PNAS Plus Significance Statements

On the role of sidechain size and charge in the aggregation of Aβ42 with familial mutations

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The aggregation of the amyloid-β (Aβ) peptide into amyloid fibrils is associated with Alzheimer's disease, and several point mutations leading to early-onset disease have been identified in Aβ. By studying the aggregation of five disease-related mutations in vitro, we rationalize their link to familial Alzheimer's disease. We have determined the effect of mutations on the individual steps of the overall Aβ42 aggregation reaction and find for four of the mutations a significant increase in the rate of self-replication of fibrils, a process that has been linked to the production of toxic oligomeric species. Furthermore, by investigating the nature of the mutation, we determine the importance of the charge and size of specific residues in the aggregation of the wild-type peptide. (See pp. E5849–E5858.)

Enhanced mRNA delivery into lymphocytes enabled by lipid-varied libraries of charge-altering releasable transporters

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The transfection of lymphocytes with genetic material is a significant unmet need in immunotherapy and the treatment of many diseases. Current transfection strategies primarily rely on physical methods that must be conducted ex vivo and are often inefficient. We identified mixtures of lipid-varied mRNA delivery vehicles (charge-altering releasable transporters, CARTs) that show enhanced uptake into multiple lymphocyte cell types. The top performing lipid mixtures were rapidly identified using a combinatorial strategy and the resulting information was used to design single-delivery agents incorporating both lipid domains using our two-step organocatalytic ring-opening polymerization. Hybrid-lipid CARTs show >80% mRNA transfection efficiency in vitro and >1.5% lymphocyte transfection efficiency in mice, which is higher than previously reported systems. These materials should enable new immunotherapy strategies and applications. (See pp. E5859–E5866.)

NMR chemical shift analysis decodes olefin oligo- and polymerization activity of d^0 group 4 metal complexes

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The rational understanding and design of catalysts pose major challenges to chemists. While catalysts are involved in around 90% of industrial chemical processes, their discovery and development are usually based on screening and serendipity. Here, we show through a detailed analysis of the NMR chemical shift that the activity of olefin polymerization and oligomerization catalysts is directly related to the chemical shift of the carbon atom bound to the metal center. This relation is traced to specific frontier molecular orbitals, which induce π-character in the metal-alkyl bond, thereby favoring insertion. This result not only reveals a surprising analogy between olefin polymerization and metathesis, but also establishes chemical shift as a predictive descriptor for catalytic activity in these industrially relevant processes. (See pp. E5867–E5876.)

Direct observation and rational design of nucleation behavior in addressable self-assembly

Martin Sajfutdinow, William M. Jacobs, Aleks Reinhardt, Christoph Schneider, and David M. Smith

Current efforts aimed at constructing complex supramolecular structures often suffer from low yields or require long assembly protocols. We address these problems by demonstrating a facile strategy for optimizing the nucleation step of a multicomponent self-assembly reaction. By tracking the formation of multisubunit clusters in situ, our experiments show that modifying the critical nucleus required to initiate structure growth can broaden the range of conditions over which self-assembly occurs and, consequently, can dramatically improve the final yield of correctly formed structures. Since varying the design of only a small portion of the target structure optimizes its yield, this strategy provides a practical route to improve the speed and accuracy of self-assembly in biomolecular, colloidal, and nanoparticle systems. (See pp. E5877–E5886.)

High-speed microjets issue from bursting oil gland reservoirs of citrus fruit

Nicholas M. Smith, Hossein Ebrahimi, Ranajay Ghosh, and Andrew K. Dickerson

Here we show a unique, natural method for microscale jetting of fluid made possible by the tuning of material properties from which the jets emanate. The composite, layered construction of the citrus exocarp allows for the buildup of fluid pressure in citrus oil gland reservoirs and their subsequent explosive rupture. Citrus jetting has not been documented in literature, and its purpose is unknown. This method for microscale fluid dispersal requires no auxiliary equipment and may open avenues for new methods of medicine and chemical delivery. We show how jet kinematics are related to substrate properties and reservoir shape. (See pp. E5887–E5895.)

