PNAS Plus Significance Statements

Concentrator photovoltaic module architectures with capabilities for capture and conversion of full global solar radiation

Kyu-Tae Lee, Yuan Yao, Junwen He, Brent Fisher, Xing Sheng, Matthew Lumb, Lu Xu, Mikayla A. Anderson, David Scheiman, Seungyong Han, Yongseon Kang, Abdurrahman Gumus, Rabab R. Bahabry, Jung Woo Lee, Ungyu Paik, Noah D. Bronstein, A. Paul Alivisatos, Matthew Meitl, Scott Burroughs, Muhammad Mustafa Hussain, Jeong Chul Lee, Ralph G. Nuzzo, and John A. Rogers

Concentrator photovoltaic (CPV) systems, wherein light focuses onto multijunction solar cells, offer the highest efficiencies in converting sunlight to electricity. The performance is intrinsically limited, however, by an inability to capture diffuse illumination, due to narrow acceptance angles of the concentrator optics. Here we demonstrate concepts where flat-plate solar cells mount onto the backplanes of the most sophisticated CPV modules to yield an additive contribution to the overall output. Outdoor testing results with two different hybrid module designs demonstrate absolute gains in average daily efficiencies of between 1.02% and 8.45% depending on weather conditions. The findings suggest pathways to significant improvements in the efficiencies, with economics that could potentially expand their deployment to a wide range of geographic locations. (See pp. E8210–E8218.)

Measuring spectroscopy and magnetism of extracted and intracellular magnetosomes using soft X-ray ptychography

Xiaohui Zhu, Adam P. Hitchcock, Dennis A. Bazylinski, Peter Denes, John Joseph, Ulysses Lins, Stefano Marchesini, Hung-Wei Shiu, Tolek Tyliszczak, and David A. Shapiro

Magnetotactic bacteria are one of the simplest systems that perform biomineralization: organisms that create inorganic materials using biochemistry under genetic control. They synthesize magnetosomes, which are intracellular, membrane-bound nanoscale single crystals of magnetite, a magnetic iron oxide. We studied the magnetism of individual magnetosomes inside individual cells with spectro-ptychography, a new technique of high-resolution X-ray microscopy. Our results help us to understand how the cells biomineralize magnetosomes and their function in the cell ecophysiology. In addition to demonstrating a large improvement in spatial resolution relative to earlier nonptychography studies, the results presented provide insights into magnetosome biomineralization. (See pp. E8219–E8227.)

Casitas B-cell lymphoma (Cbl) proteins protect mammary epithelial cells from proteotoxicity of active c-Src accumulation

Chandrani Mukhopadhyay, Aleata Triplett, Tom Bargar, Carol Heckman, Kay-Uwe Wagner, and Mayumi Naramura

Casitas B-cell lymphoma (Cbl) family proteins are RING finger-containing E3 ubiquitin ligases involved in degradation of activated tyrosine kinases. Previous studies in Cbl-deficient models focused primarily on the consequences of persistent tyrosine kinase signaling resulting in uncontrolled cell activation and proliferation. In the present study, we provide evidence that, in the complete absence of Cbl family proteins, failure to turn over active tyrosine kinases induces irreparable breakdown of the homeostasis of the protein milieu in primary mouse mammary epithelial cells and triggers stress-mediated cell death. Thus, our data reveal that well-regulated removal of active tyrosine kinases is essential for cell survival, an aspect of Cbl family protein functions that has not been previously fully appreciated. (See pp. E8228–E8237.)

Cell size and growth regulation in the *Arabidopsis thaliana* apical stem cell niche

Lisa Willis, Yassin Refahi, Raymond Wightman, Benoit Landrein, José Teles, Kerwyn Casey Huang, Elliot M. Meyerowitz, and Henrik Jönsson

How does a cell decide when to divide or initiate DNA replication? How does it regulate its own growth? These fundamental questions are not well understood in most organisms; this lack of understanding is particularly true for multicellular eukaryotes. Following classical studies in yeast, we have quantified the key aspects of cell growth and division dynamics in the *Arabidopsis* apical stem cell niche. Our results disprove various theories for plant stem cell size/cell cycle regulation, such as that cell cycle progression is triggered when a prefixed critical size is attained, and constitute the necessary first step in the development of integrative mechanistic theories for the coordinated regulation of cell cycle progression, cell growth, and cell size in plants. (See pp. E8238–E8246.)

