PNAS Plus Significance Statements

Polytypism, polymorphism, and superconductivity in $TaSe_{2-x}Te_x$

Huixia Luo, Weiwei Xie, Jing Tao, Hiroyuki Inoue, András Gyenis, Jason W. Krizan, Ali Yazdani, Yimei Zhu, and Robert Joseph Cava

Although polymorphs of a substance can often have dramatically different physical properties, polytypes, which occur when the geometry of a structural layer is maintained but the number of layers in the layer-stacking sequence is changed, rarely do. Here (pp. E1174–E1180) we find, using random substitution of Te for some of the Se to induce structural changes in $TaSe_2$, a classic layered dichalcogenide, so that the transition temperature to superconductivity (T_c) is significantly different for different polytypes and polymorphs and especially differs when going from one polytype to another. This observation implies either a surprising sensitivity of T_c to the layer-stacking sequence or a similarly surprising sensitivity of T_c to the small changes in layer geometry that accompany the change in polytype.

Comprehensive analysis of heterotrimeric G-protein complex diversity and their interactions with GPCRs in solution

Matthias Hillenbrand, Christian Schori, Jendrik Schöppe, and Andreas Plückthun

G-protein–coupled receptors (GPCRs) are the target of 30% of all drugs on the market. Nevertheless, the lack of detailed knowledge of GPCR signaling impedes the development of highly specific drugs. In this respect, additional structures of GPCR/G-protein complexes could greatly enhance our knowledge on how to design specific drugs. Unfortunately, the nature of the GPCR/G-protein complex is characterized by a transient interaction and an intrinsic instability, thereby hampering structure determination. In our study, we show (pp. E1181–E1190)—besides new insights into the combinatorial diversity of heterotrimeric G proteins—that the combination of evolved, stable GPCR mutants and G-protein combinations selected from the natural pool of G proteins yields promisingly stable GPCR/G-protein complexes.

Dramatically reduced spliceosome in *Cyanidioschyzon merolae*

Martha R. Stark, Elizabeth A. Dunn, William S. C. Dunn, Cameron J. Grisdale, Anthony R. Daniele, Matthew R. G. Halstead, Naomi M. Fast, and Stephen D. Rader

The spliceosome—the molecular particle responsible for removing interrupting sequences from eukaryotic messenger RNA—is one of the most complex cellular machines. Consisting of five snRNAs and over 200 proteins in humans, its numerous changes in composition and shape during splicing have made it difficult to study. We have characterized an algal spliceosome that is much smaller, with only 43 identifiable core proteins, the majority of which are essential for viability in other organisms. We propose (pp. E1191–E1200) that this highly reduced spliceosome has retained only the most critical splicing factors. *Cyanidioschyzon merolae* therefore provides a powerful system to examine the spliceosome's catalytic core, enabling future advances in understanding the splicing mechanism and spliceosomal organization that are challenging in more complex systems.

Myosin VI deafness mutation prevents the initiation of processive runs on actin

Olena Pylypenko, Lin Song, Ai Shima, Zhaohui Yang, Anne M. Houdusse, and H. Lee Sweeney

A number of molecular motors transport cargoes long distances on their cellular tracks as single, dimeric (two-headed) molecules. This processive movement requires specialized kinetic properties (high duty ratio) to ensure that each head of the dimeric motor spends most of its time tightly bound to its track. Additionally, processive motors exhibit intramolecular communication between the heads, called gating, whose importance is less clear. By examining a mutation in the reverse-direction myosin motor, myosin VI, that causes deafness, we provide (pp. E1201–E1209) evidence that the mutation destroys the initiation of processive runs under physiological ATP concentration. We further demonstrate that this defect may be amendable to correction by small-molecule therapeutics.