Chemoproteomics reveals baicalin activates hepatic CPT1 to ameliorate diet-induced obesity and hepatic steatosis

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Baicalin is a major flavonoid component from the herbal medicine *Scutellaria baicalensis* that has been shown to have an antisteatosis effect. Through quantitative chemoproteomic profiling, we discovered that baicalin acts as a natural allosteric activator of carnitine palmitoyltransferase 1 (CPT1), the rate-limiting enzyme of fatty acid β-oxidation (FAO). By directly binding to CPT1 and activating its activity to accelerate fatty acid degradation, baicalin can significantly ameliorate symptoms associated with hepatic steatosis and reduce diet-induced obesity (DIO). Our study provides an example of a natural product agonist for CPT1. The results provide mechanistic insights to explain the bioactivity of baicalin in reducing lipid accumulation and introduce exciting opportunities for developing novel flavonoid-based FAO activators for pharmacologically treating DIO and associated metabolic disorders. (See pp. E5896–E5905.)

Conformational control and DNA-binding mechanism of the metazoan origin recognition complex

Franziska Bleichert, Alexander Leitner, Ruedi Aebersold, Michael R. Botchan, and James M. Berger

The onset of chromosomal DNA replication relies on dedicated initiator proteins to chaperone ring-shaped helicases onto DNA. In most eukaryotes, initiators are multisubunit protein complexes that require ATP to bind DNA and to aid helicase recruitment and loading. Although structural studies have recently elucidated high-resolution views of the initiator in isolation or in helicase-containing loading intermediates, how the eukaryotic initiator itself associates with DNA and how these interactions are regulated by conformational changes are not well understood. We use a combination of biochemical and structural studies of the *Drosophila* initiator origin recognition complex (ORC) to show that conformational alterations in metazoan ORC help regulate its DNA-binding activity, and that ORC, together with its cofactor Cdc6, bends substrate DNA prior to helicase loading. (See pp. E5906–E5915.)

Flagellum couples cell shape to motility in *Trypanosoma brucei*

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Trypanosoma brucei is a highly invasive pathogen capable of penetrating deeply into host tissues. To understand how flagellar motility facilitates cell penetration, we used cryo-electron tomography (cryo-ET) to visualize two genetically anucleate mutants with different flagellar motility behaviors. We found that the *T. brucei* cell body is highly deformable as defined by changes in cytoskeletal twist and spacing, in response to flagellar beating and environmental conditions. Based on the cryo-ET models, we proposed a mechanism of how flagellum motility is coupled to cell shape changes, which may facilitate penetration through size-limiting barriers. (See pp. E5916–E5925.)

Microfluidic chambers using fluid walls for cell biology

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Despite improvements in our ability to manipulate ever-smaller volumes, most workflows in cell biology still use volumes of many microliters. We describe a method for creating microfluidic arrangements containing submicroliter volumes. It exploits interfacial forces dominant at the microscale to confine liquids with fluid (not solid) walls. We demonstrate many basic manipulations required for cell culture and some widely used downstream workflows. The method eliminates many problems associated with the fabrication of conventional microfluidic devices, thereby providing a simple on-demand approach for fabrication of microfluidic devices using materials familiar to biologists. (See pp. E5926–E5933.)

Suppression of connexin 43 phosphorylation promotes astrocyte survival and vascular regeneration in proliferative retinopathy

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Vascular regeneration during retinal ischemia is critical for curtailing hypoxia-driven aberrant neovascularization and neuronal damage. Apoptotic cell death of astrocytes is a key initiating factor for improper vascular growth. Here we report that astrocytic connexin (Cx43) gap junction (GJ) channels are major contributors to astrocyte degeneration and vascular remodeling that follow tissue ischemia. Astrocyte apoptosis is due to phosphorylation of Cx43 by casein kinase 1δ (CK1δ), which in turn leads to an increase in GJ coupling and amplification of injury. Deletion of Cx43 or inhibition of its phosphorylation by CK1δ rescues astrocytes and leads to restoration of a functional vasculature in the retina, while reducing neovascularization and improving neuroretinal function, thereby providing viable options for the treatment of ischemic retinopathies. (See pp. E5934–E5943.)

