PNAS Plus Significance Statements

Mathematical model of adult stem cell regeneration with cross-talk between genetic and epigenetic regulation

Jinzhi Lei, Simon A. Levin, and Qing Nie

This paper examines how adult stem cells maintain their ability to carry out a complex set of tasks, including tissue regeneration and replacement of defective cells. To do so, stem cell populations must coordinate differentiation, proliferation, and cell death (apoptosis) to maintain an appropriate distribution of epigenetic states. Using the tools of applied mathematics, and borrowing from the theory of intergenerational transfer of resources, this paper (pp. E880–E887) shows how control strategies during cell division should be chosen to maximize expected performance, utilizing cross-talk between genetic and epigenetic regulation and performance criteria during homeostasis. Heterogeneous proliferation, a mixed strategy in which not all cells have the same proliferation probability, is shown to increase robustness, and hence long-term performance.

A frequent, GxxxG-mediated, transmembrane association motif is optimized for the formation of interhelical Cα–H hydrogen bonds

Benjamin K. Mueller, Sabareesh Subramaniam, and Alessandro Senes

The transmembrane helices of single-span membrane proteins are commonly engaged in oligomeric interactions that are essential for structure and function. These interactions often occur in the form of recurrent structural motifs. Here we present an analysis of one of the most important motifs (GAS_{right}), showing that its geometry is optimized to form carbon hydrogen bonds at the helix–helix interface. The analysis reveals the structural basis for its characteristic GxxxG sequence signature. We built upon the analysis, creating a method that predicts known GAS_{right} structures at near-atomic precision. The work (pp. E888–E895) has implications for understanding membrane protein association, and for the prediction of unknown interacting GAS_{right} dimers among the thousands of single-span proteins in the proteomes of humans and higher organisms.

Prep1 and Meis1 competition for Pbx1 binding regulates protein stability and tumorigenesis

Leila Dardaei, Elena Longobardi, and Francesco Blasi

Tumor suppressor Pbx-regulating protein-1 (*Prep1*) and myeloid ecotropic viral integration site-1 (*Meis1*) oncogene are transcriptional regulators, which bind to the same partner, pre–B-cell leukemia homeobox-1 (*Pbx1*). *Meis1* overexpression induces tumorigenesis in $Prep1^{i/i}$ mouse embryonic fibroblasts, which is counteracted by *Prep1* reexpression. The mechanism is unique: by binding to Pbx1, Prep1 regulates the stability of Meis1 and Pbx1. Influencing Meis1 stability, Prep1 controls the transcriptional landscape of Meis1 and hence, its tumorigenic activity. We also identify (pp. E896–E905) two novel Meis1 binding proteins, Ddx3x and Ddx5 RNA helicases, that are essential for cell proliferation and tumorigenesis, and their interaction with Meis1 is impaired at low Meis1 level. Thus, the level and function of three proteins (Prep1, Meis1, and Pbx1) of the same family are regulated by their stability, which depends on their interaction.

Encoding regulatory state boundaries in the pregastrular oral ectoderm of the sea urchin embryo

Enhu Li, Miao Cui, Isabelle S. Peter, and Eric H. Davidson

Regulatory state boundary formation is a general process in early development, in which embryonic territory is divided up into spatial domains that express distinct sets of regulatory genes. We establish (pp. E906–E913) the mechanistic principles by which multiple orthogonal boundaries of this kind are progressively formed on the oral side of the sea urchin embryo, according to an encoded genomic program. These boundaries separate prospective endoderm from ectoderm domains, neurogenic from non-neurogenic domains, and ciliated band from oral ectoderm domains and produce an orthogonal grid of regulatory states. Boundary formation invariably depends on spatial transcriptional repression superimposed on more widespread domains of transcriptional activation.

Radiation dose rates now and in the future for residents neighboring restricted areas of the Fukushima Daiichi Nuclear Power Plant

Kouji H. Harada, Tamon Niisoe, Mie Imanaka, Tomoyuki Takahashi, Katsumi Amako, Yukiko Fujii, Masatoshi Kanameishi, Kenji Ohse, Yasumichi Nakai, Tamami Nishikawa, Yuuichi Saito, Hiroko Sakamoto, Keiko Ueyama, Kumiko Hisaki, Eiji Ohara, Tokiko Inoue, Kanako Yamamoto, Yukiyo Matsuoka, Hitomi Ohata, Kazue Toshima, Ayumi Okada, Hitomi Sato, Toyomi Kuwamori, Hiroko Tani, Reiko Suzuki, Mai Kashikura, Michiko Nezu, Yoko Miyachi, Fusako Arai, Masanori Kuwamori, Sumiko Harada, Akira Ohmori, Hirohiko Ishikawa, and Akio Koizumi

There is a potential risk of human exposure to radiation owing to the March 2011 Fukushima Daiichi Nuclear Power Plant accident. In this study (pp. E914–E923), we evaluated radiation dose rates from deposited radiocesium in three areas neighboring the restricted and evacuation areas in Fukushima. The mean annual radiation dose rate in 2012 associated with the accident was 0.89–2.51 mSv/y. The mean dose rate estimates in 2022 are comparable with variations of the average 2 mSv/y background radiation exposure from natural radionuclides in Japan. Furthermore, the extra lifetime integrated dose after 2012 is estimated to elevate lifetime risk of cancer incidence by a factor of 1.03 to 1.05 at most, which is unlikely to be epidemiologically detectable.