BRUCE regulates DNA double-strand break response by promoting USP8 deubiquitination of BRIT1

Chunmin Ge, Lixiao Che, Jinyu Ren, Raj K. Pandita, Jing Lu, Kaiyi Li, Tej K. Pandita, and Chunying Du

DNA damage response is essential to preserve genomic stability. Here we report a previously unknown function for the baculovirus inhibitor of apoptosis protein repeat (BIR)-containing ubiquitin-conjugating enzyme (BRUCE) and ubiquitin-specific peptidase 8 (USP8) as activators of DNA damage response. They drive recruitment of the breast cancer susceptibility gene C terminus-repeat inhibitor of human telomerase reverse transcriptase expression (BRIT1) to DNA breaks by promoting BRIT1 deubiquitination. In contrast to the established regulation of repair foci formation by ubiquitination, our data demonstrate (pp. E1210–E1219) deubiquitination as a previously unrecognized critical step in promoting foci formation. Furthermore, we define a pathway by which BRUCE and USP8 activate BRIT1–switch/sucrose nonfermentable (SWI-SNF)–mediated chromatin relaxation to maximize cell responsiveness to DNA damage. Thus, BRUCE represents a novel component in safeguarding genomic stability and a promising therapeutic target in diseases of genomic instability such as cancer.

www.pnas.org/cgi/doi/10.1073/pnas.ss11211

Proteome-wide analysis of mutant p53 targets in breast cancer identifies new levels of gain-of-function that influence PARP, PCNA, and MCM4

Alla Polotskaia, Gu Xiao, Katherine Reynoso, Che Martin, Wei-Gang Qiu, Ronald C. Hendrickson, and Jill Bargonetti

Mutant p53 (mtp53) is a driver oncogene of breast cancer. Here, for the first time, to our knowledge, using an inducible endogenous knockdown system, we explore (pp. E1220–E1229) the mtp53 driven proteome. We report this key data set that highlights mtp53-driven proteome diversity at the level of protein localization, as well as changes in protein levels without corresponding changes in transcription. We validated two protein pathways that include increased chromatin association of poly(ADP ribose) polymerase 1, and the increase of nuclear replication proteins minichromosome maintenance 4 and proliferating cell nuclear antigen. The addition of mtp53 proteomic targets to the previously identified transcriptional targets suggests that effective treatment of mtp53-driven breast cancers may be facilitated by new combination protocols blocking proteins of the metabolic pathways of cholesterol biosynthesis, DNA replication, and DNA repair.

Hadal biosphere: Insight into the microbial ecosystem in the deepest ocean on Earth

Takuro Nunoura, Yoshihiro Takaki, Miho Hirai, Shigeru Shimamura, Akiko Makabe, Osamu Koide, Tohru Kikuchi, Junichi Miyazaki, Keisuke Koba, Naohiro Yoshida, Michinari Sunamura, and Ken Takai

Although many microbial explorations for hadal sediments began in the 1950s, the hadal water is the least-explored microbial biosphere. In this study, unexpected microbial ecosystems associated with the hadal trench water were discovered down to a 10,257-m water depth in the Challenger Deep of the Mariana Trench, which is the deepest ocean on Earth. We found (pp. E1230–E1236) the enrichment of heterotrophic population in the hadal water (6,000 ~10,257 m) microbial communities, whereas the chemolithotrophic populations were more abundant in the upper abyssal waters. This observation suggested that the hadal microbial biosphere was supported by the endogenous recycling of organic matter in the hadal waters associated with the trench geomorphology.

Climate change and pollution speed declines in zebrafish populations

A. Ross Brown, Stewart F. Owen, James Peters, Yong Zhang, Marta Soffker, Gregory C. Paull, David J. Hosken, M. Abdul Wahab, and Charles R. Tyler

Climate change impacts on wildlife populations are likely to be accentuated by pollution. Small (inbred) populations may be more vulnerable to these effects, but empirical data supporting these hypotheses are lacking. We present (pp. E1237–E1246) the first substantial empirical evidence, to our knowledge, for interactive effects on population viability of elevated temperature (climate); an endocrine disrupting chemical, clotrimazole (pollution); and inbreeding. Using the zebrafish (*Danio rerio*) as a model, we show these three factors interact to skew population sex ratios toward males and that this interaction can lead to increased risk of extinction. Our results suggest that climate change and pollution impacts are likely to pose significant extinction risks for small, endangered populations exhibiting environmental sex determination and/or differentiation.