Regulation of a distinct activated RIPK1 intermediate bridging complex I and complex II in TNFα-mediated apoptosis

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This study demonstrates a distinct mode of RIPK1 activation mediated by a detergent-insoluble, highly ubiquitinated, activated RIPK1 species (iuRIPK1) which functions as a critical intermediate between TNF-receptor-associated complex I and assembly of the cytosolic caspase activation platform complex II in RIPK1-dependent apoptosis (RDA). By conducting a systematic screen for RDA regulators, we reveal the regulation of iuRIPK1 by Parkinson's disease (PD)-associated LRRK2, E3 ubiquitin ligase c-Cbl, and ALS-associated NEK1. These results point to possible mechanistic links between RIPK1-mediated apoptosis and neurodegenerative diseases such as ALS and PD. (See pp. E5944–E5953.)

Wnt/β-catenin signaling regulates ependymal cell development and adult homeostasis

Liujing Xing, Teni Anbarchian, Jonathan M. Tsai, Giles W. Plant, and Roeland Nusse

Little is known about the cellular origin and the molecular signals that regulate spinal cord ependymal cells. In this report, we characterize Wnt-responsive progenitor cells throughout spinal cord development, showing that they are restricted to the dorsal midline and give rise to dorsal ependymal cells in a spatially restricted pattern. In the postnatal and adult spinal cord, ependymal cells continue to exhibit Wnt/β-catenin signaling activity, which promotes ependymal cell proliferation. This is demonstrated by the genetic elimination of β-catenin and inhibition of Wnt secretion in Wnt-activated ependymal cells in vivo, which result in impaired proliferation. Our results thus reveal the molecular signals underlying the formation and regulation of spinal cord ependymal cells. (See pp. E5954–E5962.)

Metapopulation stability in branching river networks

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Metapopulation stability is a critical ecological property. Although ecosystem size has been considered as a fundamental driver of metapopulation stability, current theories developed in simplified landscapes may not be appropriate for complex branching ecosystems, such as rivers. Here, we show that a scale-independent characteristic of fractal river networks, branching complexity (measured as branching probability), stabilizes watershed metapopulations. We theoretically revealed that a strong association between branching complexity and metapopulation stability is a consequence of purely probabilistic processes. Furthermore, the stabilizing effect of branching complexity was consistently observed in metapopulations of four ecologically distinct riverine fishes. Hence, branching complexity may be a ubiquitous agent of metapopulation stability in branching ecosystems. The loss of such complexity may undermine resilience of metapopulations. (See pp. E5963–E5969.)

Recurrent symbiont recruitment from fungal parasites in cicadas

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Cicadas are dependent on the essential bacterial symbionts *Sulcia* and *Hodgkinia*. The symbiont genomes are extremely streamlined for provisioning of essential amino acids and other nutrients. In some cicada lineages, *Hodgkinia* genomes are fragmented into numerous minicircles, which may represent a critical stage of genomic erosion close to collapse. What would happen subsequently? Our survey of the Japanese cicada diversity revealed that while *Sulcia* is conserved among all species, the majority of them have lost *Hodgkinia* and instead harbor yeast-like fungal associates. The fungal symbionts are phylogenetically intermingled with cicada-parasitizing *Ophiocordyceps* fungi, indicating recurrent symbiont replacements by entomopathogens in cicadas and providing insights into the mechanisms underlying the parasitism-symbiosis evolutionary continuum, compensation of symbiont genome erosion, and diversification of host-symbiont associations. (See pp. E5970–E5979.)

Distinct human circulating NKp30$^+$FcεRIγ$^+$CD8$^+$ T cell population exhibiting high natural killer-like antitumor potential

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CD8$^+$ T cell recognition of tumor cells is typically based on the detection of specific MHC–peptide complexes, while natural killer (NK) cell recognition relies on the detection of NK ligands by an array of NK receptors. In this study we uncovered a distinct small population of CD8$^+$ T cells expressing NKp30, a potent activating NK receptor, on peripheral blood from healthy donors. Those innate-like CD8$^+$ T cells, coexpressing FcεRIγ and PZLF, could be generated and differentiated from a population of peripheral blood CD8$^+$ T cells as result of IL-15–driven acquisition of broad innate features. This unique effector population could potently control the growth of tumors in an NK-like manner, making it promising for cancer immunotherapy by its dual target-recognition potential. (See pp. E5980–E5989.)

