP-citrate lyase in vivo**, acting as a direct regulator of carbon flow through the TCA cycle and providing a mechanism for the coordination of cellular function.

Alternative approach to protein structure prediction based on sequential similarity of physical properties

1. Yi He[a], S. Rackovsky[a,b], Yanping Yin[a], and Harold A. Scheraga[a,1]

Abstract

The relationship between protein sequence and structure arises entirely from amino acid physical properties. An alternative method is therefore proposed to identify homologs in which residue equivalence is based exclusively on the pairwise physical property similarities of sequences. This approach, the property factor method (PFM), is entirely different from those in current use. A comparison is made between our method and PSI BLAST. We demonstrate that traditionally defined sequence similarity can be very low for pairs of sequences (which therefore cannot be identified using PSI BLAST), but similarity of physical property distributions results in almost identical 3D structures. The performance of PFM is shown to be better than that of PSI BLAST when sequence matching is comparable, based on a comparison using targets from CASP10 (89 targets) and CASP11 (51 targets). It is also shown that PFM outperforms PSI BLAST in informatically challenging targets.

Angela:

BMC Biology

snoRNAs are a novel class of biologically relevant Myc targets

Eva K Herter12, **Maria Stauch**12, **Maria Gallant**12, **Elmar Wolf**12, **Thomas Raabe**3 and **Peter Gallant**12*

- *Corresponding author: Peter Gallant peter.gallant@biozentrum.uni-wuerzburg.de.

BMC Biology 2015, **13**:25 doi:10.1186/s12915-015-0132-6
Published: 16 April 2015

Background Myc proteins are essential regulators of animal growth during normal development, and their deregulation is one of the main driving factors of human malignancies. They function as transcription factors that (in vertebrates) control many growth- and proliferation-associated genes, and in some contexts contribute to global gene regulation. Results We combine ChIPseq and RNAseq approaches in Drosophila tissue culture cells to identify a core set of less than 500 Myc target genes, whose salient function resides in the control of ribosome biogenesis. Amongst these genes we find the non-coding snoRNA genes as a large novel class of Myc targets. All assayed snoRNAs are affected by Myc, and many of them are subject to direct transcriptional activation by Myc, both in Drosophila and in vertebrates. The loss of snoRNAs impairs growth during normal development, whereas their overexpression increases tumor mass in a model for neuronal tumors. Conclusions This work shows that Myc acts as a master regulator of snoRNP biogenesis. In addition, in combination with recent observations of snoRNA involvement in human cancer, it raises the possibility that Myc's transforming effects are partially mediated by this class of non-coding transcripts.

Review

Mitophagy and the mitochondrial unfolded protein response in neurodegeneration and bacterial infection

Mark W Pellegrino1 and **Cole M Haynes**12*

- *Corresponding author: Cole M Haynes haynesc@mskcc.org

BMC Biology 2015, **13**:22 doi:10.1186/s12915-015-0129-1
The electronic version of this article is the complete one and can be found online at:http://www.biomedcentral.com/1741-7007/13/22
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Mitochondria are highly dynamic and structurally complex organelles that provide multiple essential metabolic functions. Mitochondrial dysfunction is associated with neurodegenerative conditions such as Parkinson's disease, as well as bacterial infection. Here, we explore the roles of mitochondrial autophagy (mitophagy) and the mitochondrial unfolded protein response (UPR^{mt}) in the response to mitochondrial dysfunction, focusing in particular on recent evidence on the role of mitochondrial import efficiency in the regulation of these stress pathways and how they may interact to protect the mitochondrial pool while initiating an innate immune response to protect against bacterial pathogens.

Distribution and impact of yeast thermal tolerance permissive for mammalian infection

Vincent Robert[1], **Gianluigi Cardinali**[2] and **Arturo Casadevall**[3*]

- *Corresponding author: Arturo Casadevall arturo.casadevall@einstein.yu.edu

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Background

From the viewpoint of fungal virulence in mammals, thermal tolerance can be defined as the ability to grow in the 35°C to 40°C range, which is essential for inhabiting these hosts.

Results

We used archival information in a fungal collection to analyze the relationship between thermal tolerance and genetic background for over 4,289 yeast strains belonging to 1,054 species. Fungal genetic relationships were inferred from hierarchical trees based on pairwise alignments using the rRNA internal transcribed spacer and large subunit rDNA (LSU) sequences. In addition, we searched for correlations between thermal tolerance and other archival information including antifungal susceptibility, carbon sources, and fermentative capacity. Thermal tolerance for growth at mammalian temperatures was not monophyletic, with thermally tolerant species being interspersed among families that include closely related species that are not thermal tolerant. Thermal tolerance and resistance to antifungal drugs were not correlated, suggesting that these two properties evolved independently. Nevertheless, the ability to grow at higher temperatures did correlate with origin from lower geographic latitudes, capacity for fermentation and assimilation of certain carbon sources.

