PNAS Plus Significance Statements

Two-state dynamics of the SH3–SH2 tandem of Abl kinase and the allosteric role of the N-cap

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There is increasing interest in developing pharmacological strategies to inhibit the allosteric regulatory mechanisms of signaling enzymes. The Abl tyrosine kinase is a prominent target, due to its ubiquitous cellular role and its involvement in cancer. Here (pp. E3372–E3380), computational and experimental methods are used in synergy to probe the mechanism of the regulatory unit of Abl, whose dual function is to inhibit the enzyme and to mediate its interaction with other signaling proteins. Our results provide insights into the thermodynamic basis for the mechanism of Abl autoinhibition and activation and expand our understanding of the principles that govern modular domain organization.

Consequences of domain insertion on sequence-structure divergence in a superfold

Chetanya Pandya, Shoshana Brown, Ursula Pieper, Andrej Sali, Debra Dunaway-Mariano, Patricia C. Babbitt, Yu Xia, and Karen N. Allen

Here, we determine the impact of large-domain insertions on the sequence and structure divergence of a ubiquitous protein scaffold (superfold). By performing quantitative analysis on a distinctive dataset of >150 protein structures, unique protein-design principles have been uncovered. Our work (pp. E3381–E3387) suggests that superfolds are tolerant to relatively large domain insertions when followed by accommodating mutations in the scaffold. This structural robustness may facilitate the development of directed evolution technologies that incorporate domains into existing scaffolds.

Transcriptional response to stress in the dynamic chromatin environment of cycling and mitotic cells

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We determined the transcriptional program that is rapidly provoked to counteract heat-induced stress and uncovered the broad range of molecular mechanisms that maintain cellular homeostasis under hostile conditions. Because transcriptional responses are directed in the complex chromatin environment that undergoes dramatic changes during the cell cycle progression, we identified the genome-wide transcriptional response to stress also in cells where the chromatin is condensed for mitotic division. Our results (pp. E3388–E3397) highlight the importance of the cell cycle phase in provoking cellular responses and identify molecular mechanisms that direct transcription during the progression of the cell cycle.

Establishing a hematopoietic genetic network through locus-specific integration of chromatin regulators

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Broadly expressed enzymes commonly change chromatin structure and function. How ubiquitous chromatin regulators establish specialized patterns of gene activity is not understood. We identified an important link between a histone methyltransferase and a transcription factor (GATA-1) that controls red blood cell development. We found (pp. E3398–E3407) that distinct combinations of this enzyme and additional chromatin regulators are required for GATA-1 to control transcription at different genetic loci. The resulting regulatory "matrix" provides a conceptual framework for understanding how cell-restricted factors use broadly expressed chromatin regulators to confer specialized gene-expression patterns that control important biological processes.

Inherited mutations in the helicase RTEL1 cause telomere dysfunction and Hoyeraal–Hreidarsson syndrome

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Telomeres protect the ends of eukaryotic chromosomes. Telomeres shorten with age and serve as a biological clock that limits cell proliferation. Excessive telomere shortening accelerates aging, but telomere elongation may facilitate cancer. We found (pp. E3408–E3416) inherited mutations in the regulator of telomere elongation helicase 1 (RTEL1), which cause Hoyeraal–Hreidarsson syndrome, a fatal disease characterized by accelerated telomere shortening, immunodeficiency, and developmental defects. Introducing a normal RTEL1 gene into affected cells prevented telomere shortening and extended their lifespan in culture. The telomere defects, genomic instability, and growth arrest observed in RTEL1-deficient cells help in our understanding the central roles of telomeres in aging and cancer.

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Assembler for de novo assembly of large genomes

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Assembling a large genome faces three challenges: assembly quality, computer memory requirement, and execution time. Our developed assembler (pp. E3417–E3424), JR-Assembler, uses (*a*) a strategy that selects good seeds for contig construction, (*b*) an extension strategy that uses whole sequencing reads to increase the chance to jump over repeats and to expedite extension, and (*c*) detecting misassemblies by remapping reads to assembled sequences. Compared with current assemblers, JR-Assembler achieves a better overall assembly quality, requires less execution time and requires, with one exception, less memory. The advantages of JR-Assembler in memory usage and execution time will increase slowly as the read length increases. Thus, contrary to the prevailing view, the extension approach seems superior to the de Bruijn graph approach.

Hypoxic retinal Müller cells promote vascular permeability by HIF-1–dependent up-regulation of angiopoietin-like 4

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Ischemic retinopathies include a diverse group of diseases in which immature retinal vasculature or damage to mature retinal vessels leads to retinal ischemia. The anticipated rise in the worldwide prevalence of diabetes will result in a concurrent increase in the number of patients with vision impairment from diabetic eye disease, the most common cause of ischemic retinopathy. We set out to identify novel hypoxia-inducible genes that promote vascular permeability and may therefore play a role in the pathogenesis of diabetic eye disease. We demonstrate (pp. E3425–E3434) that angiopoietin-like 4 (ANGPTL4) is up-regulated by the transcriptional enhancer, hypoxia-inducible factor-1 in hypoxic retinal Müller cells, and can promote vascular permeability. Our findings suggest that ANGPTL4 may be a potential therapeutic target for ischemic retinopathies.

Two distinct forms of functional lateralization in the human brain

Stephen J. Gotts, Hang Joon Jo, Gregory L. Wallace, Ziad S. Saad, Robert W. Cox, and Alex Martin

This study (pp. E3435–E3444) alters our fundamental understanding of the functional interactions between the cerebral hemispheres of the human brain by establishing that the left and right hemispheres have qualitatively different biases in how they dynamically interact with one another. Left-hemisphere regions are biased to interact more strongly within the same hemisphere, whereas right-hemisphere regions interact more strongly with both hemispheres. These two different patterns of interaction are associated with left-lateralized functions, such as language and motor abilities, and right-lateralized functions, such as visuospatial attention. Importantly, the magnitude of lateralization measured for individual participants in these regions predicted the level of cognitive ability for the respective function, demonstrating that lateralization of function is associated with improved cognitive ability.

Stapled α–helical peptide drug development: A potent dual inhibitor of MDM2 and MDMX for p53-dependent cancer therapy

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Stapled α–helical peptides have emerged as a promising new modality for a wide range of therapeutic targets. Here (pp. E3445–E3454), we describe the development of a stapled α–helical peptide lead molecule for the treatment of cancers that possess the intact p53 tumor suppressor protein but are resistant to drug therapy because of the overexpression of inhibitory proteins MDM2 and MDMX. The molecule ATSP-7041 is a highly potent dual inhibitor of both MDM2 and MDMX that is shown to effectively reactivate the p53 tumor suppressor pathway in a mechanism-dependent manner in p53-positive cancers in vitro and in vivo.

Subtype-specific control of P2X receptor channel signaling by ATP and Mg^{2+}

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ATP is an important extracellular signal that activates P2X receptor channels. Although a large fraction of ATP is bound to divalent cations in vivo, the forms of ATP that activate P2X receptors are unknown. Here (pp. E3455–E3463) we show how the activity of homomeric P2X receptors is tuned by Mg^{2+} in some subtypes by preventing activation by free ATP, and in others by binding to a distinct regulatory site. We also find that both regulatory mechanisms are disengaged in heteromeric channels to form a sensitive ATP signaling pathway. These fundamental properties of P2X receptors will be valuable for investigating their physiological functions.