Hypoxic tumor microenvironment activates GLI2 via HIF-1α and TGF-β2 to promote chemoresistance in colorectal cancer

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Colorectal cancer patients often relapse due to resistance to chemotherapy. The tumor microenvironment is known to contribute to tumor aggressiveness and chemoresistance, but the underlying mechanisms remain elusive. In the current study, we have shown that cancer-associated fibroblasts (CAFs) which are often present in the tumor can greatly promote resistance of colorectal cancer cells to chemotherapy. In the low-oxygen condition (hypoxia), CAFs-secreted growth factor TGF-β2 can induce strong expression of *GLI2*, a gene that can induce resistance to therapy. As such, therapeutic targeting of TGF-β and GLI2 can be developed into a useful adjuvant to enhance the effect of chemotherapies. (See pp. E5990–E5999.)

Glycosylation-dependent galectin–receptor interactions promote *Chlamydia trachomatis* infection

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Chlamydia trachomatis (*Ct*) is the most common bacterium responsible for sexually transmitted infections. It constitutes a major public health burden, with the greatest clinical impact occurring in women of reproductive age. A vast proportion of *Ct* infections

are underestimated because they are asymptomatic in nature. This leads to chronic infections with severe consequences, such as ectopic pregnancy, tubal obstruction, infertility, and blindness. *Ct* is an obligate intracellular pathogen that completes its entire developmental cycle in humans. Here, we demonstrate that galectin-1 (Gal1), an endogenous glycan-binding protein, promotes *Ct*–host adhesion and invasion. Through glycosylation-dependent mechanisms, Gal1 enhances chlamydial infection by favoring *Ct*–host cell interactions. Thus, novel therapeutic approaches aimed at disrupting Gal1–*N*-glycan interactions may reduce the severity of *Ct* infections. (See pp. E6000–E6009.)

Cancer-mutation network and the number and specificity of driver mutations

Jaime Iranzo, Iñigo Martincorena, and Eugene V. Koonin

Cancer genomics yields a wealth of information on cancer-associated mutations in various cancer types, but current understanding of the number and tissue specificity of the driver mutations remains limited. We applied mathematical methods for network analysis to identify distinct modules linking tumors to driver mutations. About 27% of the tumors belong to such modules, whereas the rest form a diffuse component of the gene–tumor network. The cancers from the diffuse component show an onset later in life than those in the modules and have fewer associated known drivers, implying the existence of multiple unidentified and/or interchangeable drivers in the former. (See pp. E6010–E6019.)

A disordered acidic domain in GPIHBP1 harboring a sulfated tyrosine regulates lipoprotein lipase

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Dietary fats absorbed by intestinal enterocytes are packaged into chylomicrons, which circulate in the bloodstream until docking along capillary endothelial cells, primarily in striated muscle and adipose tissue. There, a functional unit composed of lipoprotein lipase (LPL) and GPIHBP1 hydrolyzes the triglycerides in chylomicrons, releasing free fatty acids for use by surrounding parenchymal cells. The current study describes the interactions between LPL and GPIHBP1 and describes how a disordered region of GPIHBP1 results in order and functional stability within LPL. The elucidation of LPL–GPIHBP1 interactions sheds light on the regulation of intravascular triglyceride processing and provides insights into plasma triglyceride metabolism in health and disease. (See pp. E6020–E6029.)

YES1 amplification is a mechanism of acquired resistance to EGFR inhibitors identified by transposon mutagenesis and clinical genomics

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Despite high response rates to treatment with small molecule inhibitors of EGFR tyrosine kinase activity, patients with *EGFR*-mutant lung adenocarcinomas eventually develop resistance to these drugs. In many cases, the basis of acquired resistance remains unclear. We have used a transposon mutagenesis screen in an *EGFR*-mutant cell line and clinical genomic sequencing in cases of acquired resistance to identify amplification of *YES1* as a targetable mechanism of resistance to EGFR inhibitors in *EGFR*-mutant lung cancers. (See pp. E6030–E6038.)

A noncanonical PPARγ/RXRα-binding sequence regulates leptin expression in response to changes in adipose tissue mass

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Leptin gene expression is highly correlated with the lipid content of individual fat cells, suggesting that it is regulated by a "fat-sensing" signal transduction pathway. This possibility is thus analogous to the identification of a cholesterol-sensing pathway by studying the regulation of the LDL receptor gene by intracellular cholesterol. Several lines of investigation have suggested that, in addition to adipocytes, liver, neurons, and other cell types can sense changes in lipid content, although the molecular mechanisms are unknown. The data here provide a critical step toward elucidating the components of this putative system, which would be of great importance. These studies also identify a previously underappreciated role of the PPARγ/RXRα complex to regulate leptin expression. (See pp. E6039–E6047.)

