PNAS Plus Significance Statements

MuB is an AAA+ ATPase that forms helical filaments to control target selection for DNA transposition

Naoko Mizuno, Marija Dramićanin, Michiyo Mizuuchi, Julia Adam, Yi Wang, Yong-Woon Han, Wei Yang, Alasdair C. Steven, Kiyoshi Mizuuchi, and Santiago Ramón-Maiques

DNA transposons move from one genomic location to another using a transposase. A regulatory protein might assist in target selection and avoiding self-destruction. MuB is the regulatory protein of Mu transposon. Here we report that MuB is an AAA+ (ATPase associated with diverse cellular activities) ATPase and forms right-handed helical filaments around DNA. The helical parameters of MuB and DNA are mismatched and their interactions are nonuniform. We propose (pp. E2441–E2450) that enhanced ATP hydrolysis by MuB, induced by contacts with the MuA-transposon-end complex, leads to DNA deformation and bending at the MuB filament end, thus creating a favored target for transposition.

Measuring how much work the chaperone GroEL can do

Nicholas C. Corsepius and George H. Lorimer

Noncovalently "stacked" tetramethylrhodamine dimers are used (pp. E2451–E2459) to report and perturb the allosteric equilibrium in GroEL. The spectroscopic differences between the TMR monomers and dimers allow for quantitative measurements of the population of allosteric states. The noncovalent intersubunit stacking interaction within a dimer mimics the cross-linking constraint that SP places on the structure of GroEL. This feature allows TMR dimers to be used as SP surrogates to quantitate the impact of SP on the chaperonin cycle of GroEL. GroEL overcomes a load of 7.8 kJ/mol, demonstrating its ability to perform work on SP.

Model for macroevolutionary dynamics

Yosef E. Maruvka, Nadav M. Shnerb, David A. Kessler, and Robert E. Ricklefs

Genera are often viewed as artificial constructs of taxonomic practice. Here (pp. E2460–E2469), we show that a stochastic model that includes three events with constant rates—species formation, extinction of species, and origination of new genera—can describe well the species-within-genus distributions for large taxa. Predictions from the model, including origination times of large taxa and origination rates of genera, match values obtained by other methods. Likewise, estimated extinction rates are close to speciation rates, which is consistent with the paleontological record. The model's success emphasizes that, although taxonomic groupings are manmade, they nonetheless reflect natural evolutionary processes.

Mammalian *Exo1* encodes both structural and catalytic functions that play distinct roles in essential biological processes

Sonja Schaetzlein, Richard Chahwan, Elena Avdievich, Sergio Roa, Kaichun Wei, Robert L. Eoff, Rani S. Sellers, Alan B. Clark, Thomas A. Kunkel, Matthew D. Scharff, and Winfried Edelmann

Exonuclease1 (EXO1) is involved in a variety of DNA repair pathways and is implicated in multiple biological processes. To determine the contribution of the enzymatic and structural functions of EXO1 in these processes, we compared mice with catalytically inactive EXO1-knockin and complete EXO1-knockout mutations. We found (pp. E2470–E2479) that the catalytic function of EXO1 is essential for the DNA damage response, double-strand break repair, chromosomal stability, and tumor suppression, whereas EXO1's structural role alone is critical for mismatch repair, antibody diversification, and meiosis. Our study reveals differential requirements for both EXO1 functions in DNA repair and tumorigenesis in vivo.

Lineage tracing reveals multipotent stem cells maintain human adenomas and the pattern of clonal expansion in tumor evolution

Adam Humphries, Biancastella Cereser, Laura J. Gay, Daniel S. J. Miller, Bibek Das, Alice Gutteridge, George Elia, Emma Nye, Rosemary Jeffery, Richard Poulsom, Marco R. Novelli, Manuel Rodriguez-Justo, Stuart A. C. McDonald, Nicholas A. Wright, and Trevor A. Graham

The organization of cells within human colorectal adenomas, and specifically whether the tumors are maintained by stem cells, is unclear. Furthermore, the patterns of clonal evolution leading to the development of a malignant tumor have not been determined. We performed lineage tracing in human adenomas using a combination of nuclear and mitochondrial DNA lesions and epigenetic markers. Our data (pp. E2490–E2499) identify a stem cell population within adenomas and suggest that new growth of intratumor clones occurs infrequently, not as a steady continual process as often is assumed. Our work offers a unique insight into human cancer development.