An NAD^+-dependent transcriptional program governs self-renewal and radiation resistance in glioblastoma

Amit D. Gujar, Son Le, Diane D. Mao, David Y. A. Dadey, Alice Turski, Yo Sasaki, Diane Aum, Jingqin Luo, Sonika Dahiya, Liya Yuan, Keith M. Rich, Jeffrey Milbrandt, Dennis E. Hallahan, Hiroko Yano, David D. Tran, and Albert H. Kim

Glioblastoma, the most common primary malignant brain tumor in adults, remains challenging despite multimodality therapy, necessitating the discovery of new

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therapies. Nicotinamide adenine dinucleotide (NAD^+) plays a pivotal role in cancer cell metabolism, but how NAD^+ impacts functional signaling events in glioblastoma is not well understood. We provide clinical evidence that high expression of NAMPT, the rate-limiting step in NAD^+ biosynthesis, in glioblastoma tumors is associated with poor overall survival in patients, and demonstrate NAMPT and NAD^+ are required for the maintenance of patient-derived glioblastoma stem-like cells (GSCs). Moreover, we delineate a NAD^+-dependent transcriptional program that governs GSC self-renewal and dictates the radiation resistance of these cells. These findings identify potential new therapeutic avenues for the treatment of glioblastoma. (See pp. E8247–E8256.)

Reprogramming cell fate with a genome-scale library of artificial transcription factors

Asuka Eguchi, Matthew J. Wleklinski, Mackenzie C. Spurgat, Evan A. Heiderscheit, Anna S. Kropornicka, Catherine K. Vu, Devesh Bhimsaria, Scott A. Swanson, Ron Stewart, Parameswaran Ramanathan, Timothy J. Kamp, Igor Slukvin, James A. Thomson, James R. Dutton, and Aseem Z. Ansari

The ability to convert cells into desired cell types enables tissue engineering, disease modeling, and regenerative medicine; however, methods to generate desired cell types remain difficult, uncertain, and laborious. We developed a strategy to screen gene regulatory elements on a genome scale to discover paths that trigger cell fate changes. The proteins used in this study cooperatively bind DNA and activate genes in a synergistic manner. Subsequent identification of transcriptional networks does not depend on prior knowledge of specific regulators important in the biological system being tested. This powerful forward genetic approach enables direct cell state conversions as well as other challenging manipulations of cell fate. (See pp. E8257–E8266.)

Tet proteins influence the balance between neuroectodermal and mesodermal fate choice by inhibiting Wnt signaling

Xiang Li, Xiaojing Yue, William A. Pastor, Lizhu Lin, Romain Georges, Lukas Chavez, Sylvia M. Evans, and Anjana Rao

Methylation of cytosine bases in DNA is an epigenetic modification that influences gene expression. TET (ten-eleven translocation)-family dioxygenases catalyze conversion of 5-methylcytosine (5mC) to 5-hydroxymethylcytosine (5hmC) and additional oxidized methylcytosines in DNA. Here, we show that both Tet3- and Tet1/2/3-deficient mouse ES cells showed impaired neural conversion, with skewing toward cardiac mesoderm. Genome-wide analyses showed that Tet3 mediates cell-fate decisions by inhibiting Wnt signaling. Consistent with these findings, Wnt signaling was hyperactivated in Tet1/2/3-deficient embryos, leading to aberrant differentiation of bipotent neuromesodermal progenitors into mesoderm at the expense of neuroectoderm. Our data demonstrate a key role for TET proteins in modulating Wnt signaling and establishing the proper balance between neural and mesoderm cell fate determination. (See pp. E8267–E8276.)