Direct activation of a phospholipase by cyclic GMP-AMP in El Tor *Vibrio cholerae*

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Second messengers are employed by all organisms to regulate fundamental behaviors, including biofilm formation, motility, metabolism, and pathogenesis in bacteria. We have identified a phospholipase in the El Tor *Vibrio cholerae* biotype, responsible for the current cholera pandemic, that is directly activated by the second messenger 3′, 3′-cyclic GMP-AMP (cGAMP). Discovery of this proteinaceous bacterial cGAMP effector sheds light on the functions and basic principles of cGAMP signaling. Both this phospholipase and the cGAMP synthase are encoded within the VSP-1 pathogenicity island, unique to the El Tor biotype, and our findings assign a biochemical function to VSP-1 that may contribute to the epidemiological success of El Tor *V. cholerae*. (See pp. E6048–E6055.)

Neural network retuning and neural predictors of learning success associated with cello training

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In sophisticated auditory–motor learning such as musical instrument learning, little is understood about how brain plasticity develops over time and how the related individual variability is reflected in the neural architecture. In a longitudinal fMRI training study on cello learning, we reveal the integrative function of the dorsal cortical stream in auditory–motor information processing, which comes online quickly during learning. Additionally, our data show that better performers optimize the recruitment of regions involved in auditory encoding and motor control and reveal the critical role of the pre-supplementary motor area and its interaction with auditory areas as predictors of musical proficiency. The present study provides unprecedented understanding of the neural substrates of individual learning variability and therefore has implications for pedagogy and rehabilitation. (See pp. E6056–E6064.)

Caspase-1 inhibition prevents glial inflammasome activation and pyroptosis in models of multiple sclerosis

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The pore-forming protein gasdermin D (GSDMD) was recently identified as the principal executioner of pyroptosis ("fiery death"), a type of proinflammatory programmed cell death driven by inflammasomes. Caspase-1 cleaves GSDMD, but whether this process contributes to neuroinflammation is unknown. Here, we report evidence of GSDMD-mediated pyroptosis as a primary mechanism of inflammatory demyelination in the central nervous system during multiple sclerosis (MS), a debilitating and incurable demyelinating disease that causes profound loss of myelin-forming oligodendrocytes. By identifying GSDMD induction and pyroptosis in oligodendrocytes and microglia, we discovered a previously unrecognized mechanism driving neuroinflammation and demyelination. Pharmacologically inhibiting caspase-1 prevented pyroptosis in experimental models of MS, reducing demyelination and neurodegeneration. These findings highlight therapeutic approaches for understanding and treating inflammatory demyelination. (See pp. E6065–E6074.)

LOW PHOTOSYNTHETIC EFFICIENCY 1 is required for light-regulated photosystem II biogenesis in *Arabidopsis*

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Photosystem II (PSII) reaction center protein D1 is encoded by chloroplast gene *psbA* and is crucial to the biogenesis and functional maintenance of PSII. D1 proteins are highly dynamic under varying light conditions and thus require efficient synthesis, but the mechanism remains poorly understood. We reported that *Arabidopsis* LPE1 directly binds to the 5′ UTR of *psbA* mRNA in a light-dependent manner through a redox-based mechanism and facilitates the association of HCF173 with *psbA* mRNA to regulate D1 translation. These findings fill a major gap in our understanding of the mechanism of light-regulated D1 synthesis in higher plants and imply that higher plants and primitive photosynthetic organisms share conserved mechanisms but use distinct regulators to regulate biogenesis of PSII subunits. (See pp. E6075–E6084.)

A stress recovery signaling network for enhanced flooding tolerance in *Arabidopsis thaliana*

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Flooding due to extreme weather events can be highly detrimental to plant development and yield. Speedy recovery following stress removal is an important determinant of tolerance, yet mechanisms regulating this remain largely uncharacterized. We identified a regulatory network in *Arabidopsis thaliana* that controls water loss and senescence to influence recovery from prolonged submergence. Targeted control of the molecular mechanisms facilitating stress recovery identified here could potentially improve performance of crops in flood-prone areas. (See pp. E6085–E6094.)