Extraordinary diversity of visual opsin genes in dragonflies

Ryo Futahashi, Ryouka Kawahara-Miki, Michiyo Kinoshita, Kazutoshi Yoshitake, Shunsuke Yajima, Kentaro Arikawa, and Takema Fukatsu

Human color vision is tri-chromatic, with three opsins expressed in cone photoreceptors that are sensitive in the red, green, and blue region of the spectrum. As theories predict, such tri- or tetra-chromacy with three or four opsin genes is common among mammals, birds, and other animals, including insects. However, we discovered (pp. E1247–E1256) that dragonflies possess as many as 15–33 opsin genes that have evolved through dynamic gene multiplications and losses within the lineage of dragonflies. These opsin genes are differentially expressed between adult and larva, as well as between dorsal and ventral regions of adult compound eyes, which plausibly underpin the versatile behavioral and ecological adaptations of actively flying adults to aerial lifestyle and sedentary larvae to aquatic lifestyle.

Whole-genome sequence of the Tibetan frog *Nanorana parkeri* and the comparative evolution of tetrapod genomes

Yan-Bo Sun, Zi-Jun Xiong, Xue-Yan Xiang, Shi-Ping Liu, Wei-Wei Zhou, Xiao-Long Tu, Li Zhong, Lu Wang, Dong-Dong Wu, Bao-Lin Zhang, Chun-Ling Zhu, Min-Min Yang, Hong-Man Chen, Fang Li, Long Zhou, Shao-Hong Feng, Chao Huang, Guo-Jie Zhang, David Irwin, David M. Hillis, Robert W. Murphy, Huan-Ming Yang, Jing Che, Jun Wang, and Ya-Ping Zhang

We provide (pp. E1257–E1262) a de novo genome of the Tibetan frog, *Nanorana parkeri*, and conduct a series of comparisons with other vertebrates. Approximately one-half of the genome of *Nanorana* consists of transposable elements (TEs). The frequencies and distributional patterns of TEs differ considerably between *Nanorana* and *Xenopus*, the only other amphibian for which a genome has been sequenced. The genomes of these two frogs exhibit substantial homologous synteny blocks with rare interchromosomal and intrachromosomal rearrangements. We also identify 11 Mb of amphibian-specific conserved elements comprising 217 genes. These highly conserved genes provide a basis for comparative genomic analyses throughout frogs.

Sequential de novo centromere formation and inactivation on a chromosomal fragment in maize

Yalin Liu, Handong Su, Junling Pang, Zhi Gao, Xiu-Jie Wang, James A. Birchler, and Fangpu Han

The centromere is the part of the chromosome that is involved with movement in mitosis and meiosis. The activity of the centromere is epigenetic in that the underlying DNA sequences do not necessarily determine function. In the present study (pp. E1263–E1271), a chromosomal fragment was followed in which a sequential de novo formation and inactivation occurred for the position of the active centromere. The results suggest that de novo centromere formation occurs regularly. However, when coupled with previous findings that larger centromeres can inactivate smaller ones when present

together, it is hypothesized that such frequent de novo centromere formations are cleared from normal chromosomes by inactivation, but can persist on structurally acentric fragments and be inherited.