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The antibiotic planosporicin coordinates its own production in the actinomycete *Planomonospora alba*

Emma J. Sherwood and Mervyn J. Bibb

A mechanism for regulating production of the antibiotic planosporicin by *Planomonospora alba* is described. A low level of planosporicin biosynthesis, probably stimulated by nutrient limitation, functions in a feed-forward mechanism to release a key regulatory protein required for high level production. Planosporicin also functions as an extracellular signaling molecule to induce its own synchronous production, presumably ensuring ecologically effective levels of the antibiotic by coordinating biosynthesis in the multicellular colony, regions of which have reached different levels of maturity. This information (pp. E2500–E2509) was used to increase the level of planosporicin production, with important implications for strain improvement.

Identification of a small molecule with activity against drug-resistant and persistent tuberculosis

Feng Wang, Dhinakaran Sambandan, Rajkumar Halder, Jianing Wang, Sarah M. Batt, Brian Weinrick, Insha Ahmad, Pengyu Yang, Yong Zhang, John Kim, Morad Hassani, Stanislav Huszar, Claudia Trefzer, Zhenkun Ma, Takushi Kaneko, Khisi E. Mdluli, Scott Franzblau, Arnab K. Chatterjee, Kai Johnson, Katarina Mikusova, Gurdyal S. Besra, Klaus Fütterer, William R. Jacobs, Jr., and Peter G. Schultz

The global problem of TB has worsened in recent years with the emergence of drug-resistant organisms, and new drugs are clearly needed. In a cell-based high-throughput screen, a small molecule, TCA1, was discovered that has activity against replicating and nonreplicating *Mycobacterium tuberculosis*. It is also efficacious in acute and chronic rodent models of TB alone or combined with frontline TB drugs. TCA1 functions by a unique mechanism, inhibiting enzymes involved in cell wall and molybdenum cofactor biosynthesis. This discovery (pp. E2510–E2517) represents a significant advance in the search for new agents to treat persistent and drug-resistant TB.

Aβ induces astrocytic glutamate release, extrasynaptic NMDA receptor activation, and synaptic loss

Maria Talantova, Sara Sanz-Blasco, Xiaofei Zhang, Peng Xia, Mohd Waseem Akhtar, Shu-ichi Okamoto, Gustavo Dziewczapolski, Tomohiro Nakamura, Gang Cao, Alexander E. Pratt, Yeon-Joo Kang, Shichun Tu, Elena Molokanova, Scott R. McKercher, Samuel Andrew Hires, Hagit Sason, David G. Stouffer, Matthew W. Buczynski, James P. Solomon, Sarah Michael, Evan T. Powers, Jeffery W. Kelly, Amanda Roberts, Gary Tong, Traci Fang-Newmeyer, James Parker, Emily A. Holland, Dongxian Zhang, Nobuki Nakanishi, H.-S. Vincent Chen, Herman Wolosker, Yuqiang Wang, Loren H. Parsons, Rajesh Ambasudhan, Eliezer Masliah, Stephen F. Heinemann, Juan C. Piña-Crespo, and Stuart A. Lipton

Communication between nerve cells occurs at specialized cellular structures known as synapses. Loss of synaptic function is associated with cognitive decline in Alzheimer's disease (AD). However, the mechanism of synaptic damage remains incompletely understood. Here (pp. E2518–E2527) we describe a pathway for synaptic damage whereby amyloid-β_{1-42} peptide ($A\beta_{1-42}$) releases, via stimulation of α7 nicotinic receptors, excessive amounts of glutamate from astrocytes, in turn activating extrasynaptic NMDA-type glutamate receptors (eNMDARs) to mediate synaptic damage. The Food and Drug Administration-approved drug memantine offers some beneficial effect, but the improved eNMDAR antagonist NitroMemantine completely ameliorates Aβ-induced synaptic loss, providing hope for disease-modifying intervention in AD.

Molecular mechanisms of multiple toxin–antitoxin systems are coordinated to govern the persister phenotype

Rick A. Fasani and Michael A. Savageau

Persisters are drug-tolerant bacteria that account for the majority of bacterial infections. They are not mutants, but rather slowly growing cells in a heterogeneous population. Evidence links them to the toxin–antitoxin systems present in nearly all bacteria. To explore the connection, we have created a system-level model of toxin–antitoxin systems that includes molecular mechanisms, stochastic fluctuations, variable growth rate, and population dynamics. The results (pp. E2528–E2537) quantitatively describe how a noisy environment can give rise to a bet-hedging subpopulation of persisters that always exists, not just in reaction to stress. Furthermore, multiple toxin–antitoxin systems can cooperate to increase the persister frequency.