Conclusions

Thermal tolerance was significantly more common among ascomycetous than basidiomycetous yeasts, suggesting an explanation for the preponderance of ascomycetous yeasts among human pathogenic fungi. Analysis of strain maximum tolerable temperature as a function of collection time suggested that basidiomycetous yeasts are rapidly adapting to global warming. The analysis identified genera with a high prevalence of the thermal-tolerant species that could serve as sources of emerging pathogenic fungi.

Open questions: seeking a holistic approach for mitochondrial research

Heidi M McBride

- Correspondence: Heidi M McBride heidi.mcbride@mcgill.ca

Montreal Neurological Institute, McGill University, 3801 University Avenue, Rm 622C H3A 2B4, Montreal H3A 0G4, QC, Canada

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In addition to their role as energy generators, mitochondria play critical and active roles in diverse signalling pathways, from immunity to cell survival and cell fate decisions. However, there remain many open questions and challenges as we work towards integrating this mighty organelle into established paradigms of cellular physiology.

Mitochondria are complicated. One of the most interesting things that struck me in the 20 years that I have been studying the cell biology of mitochondria is the compartmentalization of both the organelle and the field. Historically there were those who studied mitochondrial protein import or mitochondrial genetics. Others worked on bioenergetics or metabolism, and still others focused on mitochondrial dynamics, or calcium flux, cell death, and so on. It is amazing that we could focus so intently on isolated functions within this complex organelle. In fairness, to consider the entire organelle is overwhelming, and a truly integrated view of mitochondria in their native cellular environment is not an easy target. But we have now come to a moment in history where these islands of understanding must unite. I offer a few suggestions to those both old and new in the field: humble thoughts for a way forward.

The small protein floodgates are opening; now the functional analysis begins

Kumaran S Ramamurthi[1] and **Gisela Storz**[2]

- Corresponding authors: Kumaran S Ramamurthi ramamurthiks@mail.nih.gov - Gisela Storz storzg@mail.nih.gov

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Aside from a few serendipitous discoveries, small proteins of less than 50 amino acids in bacteria and 100 amino acids in eukaryotes were largely ignored due to challenges in their genetic and biochemical detection. However, with the ever-increasing availability of completed genome sequences and deep sequencing, which allows analysis of genome-wide ribosome occupancy, hundreds of small proteins are now being identified. This brings to the forefront the challenges and opportunities associated with the characterization of these proteins. See research article: http://www.biomedcentral.com/1471-2164/15/946 *webcite*.

'Small proteins' is a description given to proteins that traditionally escaped detection and thus detailed study due to their extremely small size. We also define 'small proteins' to be polypeptides that, in contrast to 'peptides', are encoded by small open reading frames (ORFs), are synthesized by ribosomes, and are not produced by proteolytic cleavage of a much larger precursor protein. Small proteins are difficult to identify for a variety of reasons. From a bioinformatics perspective, due to the problem of a high background, only ORFs of greater than approximately 50 or 100 codons were typically annotated as encoding proteins in sequenced bacterial and eukaryotic genomes, respectively. The lack of annotation coupled with few known phenotypes associated with mutations in small protein genes has restricted the detection of these genes by genetic approaches. Detection of small proteins biochemically requires optimized approaches so that, for instance, small proteins are not simply run off gels during electrophoresis. However, several recent lines of evidence suggest that small proteins are far more prevalent than previously imagined, indicating that a significant portion of the proteome of all organisms remains to be identified and studied.

Interview

Vaccines, emerging viruses, and how to avoid disaster

Rino Rappuoli

- Correspondence: Rino Rappuoli rino.rappuoli@novartis.com

Novartis Vaccines, Siena 53100, Italy

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Rino Rappuoli is a graduate of Siena University, where he also earned his PhD before moving to the Sclavo Research Center, the Italian vaccine institute, also in Siena. He then spent two years in the USA, mostly at Harvard with John Murphy and Alwin Pappenheimer working on a new diphtheria vaccine based on a non-toxic mutant of diphtheria toxin which has since become the basis for conjugate vaccines against *haemophilus*, *meningococcus*, and pneumococcal infections, before returning to the Sclavo Research Center where he developed an acellular vaccine based on a mutant pertussis toxin. With many achievements in vaccine development to his credit, he is now Global Head of Vaccines Research and Development for Novartis Vaccines in Siena, and has most recently pioneered reverse vaccinology, in which the genome of the pathogen is screened for candidate antigenic and immunogenic vaccine components. We spoke to him about the potential for outbreaks of the kind we are now seeing with Ebolavirus in West Africa, and what can be done to prevent them.