Homology-directed repair of DNA nicks via pathways distinct from canonical double-strand break repair

Luther Davis and Nancy Maizels

Nicks are a very common form of DNA damage, but their threat to genomic integrity has been neglected because it is assumed that all nicks are repaired by simple religation. Here we challenge that assumption. We identify (pp. E924–E932) a robust pathway for homology-directed repair (HDR) that is active at DNA nicks. This alternative HDR pathway is stimulated upon down-regulation of key factors in canonical HDR at double-strand breaks. Alternative HDR at targeted nicks has immediate practical applications to genome engineering. Alternative HDR can promote repair of a nicked target by a nicked donor and may thereby contribute to loss of heterozygosity, a common form of genomic instability in tumors.

Selective treatment and monitoring of disseminated cancer micrometastases in vivo using dual-function, activatable immunoconjugates

Bryan Q. Spring, Adnan O. Abu-Yousif, Akilan Palanisami, Imran Rizvi, Xiang Zheng, Zhiming Mai, Sriram Anbil, R. Bryan Sears, Lawrence B. Mensah, Ruth Goldschmidt, S. Sibel Erdem, Esther Oliva, and Tayyaba Hasan

Residual micrometastases following standard therapies limit our ability to cure many cancers. This article (pp. E933–E942) demonstrates a new therapy and visualization platform that targets residual cancer micrometastases with enhanced sensitivity and selectivity based on "tumor-targeted activation." This targeted activation feature not only provides a potent therapeutic arm that is effective against chemoresistant disease while minimizing side effects due to nonspecific toxicities but also enables micrometastasis imaging in common sites of disease recurrence to screen patients harboring residual tumor deposits. This approach offers promise for treating and monitoring drug-resistant micrometastases presently "invisible" to clinicians.

Mycobacterium abscessus cording prevents phagocytosis and promotes abscess formation

Audrey Bernut, Jean-Louis Herrmann, Karima Kissa, Jean-François Dubremetz, Jean-Louis Gaillard, Georges Lutfalla, and Laurent Kremer

Mycobacterium abscessus is the most frequently isolated rapidly growing mycobacterium in human disease and recently has emerged as responsible for severe pulmonary infections in cystic fibrosis patients. However, little is known about the virulence mechanisms of this human pathogen. We adapted the zebrafish embryo as a tractable infection model to study, at a spatiotemporal level, the physiopathology of *M. abscessus* infection. We describe the high propensity of virulent rough variant *M. abscessus* to produce serpentine cords in vivo, which are not observed with the less virulent smooth variant. We demonstrate (pp. E943–E952) that extracellular cording allows the bacterium to withstand phagocytosis, leading to uncontrolled growth and establishment of an acute and lethal infection, thus constituting a determinant of virulence.

Peptidoglycan-binding protein TsaP functions in surface assembly of type IV pili

Katja Siewering, Samta Jain, Carmen Friedrich, Mariam T. Webber-Birungi, Dmitry A. Semchonok, Ina Binzen, Alexander Wagner, Stuart Huntley, Jörg Kahnt, Andreas Klingl, Egbert J. Boekema, Lotte Søgaard-Andersen, and Chris van der Does

Type IV pili (T4P) are ubiquitous and versatile bacterial cell surface structures involved in different processes like adhesion to host cells, biofilm formation, motility, and DNA uptake. T4P play an important role in the pathogenesis of many bacteria. We identify (pp. E953–E961) a protein whose presence in bacterial genomes is strongly linked to the presence of T4P systems and that is involved in the surface assembly of T4P. TsaP, the T4P secretin-associated protein is proposed to anchor the outer membrane secretin complex to the peptidoglycan and/or to align the secretin to inner membrane components.

Task context impacts visual object processing differentially across the cortex

Assaf Harel, Dwight J. Kravitz, and Chris I. Baker

Visual recognition is often thought to depend on neural representations that primarily reflect the physical properties of the environment. However, in this study (pp. E962–E971) we demonstrate that the intent of the observer fundamentally perturbs cortical representations of visual objects. Using functional MRI we measured the patterns of response to identical objects under six different tasks. In any given task, these patterns could be used to distinguish which object was being viewed. However, this ability was disrupted when the task changed, indicating that object representations reflect not only the physical properties of the stimulus, but also the internal state of the observer.