Genetic, immunological, and clinical features of patients with bacterial and fungal infections due to inherited IL-17RA deficiency

Romain Lévy, Satoshi Okada, Vivien Béziat, Kunihiko Moriya, Caini Liu, Louis Yi Ann Chai, Mélanie Migaud, Fabian Hauck, Amein Al Ali, Cyril Cyrus, Chittibabu Vatte, Turkan Patiroglu, Ekrem Unal, Marie Ferneiny, Nobuyuki Hyakuna, Serdar Nepesov, Matias Oleastro, Aydan Ikinciogullari, Figen Dogu, Takaki Asano, Osamu Ohara, Ling Yun, Erika Della Mina, Didier Bronnimann, Yuval Itan, Florian Gothe, Jacinta Bustamante, Stéphanie Boisson-Dupuis, Natalia Tahuil, Caner Aytekin, Aicha Salhi, Saleh Al Muhsen, Masao Kobayashi, Julie Toubiana, Laurent Abel, Xiaoxia Li, Yildiz Camcioglu, Fatih Celmeli, Christoph Klein, Suzan A. AlKhater, Jean-Laurent Casanova, and Anne Puel

Chronic mucocutaneous candidiasis (CMC) is defined as persistent or recurrent infections of the skin and/or mucosae by commensal fungi of the *Candida* genus. It is often seen in patients with T-cell deficiencies, whether inherited or acquired, who typically suffer from multiple infectious diseases. Rare patients are otherwise healthy and display isolated CMC, which often segregates as a Mendelian trait. In 2011, we described the first genetic cause of isolated CMC, with autosomal recessive (AR), complete IL-17 receptor A (IL-17RA) deficiency, in a single patient. We report here 21 patients from 12 unrelated kindreds, homozygous for 12 different mutant alleles that underlie AR IL-17RA deficiency. All patients have isolated CMC and their cells do not respond to IL-17A, -17F, and -17E/IL-25. (See pp. E8277–E8285.)

miR-17∼92 family clusters control iNKT cell ontogenesis via modulation of TGF-β signaling

Maya Fedeli, Michela Riba, Jose Manuel Garcia Manteiga, Lei Tian, Valentina Viganò, Grazisa Rossetti, Massimiliano Pagani, Changchun Xiao, Adrian Liston, Elia Stupka, Davide Cittaro, Sergio Abrignani, Paolo Provero, Paolo Dellabona, and Giulia Casorati

CD1d-restricted invariant natural killer T (iNKT) cells are innate-like T lymphocytes that play fundamental roles in cancer, autoimmunity, and infections. iNKT cells acquire effector functions already in the thymus, because of a distinct developmentally regulated genetic program that is critically controlled by miRNAs. Our study unveils the unexpected requirement for miRNA-dependent fine-tuning of TGF-β signaling in the control of iNKT cell development and functional differentiation. The targeting of a lineage-specific cytokine signaling by miRNA represents a previously unknown level of developmental regulation in the thymus. Furthermore, our study provides a comprehensive atlas of miRNA-regulated molecular pathways involved in iNKT cell ontogenesis, and highlights molecular pathways targeted by defined miRNAs that are predicted to be involved in the development and maturation of CD1d-restricted iNKT cells. (See pp. E8286–E8295.)

Development of high-yield influenza B virus vaccine viruses

Jihui Ping, Tiago J. S. Lopes, Gabriele Neumann, and Yoshihiro Kawaoka

The yield of vaccine viruses is important from an economic point of view. Even more important, the ability to produce high numbers of vaccine doses under tight timelines may save many lives

during a virus outbreak. Applying an approach that we recently used to develop high-yield influenza A virus vaccine candidates, we now developed high-yield vaccine candidates for both influenza B virus lineages circulating in humans. These vaccine virus candidates confer higher yield in commonly used propagation systems for influenza vaccine virus production: that is, embryonated chicken eggs, Madin–Darby canine kidney cells, and African green monkey (Vero) cells. Our vaccine candidates could be used to improve the influenza B virus vaccine production process. (See pp. E8296–E8305.)

Long-range projections coordinate distributed brain-wide neural activity with a specific spatiotemporal profile

Alex T. L. Leong, Russell W. Chan, Patrick P. Gao, Ying-Shing Chan, Kevin K. Tsia, Wing-Ho Yung, and Ed X. Wu

What makes the brain tick? A simple yet challenging question that has captivated our minds for centuries. This sentiment was fittingly reflected in the launch of The BRAIN Initiative 3 years ago, spurred by the rapid advancement of noninvasive brain imaging and neuronal mapping technologies that have advanced our understanding of neural networks, which are central to brain functions and behavior. Here, we study the patterns of large-scale brain-wide interactions mediated by thalamo-cortical networks through optogenetics and functional MRI. We found that the thalamus can recruit long-range cortical and subcortical networks and initiate their interactions in a spatiotemporally specific manner. This finding provides a fresh impetus to study the mysteries of the brain. (See pp. E8306–E8315.)