Molecular Plant

Nitric Oxide: A Multitasked Signaling Gas in Plants

Patricia Domingos, Ana Margarida Prado, Aloysius Wong, Christoph Gehring, Jose A. Feijo

Nitric oxide (NO) is a reactive oxygen species that has evolved as a gas signaling hormone in many physiological processes in plants. Despite all these effects, the fundamental knowledge of NO production, sensing, and transducing in plants remains inadequately characterized. In this review we cover the current understanding of NO production, perception, and action, with a special focus on the importance of NO in cell–cell communication during developmental processes, sexual reproduction, pathogen defense, and responses to abiotic stress.

A robustCRISPR/Cas9 system for convenient, high-efficiency multiplex genome editing in monocot and dicotplants

Xingliang Ma, Qunyu Zhang, Qinlong Zhu, Wei Liu, Yan Chen, Rong Qiu, Bin Wang, Zhongfang Yang, Heying Li, Yuru Lin, Yongyao Xie, Rongxin Shen, Shuifu Chen, Zhi Wang, Yuanling Chen, Jingxin Guo, Letian Chen, Xiucai Zhao, Zhicheng Dong, Yao-Guang Liu
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A robust CRISPR/Cas9 vector system for multiplex genome editing in monocot and dicot plants was developed. Multiple sgRNA expression cassettes can be assembled into the binary CRISPR/Cas9 vectors in one round of cloning. This system can uniformly, efficiently and simultaneously produce multiple heritable mutations in rice and *Arabidopsis* by targeting multiple genes or genomic sites via single transformation events.

Loss of GSNOR1 function leads to compromised auxin signaling and polar auxin transport

Ya-Fei Shi, Da-li Wang, Chao Wang, Angela Hendrickson Culler, Molly A. Kreiser, Jayanti Suresh, Jerry D. Cohen, Jianwei Pan, Barbara Baker, Jian-Zhong Liu
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S-nitrosoglutathione reductase 1 (GSNOR1) is a evolutionary conserved enzyme that plays a critical role in maintaining the cell's redox homeostasis and the level of protein S-nitrosylation. Impairment in GSNOR1 function inhibits auxin sensitivity and polar auxin transport in Arabidopsis, leading to defective growth and development.

Rapid Decoding of Sequence-Specific Nuclease-Induced Heterozygous and Biallelic Mutations by Direct Sequencing of PCR Products

Xingliang Ma, Letian Chen, Qinlong Zhu, Yuanling Chen, Yao-Guang Liu

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Dear Editor,

The recent development of sequence-specific nuclease systems, i.e., TALENs and CRISPR/Cas9, has made genomic targeting easier in many organisms including plants (Li et al., 2012, Cong et al., 2013, Joung and Sander, 2013, Li et al., 2013, Shan et al., 2013, Liang et al., 2014, Zhang et al., 2014). Mutations induced by CRISPR/Cas9 usually occur around the cleavage sites at three bases upstream of the protospacer-adjacent motif (PAM), producing insertion and deletion of nucleotides. For diploid organisms, such targeted mutations may happen in one or both homologous chromosomes. Previous reports showed that CRISPR/Cas9-based genomic editing in some plants mainly produced complicated mosaic (chimeric) mutations in the somatic cells of the first generation transgenic plants (Li et al., 2013, Mao et al., 2013), and the presence of targeted mutations could be detected by a combination of Cas9 protein and in vitro produced single guide RNAs (sgRNAs) (Gao and Zhao, 2014). However, genomic targeting (Zhang et al., 2014) and our results (Ma X et al., unpublished results) in rice T_0 plants show that the majority of targeted mutations are in uniform allelic statuses, mostly biallelic (two distinct variations), homozygous (two identical mutations), and heterozygous (wild-type/single mutation), and many targeted mutations in *Arabidopsis* T_1 plants using our CRISPR/Cas9 system are simple heterozygous and biallelic mutations. Most of the targeted mutations are 1-bp insertions and small segment deletions; nucleotide substitutions and insertions of 2 bp or more are very rare. Direct sequencing of PCR products containing such heterozygous and biallelic mutations results in superimposed sequencing chromatograms. A commercial sequence analysis software package, CodonCode Aligner (http://www.codoncode.com/), has been developed to decode heterozygous DNA sequences by splitting the overlapping sequencing traces into pseudo-alleles. However, this decoding program is very sensitive to the quality of sequencing chromatograms and often outputs false results. For example, we tested decoding of 21 sequencing chromatograms with heterozygous and biallelic mutations from T_0 rice plants using CodonCode Aligner but 16 cases produced false results; four cases of the decoding are shown in Supplemental Figure 1. Therefore, PCR products containing non-homozygous mutations need to be cloned and multiple clones for each targeted site are sequenced, which is tedious, inefficient, and expensive. Here, we present a simple and highly reliable method for rapid decoding of such superimposed sequencing chromatograms from direct sequencing of PCR products with heterozygous and biallelic mutations.