Recurrent *BCAM-AKT2* fusion gene leads to a constitutively activated AKT2 fusion kinase in high-grade serous ovarian carcinoma

Kalpana Kannan, Cristian Coarfa, Pei-Wen Chao, Liming Luo, Yan Wang, Amy E. Brinegar, Shannon M. Hawkins, Aleksandar Milosavljevic, Martin M. Matzuk, and Laising Yen

High-grade serous ovarian cancer (HGSC) is the most common subtype of ovarian cancer and is typically detected only at advanced stages due to lack of effective early screening tools. Fusion genes are among the most cancer-specific signatures known and, when highly recurrent, they have the potential to serve as screening tools. Here (pp. E1272–E1277) we identified *BCAM-AKT2* as a cancer-specific fusion gene present in 7% of HGSC tumors, a significant frequency in this highly heterogeneous disease. This fusion results in an aberrant kinase whose constant activity contributes to cancer formation. Thus, the *BCAM-AKT2* fusion gene could be important for understanding and identifying clinically relevant subtypes of HGSC, and could be a novel therapeutic target for developing small-molecule drugs.

Implantable hydrogel embedded dark-gold nanoswitch as a theranostic probe to sense and overcome cancer multidrug resistance

João Conde, Nuria Oliva, and Natalie Artzi

The integration of biomaterials science, innovative imaging, and cancer biology now enables the design of smart responsive material platforms for cancer theranostics. We show (pp. E1278–E1287) herein that our developed nanovehicle is able to sense and silence a multidrug resistance gene based on its expression in the tumor microenvironment, followed by local chemotherapeutic drug release, with a significant tumor regression not achieved otherwise. This ON/OFF molecular nanoswitch approach can be used to reverse the resistance to many other chemotherapeutic drugs and can serve as a universal gene therapy and drug delivery vehicle for cancer therapy. This disease-responsive platform can revolutionize clinical outcome and cancer patients' point of care.

Assessment of ABT-263 activity across a cancer cell line collection leads to a potent combination therapy for small-cell lung cancer

Anthony C. Faber, Anna F. Farago, Carlotta Costa, Anahita Dastur, Maria Gomez-Caraballo, Rebecca Robbins, Bethany L. Wagner, William M. Rideout III, Charles T. Jakubik, Jungoh Ham, Elena J. Edelman, Hiromichi Ebi, Alan T. Yeo, Aaron N. Hata, Youngchul Song, Neha U. Patel, Ryan J. March, Ah Ting Tam, Randy J. Milano, Jessica L. Boisvert, Mark A. Hicks, Sarah Elmiligy, Scott E. Malstrom, Miguel N. Rivera, Hisashi Harada, Brad E. Windle, Sridhar Ramaswamy, Cyril H. Benes, Tyler Jacks, and Jeffrey A. Engelman

Small-cell lung cancer (SCLC) is an aggressive carcinoma with few effective treatment options beyond first-line chemotherapy. BH3 mimetics, such as ABT-263, promote apoptosis in SCLC cell lines, but early phase clinical trials demonstrated no significant clinical benefit. Here (pp. E1288–E1296), we examine the sensitivity of a large panel of cancer cell lines, including SCLC, to ABT-263 and find that high Bcl2-interacting mediator of cell death (BIM) and low myeloid cell leukemia 1 (MCL-1) expression together predict sensitivity. SCLC cells relatively resistant to ABT-263 are sensitized by TORC1/2 inhibition via MCL-1 reduction. Combination of ABT-263 and TORC1/2 inhibition stabilizes or shrinks tumors in xenograft models, in autochthonous SCLC tumors in a genetically engineered mouse model, and in a patient-derived xenograft SCLC model. Collectively, these data support a compelling new therapeutic strategy for treating SCLC.