Gamma motor neurons survive and exacerbate alpha motor neuron degeneration in ALS

Melanie Lalancette-Hebert, Aarti Sharma, Alexander K. Lyashchenko, and Neil A. Shneider

Clinical and pathological hallmarks shared by various familial and sporadic forms of amyotrophic lateral sclerosis (ALS) suggest common underlying mechanisms of disease. Using a series of ALS mouse models, we demonstrate that one shared feature of ALS is the selective sparing of gamma motor neurons (γ-MNs), which innervate muscle spindles and regulate primary proprioceptive afferent (I_A) feedback on alpha motor neurons (α-MNs). Genetic evidence presented here implicates this major excitatory input in the selective degeneration of α-MNs in ALS. Functional elimination of I_A inputs or partial elimination of γ-MNs is protective in superoxide dismutase-1 (SOD1) mutant mice, suggesting that surviving γ-MNs contribute to α-MN loss by increasing muscle afferent-mediated excitation. This study highlights the role of synaptic connectivity and circuit function in motor neuron disease. (See pp. E8316–E8325.)

Receptor kinase complex transmits RALF peptide signal to inhibit root growth in *Arabidopsis*

Changqing Du, Xiushan Li, Jia Chen, Weijun Chen, Bin Li, Chiyu Li, Long Wang, Jianglin Li, Xiaoying Zhao, Jianzhong Lin, Xuanming Liu, Sheng Luan, and Feng Yu

Receptor-like kinase FERONIA (FER) is a versatile regulator of cell growth under both normal and stress environments. FER binds its peptide ligand, rapid alkalinization factor 1 (RALF1), and triggers downstream events to inhibit cell growth in primary roots. However, the mechanism of RALF1 reception by FER is still largely unknown. In this study, we identified a receptor-like cytoplasmic kinase (RPM1-induced protein kinase, RIPK) that directly interacts with and is phosphorylated by FER in a RALF1 peptide-dependent manner. The defects of *fer-4* mutant in RALF1 response and root hair development are mimicked by *ripk* loss-of-function but partially compensated by RIPK overexpression. These and other data suggest that formation of the FER–RIPK complex serves as a crucial step in the RALF1 signaling pathway. (See pp. E8326–E8334.)

Light affects salt stress-induced transcriptional memory of *P5CS1* in *Arabidopsis*

Xuan Jun Feng, Jing Rui Li, Shi Lian Qi, Qing Fang Lin, Jing Bo Jin, and Xue Jun Hua

Light, a prevailing environmental factor, plays important roles in various processes during plant development and stress response. Whether light could also regulate stress-induced transcriptional memory, however, is not clear. Herein we reported that light signal is positively involved in salt-induced transcriptional memory of Δ^1-pyrroline-5-carboxylate synthetase 1 (*P5CS1*) and subsequent proline accumulation. Furthermore, HY5-dependent light signaling is required for the maintenance of salt-induced H3K4me3 in *P5CS1* during the recovery stage. This mechanism is likely operating during other stress as well, and could shed light on future research into the concerted effects of different environmental factors on plant response to stresses. (See pp. E8335–E8343.)

Unique attributes of cyanobacterial metabolism revealed by improved genome-scale metabolic modeling and essential gene analysis

Jared T. Broddrick, Benjamin E. Rubin, David G. Welkie, Niu Du, Nathan Mih, Spencer Diamond, Jenny J. Lee, Susan S. Golden, and Bernhard O. Palsson

Genome-scale models of metabolism are important tools for metabolic engineering and production strain development. We present an experimentally validated and manually curated model of metabolism in *Synechococcus elongatus* PCC 7942 that (*i*) leads to discovery of unique metabolic characteristics, such as the importance of a truncated, linear TCA pathway, (*ii*) highlights poorly understood areas of metabolism as exemplified by knowledge gaps in nucleotide salvage, and (*iii*) accurately quantifies light input and self-shading. We now have a metabolic model that can be used as a basis for metabolic design in *S. elongatus*. (See pp. E8344–E8353.)