Fionn:

Plant cell

Cytoplastic Glyceraldehyde-3-Phosphate Dehydrogenases
Interact with ATG3 to Negatively Regulate Autophagy and
Immunity in Nicotiana benthamiana
Shaojie Han,a,1 Yan Wang,a,1 Xiyin Zheng,a,1 Qi Jia,a Jinping Zhao,a,b Fan Bai,a Yiguo Hong,c and Yule Liua,2

Autophagy as a conserved catabolic pathway can respond to reactive oxygen species (ROS) and plays an important role in degrading oxidized proteins in plants under various stress conditions. However, how ROS regulates autophagy in response to oxidative stresses is largely unknown. Here, we show that autophagy-related protein 3 (ATG3) interacts with the cytosolic glyceraldehyde-3-phosphate dehydrogenases (GAPCs) to regulate autophagy in Nicotiana benthamiana plants. We found that oxidative stress inhibits the interaction of ATG3 with GAPCs. Silencing of GAPCs significantly activates ATG3-dependent autophagy, while overexpression of GAPCs suppresses autophagy in N. benthamiana plants. Moreover, silencing of GAPCs enhances N gene-mediated cell death and plant resistance against both incompatible pathogens Tobacco mosaic virus and Pseudomonas syringae pv tomato DC3000, as well as compatible pathogen P. syringae pv tabaci. These results indicate

Modulation of the Chaperone DnaK Allosterism by the

Nucleotide Exchange Factor GrpE

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Roberto Melero[‡1,2], Fernando Moro[§2], María Ángeles Pérez-Calvo[¶2], Judit Perales-Calvo[§], Lucía Quintana-Gallardo[¶], Oscar Llorca[‡3], Arturo Muga[§4], and José María Valpuesta[¶5]

[‡]Centro de Investigaciones Biológicas (CIB-CSIC), 28040 Madrid, the [§]Unidad de Biofísica (CSIC/UPV-EHU) and Departamento de Bioquímica y Biología Molecular, Facultad de Ciencia y Tecnología, Universidad del País Vasco, 48080 Bilbao, and

the [¶]Centro Nacional de Biotecnología (CNB-CSIC), 28049 Madrid, Spain

Hsp70 chaperones comprise two domains, the nucleotide-binding domain ($Hsp70_{NBD}$), responsible for structural and functional changes in the chaperone, and the substrate-binding domain ($Hsp70_{SBD}$), involved in substrate interaction. Substrate binding and release in Hsp70 is controlled by the nucleotide state of $DnaK_{NBD}$, with ATP inducing the open, substrate-receptive $DnaK_{SBD}$ conformation, whereas ADP forces its closure. DnaK cycles between the two conformations through interaction with two cofactors, the Hsp40 co-chaperones (DnaJ in Escherichia coli) induce the ADP state, and the nucleotide exchange factors (GrpE in E. coli) induce the ATP state. X-ray crystallography showed that the GrpE dimer is a nucleotide exchange factor that works by interaction of one of its monomers with $DnaK_{NBD}$. $DnaK_{SBD}$ location in this complex is debated; there is evidence that it interacts with the GrpE N-terminal disordered region, far from $DnaK_{NBD}$. Although we confirmed this interaction using biochemical and biophysical techniques, our EM-based three-dimensional reconstruction of the DnaK-GrpE complex located $DnaK_{SBD}$ near $DnaK_{NBD}$. This apparent discrepancy between the functional and structural results is explained by our finding that the tail region of the GrpE dimer in the DnaK-GrpE complex bends and its tip contacts $DnaK_{SBD}$, whereas the $DnaK_{NBD}$-$DnaK_{SBD}$ linker contacts the GrpE helical region. We suggest that these interactions define a more complex role for GrpE in the control of DnaK function.