Controlled tetra-Fc sialylation of IVIg results in a drug candidate with consistent enhanced anti-inflammatory activity

Nathaniel Washburn, Inessa Schwab, Daniel Ortiz, Naveen Bhatnagar, Jonathan C. Lansing, Amy Medeiros, Steven Tyler, Divya Mekala, Edward Cochran, Hetal Sarvaiya, Kevin Garofalo, Robin Meccariello, James W. Meador III, Laura Rutitzky, Birgit C. Schultes, Leona Ling, William Avery, Falk Nimmerjahn, Anthony M. Manning, Ganesh V. Kaundinya, and Carlos J. Bosques

IgG fragment crystallizable domain (Fc) sialylation has emerged as an important but controversial concept for regulating anti-inflammatory activity of antibodies. Moreover, translating this concept to potent anti-inflammatory therapeutics has been hampered by the difficulty of generating suitable sialylated products for human use. We describe (pp. E1297–E1306) for the first time, to our knowledge, the development of a robust, scalable process to generate a sialylated intravenous immunoglobulin (IVIg) drug candidate with maximum Fc sialylation devoid of unwanted modifications. By using a wide panel of physicochemical analytics and in vivo models, we have validated the quality and potent anti-inflammatory activity of this clinical candidate. This report not only confirms the controversial anti-inflammatory activity of IgG-Fc sialylation, it also represents the first sialylated IVIg preparation, to our knowledge, with consistent anti-inflammatory potency suitable for clinical development.

Oncogenic fusion protein EWS-FLI1 is a network hub that regulates alternative splicing

Saravana P. Selvanathan, Garrett T. Graham, Hayriye V. Erkizan, Uta Dirksen, Thanemozhi G. Natarajan, Aleksandra Dakic, Songtao Yu, Xuefeng Liu, Michelle T. Paulsen, Mats E. Ljungman, Cathy H. Wu, Elizabeth R. Lawlor, Aykut Üren, and Jeffrey A. Toretsky

Alternative splicing of RNA allows a limited number of coding regions in the human genome to produce proteins with diverse functionality. Alternative splicing has also been implicated as an oncogenic process. Identifying aspects of cancer cells that differentiate them from noncancer cells remains an ongoing challenge, and our research suggests that alternatively spliced mRNA and subsequent protein isoforms will provide new anticancer targets. We determined (pp. E1307–E1316) that the key oncoprotein of Ewing sarcoma (ES), EWS-FLI1, regulates alternative splicing in multiple cell line models. These experiments establish oncogenic aspects of splicing that are specific to cancer cells and thereby illuminate potentially oncogenic splicing shifts as well as provide a useful stratification mechanism for ES patients.

Lengthening and shortening of plasma DNA in hepatocellular carcinoma patients

Peiyong Jiang, Carol W. M. Chan, K. C. Allen Chan, Suk Hang Cheng, John Wong, Vincent Wai-Sun Wong, Grace L. H. Wong, Stephen L. Chan, Tony S. K. Mok, Henry L. Y. Chan, Paul B. S. Lai, Rossa W. K. Chiu, and Y. M. Dennis Lo

We used massively parallel sequencing to study the size profiles of plasma DNA samples at single-base resolution and in a genome-wide manner. We used chromosome arm-level *z*-score analysis (CAZA) to identify tumor-derived plasma DNA for studying their specific size profiles. We showed (pp. E1317–E1325) that populations of aberrantly short and long DNA molecules existed in the plasma of patients with hepatocellular carcinoma. The short ones preferentially carried the tumor-associated copy number aberrations. We further showed that there were elevated amounts of mitochondrial DNA in the plasma of hepatocellular carcinoma patients. Such molecules were much shorter than the nuclear DNA in plasma. These findings have shed light on fundamental biological characteristics of plasma DNA and related diagnostic applications for cancer.

Disentangling mechanisms that mediate the balance between stochastic and deterministic processes in microbial succession

Francisco Dini-Andreote, James C. Stegen, Jan Dirk van Elsas, and Joana Falcão Salles

Across ecology, and particularly within microbial ecology, there is limited understanding of the mechanisms governing the relative influences of stochastic and deterministic processes. Filling this knowledge gap is a major challenge that requires the development of novel conceptual paradigms, experiments, and ecological models. Here (pp. E1326–E1332) we (*i*) present a conceptual model that couples the stochastic/deterministic balance to primary and secondary ecological succession, thereby integrating previously isolated conceptual domains; (*ii*) evaluate this model over 105 years of ecosystem development, revealing a systematic shift in the type and strength of ecological selection; and (*iii*) couple empirical data with a new simulation model to elucidate underlying mechanisms and characterize their scale dependency. The insights and conceptual framework provided here represent a nexus for cross-system integration.

