PNAS Plus Significance Statements

Nascent peptides that block protein synthesis in bacteria

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Ribosomes synthesize all proteins in living cells. There are limits, however, to which sequences they can make. We identified (pp. E878–E887) short motifs within translating proteins that inhibit their own synthesis. We developed in vitro methods to determine the molecular mechanism of ribosome stalling by these motifs. Some act by blocking the formation of peptide bonds; in a few of these cases, a translation factor, elongation factor P, alleviates stalling. Other motifs block release of the protein at stop codons. Stalling motifs occur less often than expected in bacterial proteins, suggesting that proteins have evolved to be synthesized efficiently.

Phenotypic model for early T-cell activation displaying sensitivity, specificity, and antagonism

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Early immune response has to discriminate a few foreign peptides rapidly from a vast excess of self-peptides, and it is unclear in quantitative terms how this is possible. We show (pp. E888–E897) that a generic proofreading cascade supplemented by a single negative feedback mediated by the Src homology 2 domain phosphatase-1 (SHP-1) accounts quantitatively for this discrimination. Our model, with minimal variables and parameters, can fit a large body of experimental data and accounts for phenotypes in T-cell activation. New experiments validate our predictions and provide a quantitative understanding of antagonism, the effect by which foreign ligands close to activation alter the immune response.

Responses of hair follicle–associated structures to loss of planar cell polarity signaling

Hao Chang and Jeremy Nathans

In mammals, hair follicles reside in the skin together with a set of follicle-associated structures: sebaceous glands, nerve fibers, specialized sensory cells, and muscle fibers. In general, the follicle and its associated structures are precisely oriented with respect to the body axes. The present study (pp. E908–E917) shows that, in mice genetically engineered to lack the follicle orienting system, the follicle-associated structures—with the exception of the specialized sensory cells—acquire an orientation that matches that of the follicle. These experiments imply that hair follicles communicate local orienting information to most of their associated structures.

Wnt and CDK-1 regulate cortical release of WRM-1/β-catenin to control cell division orientation in early *Caenorhabditis elegans* embryos

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Cellular asymmetry, or polarity, is essential for development and tissue homeostasis. In *Caenorhabditis elegans*, the conserved Wnt signal transduction pathway orients the cell division axis and polarizes the EMS blastomere to promote endoderm fate. This work (pp. E918–E927) provides a mechanism for how the Wnt/β-catenin pathway integrates spatial and temporal cues important for the cell division axis. We show that CDK-1 phosphorylates and promotes the release of cortical β-catenin, which brings Wnt signaling under cell cycle control and facilitates spindle rotation. Cell cycle control of developmental decisions may be particularly important in embryos or tissues that undergo rapid cell divisions and patterning.

Unraveling the signaling pathways promoting fibrosis in Dupuytren's disease reveals TNF as a therapeutic target

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Fibrosis, a hallmark of many clinical disorders, occurs because of uncontrolled myofibroblast activity. We studied Dupuytren's disease, a common hereditable fibrotic condition that causes the fingers to irreversibly curl toward the palm. We found (pp. E928–E937) that freshly isolated tissue from Dupuytren's patients contained macrophages and released proinflammatory protein mediators (cytokines). Of the cytokines, only TNF selectively converted normal fibroblasts from the palm of patients with Dupuytren's disease into myofibroblasts via activation of the Wnt signaling pathway. Conversely, blockade of TNF resulted in reversal of the myofibroblast phenotype. Therefore, TNF inhibition may prevent progression or recurrence of Dupuytren's disease.

Mechanistic link between β barrel assembly and the initiation of autotransporter secretion

Olga Pavlova, Janine H. Peterson, Raffaele Ieva, and Harris D. Bernstein

Most proteins that reside in the bacterial outer membrane are β sheets that fold into a unique cylindrical structure known as a "β barrel." Here (pp. E938–E947) we describe significant insights into the function of the Bam complex, a protein machine that catalyzes the insertion of β barrel proteins into the membrane by an unknown mechanism. By analyzing the assembly of autotransporters, a specialized family of outer membrane proteins, we found that the function of the Bam complex can be divided into an initial substrate binding stage and a subsequent insertion stage that is surprisingly sensitive to structural distortions in client proteins.

The δ2 glutamate receptor gates long-term depression by coordinating interactions between two AMPA receptor phosphorylation sites

Kazuhisa Kohda, Wataru Kakegawa, Shinji Matsuda, Tadashi Yamamoto, Hisashi Hirano, and Michisuke Yuzaki

Long-term depression (LTD) commonly affects learning and memory in various brain regions. Although LTD in the cerebellum absolutely requires δ2 glutamate receptors, its underlying mechanisms remain elusive. LTD is caused by endocytosis of AMPA receptors, which is triggered by activity-induced serine phosphorylation of the GluA2 subunit. Our work (pp. E948–E957) showed that this serine phosphorylation required prior dephosphorylation of the nearby tyrosine residue. By interaction with a tyrosine phosphatase, δ2 glutamate receptors regulated tyrosine dephosphorylation status of GluA2 to gate inducibility of LTD. These findings will provide better understanding of general mechanisms regulating AMPA receptor endocytosis during synaptic plasticity.