NFκB activation by modified vaccinia virus as a novel strategy to enhance neutrophil migration and HIV-specific T-cell responses

Mauro Di Pilato, Ernesto Mejías-Pérez, Manuela Zonca, Beatriz Perdiguero, Carmen Elena Gómez, Marianna Trakala, Jacobo Nieto, José Luis Nájera, Carlos Oscar S. Sorzano, Christophe Combadière, Giuseppe Pantaleo, Lourdes Planelles, and Mariano Esteban

Although poxvirus vectors are widely used in preclinical and clinical trials as candidate vaccines for multiple pathogens, how these vectors affect the host immune response is not clear. In this study (pp. E1333–E1342), we developed a poxvirus vector based on the attenuated New York vaccinia virus (NYVAC), which is able to target a central host-cell signaling pathway, NFκB. In mice, the modified NYVAC acts on the immune system by increasing specific neutrophil migration via NFκB activation and in turn enhances CD8 T-cell responses to HIV antigens delivered by the viral vector. We show that these inherent properties define a mechanism for poxvirus-induced immune responses and offer novel approaches to vaccine vector design.

Origin of the HIV-1 group O epidemic in western lowland gorillas

Mirela D'arc, Ahidjo Ayouba, Amandine Esteban, Gerald H. Learn, Vanina Boué, Florian Liegeois, Lucie Etienne, Nikki Tagg, Fabian H. Leendertz, Christophe Boesch, Nadège F. Madinda, Martha M. Robbins, Maryke Gray, Amandine Cournil, Marcel Ooms, Michael Letko, Viviana A. Simon, Paul M. Sharp, Beatrice H. Hahn, Eric Delaporte, Eitel Mpoudi Ngole, and Martine Peeters

Understanding emerging disease origins is important to gauge future human infection risks. This is particularly true for the various forms of the AIDS virus, HIV-1, which were transmitted to humans on four independent occasions. Previous studies identified chimpanzees in southern Cameroon as the source of the pandemic M group, as well as the geographically more restricted N group. Here (pp. E1343–E1352), we show that the remaining two groups also emerged in southern Cameroon but had their origins in western lowland gorillas. Although group P has only been detected in two individuals, group O has spread extensively throughout west central Africa. Thus, both chimpanzees and gorillas harbor viruses that are capable of crossing the species barrier to humans and causing major disease outbreaks.

Disruption of hierarchical predictive coding during sleep

Melanie Strauss, Jacobo D. Sitt, Jean-Remi King, Maxime Elbaz, Leila Azizi, Marco Buiatti, Lionel Naccache, Virginie van Wassenhove, and Stanislas Dehaene

Sleeping disrupts the conscious awareness of external sounds. We investigated (pp. E1353–E1362) the stage of processing at which this disruption occurs. In the awake brain, when a regular sequence of sounds is presented, a hierarchy of brain areas uses the available regularities to predict forthcoming sounds and to respond with a series of "prediction error" signals when these predictions are violated. Using simultaneous recordings of electroencephalography and magnetoencephalography signals, we discovered that both short-term and long-term brain responses to auditory prediction errors are disrupted during non-rapid eye movement and rapid eye movement sleep; however, the brain still exhibits detectable auditory responses and a capacity to habituate to frequently repeated sounds. Thus, sleep appears to selectively affect the brain's prediction and error detection systems.

Activation of TRPM3 by a potent synthetic ligand reveals a role in peptide release

Katharina Held, Tatjana Kichko, Katrien De Clercq, Hugo Klaassen, Rieta Van Bree, Jean-Christophe Vanherck, Arnaud Marchand, Peter W. Reeh, Patrick Chaltin, Thomas Voets, and Joris Vriens

The cation channel TRPM3 is highly expressed in the sensory system, where it plays a key role in the detection of noxious heat and the development of inflammatory heat hypersensitivity. Our understanding of the physiological role of TRPM3 in the sensory system and other tissues is hampered by the lack of potent pharmacologic tools, however. This study (pp. E1363–E1372) describes CIM0216, a small-molecule TRPM3 agonist. Our results indicate

that CIM0216 is much more potent than established TRPM3 agonists, particularly owing to its ability to open two distinct cation-permeable pores in TRPM3. Using CIM0216 as a pharmacologic tool, we reveal that activation of TRPM3 evokes the release of calcitonin gene-related peptide from sensory nerve terminals and of insulin from pancreatic islets.

Up-regulation of lysosomal TRPML1 channels is essential for lysosomal adaptation to nutrient starvation

Wuyang Wang, Qiong Gao, Meimei Yang, Xiaoli Zhang, Lu Yu, Maria Lawas, Xinran Li, Marthe Bryant-Genevier, Noel T. Southall, Juan Marugan, Marc Ferrer, and Haoxing Xu

Lysosomes are the cell's degradation center. To adapt to different environmental conditions, the cell has evolved a set of delicate mechanisms to rapidly change lysosome function, which is referred to as lysosomal adaptation. Notably, lysosomal adaptation is required for cell survival under low nutrient conditions. In this study, we identified (pp. E1373–E1381) TRPML1, a lysosomal Ca^{2+}-permeant ion channel, as an essential player required for lysosomal adaptation. The activity of TRPML1 is potently (up to 10-fold) and rapidly increased upon nutrient starvation. Furthermore, pharmacological inhibition or genetic deletion of TRPML1 completely abolished the effects of starvation on boosting the degradation capability of lysosomes.

Activation of protein synthesis in mouse uterine epithelial cells by estradiol-17β is mediated by a PKC–ERK1/2–mTOR signaling pathway

Yuxiang Wang, Liyin Zhu, Satu Kuokkanen, and Jeffrey W. Pollard

Estrogen exposure is the major risk factor for diseases of the endometrium such as endometriosis and endometrial cancer. This is thought to be through its constant stimulation of epithelial cell proliferation. Progesterone blocks the estrogen-induced cell proliferation and exposure to it mitigates the risk for these diseases. However endometriotic tissue and cancer become progesterone resistant. Here (pp. E1382–E1391) we identify an estrogen induced pathway in uterine epithelial cells that activates protein synthesis through mechanistic target of rapamycin (mTOR) in a progesterone independent way. This indicates how protein and DNA synthesis regulation can be differentially controlled in vivo as progesterone blocks only the latter response. Inhibition of mTOR by rapamycin blocked E_2-induced protein and DNA synthesis, suggesting that it might be a therapeutic target for these diseases.

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

Danilo M. Daloso, Karolin Müller, Toshihiro Obata, Alexandra Florian, Takayuki Tohge, Alexandra Bottcher, Christophe Riondet, Laetitia Bariat, Fernando Carrari, Adriano Nunes-Nesi, Bob B. Buchanan, Jean-Philippe Reichheld, Wagner L. Araújo, and Alisdair R. Fernie

The present work extends redox-based change in enzyme activity to the TCA cycle of plant mitochondria. Thioredoxin (TRX) was found to regulate the activity of enzymes of the mitochondrial cycle (succinate dehydrogenase and fumarase) and of an enzyme associated with it (ATP-citrate lyase) by modulating thiol redox status. A combination of experiments based on mutant and carbon isotope labeling analyses provides evidence that flux through this pathway is coordinately modulated by TRX at the enzyme level of both mitochondria and cytosol. The results (pp. E1392–E1400) provide in vivo confirmation of earlier in vitro results and further show that mitochondria resemble plastids in using TRX and redox status to regulate the main carbon flux pathway of the organelle.