PNAS Plus Significance Statements

A unique squalenoylated and nonpegylated doxorubicin nanomedicine with systemic long-circulating properties and anticancer activity

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We identified (pp. E217–E226) that the chemical linkage of the anticancer drug doxorubicin onto squalene, a natural lipid precursor of the cholesterol's biosynthesis, led to the formation of squalenoyl doxorubicin nanoassemblies of 130-nm mean diameter, with an original "loop-train" structure. This unique nanomedicine demonstrates: (*i*) high drug payload, (*ii*) decreased toxicity of the coupled anticancer compound, (*iii*) improved therapeutic response, (*iv*) use of biocompatible transporter material, and (*v*) ease of preparation, all criteria that are not combined in the currently available nanodrugs. Taken together, these findings demonstrate that the squalenoylated doxorubicin nanoassemblies make tumor cells more sensitive to doxorubicin and reduce the cardiac toxicity.

Calmodulin regulates dimerization, motility, and lipid binding of *Leishmania* myosin XXI

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Myosin XXI is the only myosin isoform expressed in the *Leishmania* parasite. The myosin-XXI homozygous knockout is lethal, and a reduction in expression levels leads to loss of endocytosis and affects other intracellular trafficking processes. In this paper (pp. E227–E236) we show that myosin XXI can adopt a monomeric or dimeric state. The states are determined by calmodulin binding to an IQ motif that, when bound, prevents dimerization of a coiled-coil motif. In the monomeric state the motor binds phospholipids and is motile whereas the dimeric state is unable to bind lipids or to generate motility, but can cross-link actin filaments. Regulation of dimerization, motility, and lipid binding by calmodulin is a mechanism for the myosin family of motor proteins.

Apo-bacteriophytochromes modulate bacterial photosynthesis in response to low light

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Bacteriophytochromes (BphPs) are regulatory proteins that bind a light-absorbing chromophore called biliverdin. Recombinant BphPs show promise for use in regulating neuron function in mammals with light. We explored the possibility that BphPs may sense cues in addition to light. Our motivation was that biliverdin requires oxygen for its synthesis, and some bacteria use BphPs to control photosynthesis in the absence of oxygen. We found (pp. E237–E244) that the photosynthetic bacterium *Rhodopseudomonas palustris* requires two BphP proteins to sense low light when grown in the absence of oxygen; however, the BphPs do not need to have their chromophore to sense low light intensities. BphPs may respond to intracellular signals, such as reducing conditions, in addition to light to regulate downstream functions.

TRIM14 is a mitochondrial adaptor that facilitates retinoic acid-inducible gene-I–like receptor-mediated innate immune response

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The innate immune system plays a key role in host defense that involves the detection of microbial components and a series of signaling events that lead to production of interferons and cytokines. Recently, the identification of mitochondrial antiviral-signaling (MAVS) protein placed mitochondria at the forefront of the innate immune response against virus infection. However, how the MAVS signaling complex is assembled and regulated on the mitochondria outer membrane is only partially understood. Here (pp. E245–E254) we show that tripartite motif 14 (TRIM14) facilitates the assembly of the MAVS complex assembly. Upon virus infection, TRIM14 recruits NF-κB essential modulator (NEMO) to the MAVS complex via ubiquitin chains. Knockdown of TRIM14 disrupts the MAVS–NEMO association and attenuates the antiviral response. Our results thus provide a missing link in MAVS-mediated innate immune signaling.

ParP prevents dissociation of CheA from chemotactic signaling arrays and tethers them to a polar anchor

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Targeting of cellular components to a particular site in a cell is often a highly regulated process, even in cells as small as bacteria. Robust chemotactic signaling, which is used by motile bacteria to survey their environments and navigate in response to them, requires appropriate cellular distribution of a large chemosensory apparatus. Here (pp. E255–E264), we report how polarly flagellated vibrios ensure polar localization of their chemotactic machinery by capturing signaling proteins at the pole. Polar localization is mediated by a tripartite protein interaction network in which one protein prevents disassociation of a key signaling component from chemotactic complexes and tethers the complexes to a polar anchor. Polar tethering and localization are prerequisites for proper chemotaxis.

Inhibition of interferon gene activation by death-effector domain-containing proteins from the molluscum contagiosum virus

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Viruses express proteins that circumvent immune responses. In some cases, these viral proteins are homologous to cellular proteins. For example the poxviral MC159 and MC160 proteins are homologous to cellular FLICE-like inhibitory protein (FLIP). Each protein inhibited IFN-β activation, identifying a unique function for FLIPs. Surprisingly, the viral proteins possessed different biological mechanisms for inhibition (pp. E265–E272). MC159 bound to upstream activators of this pathway (namely TBK1 and IKKε) to inhibit IRF3 but MC160 did not. Moreover, the MC159 and MC160 regions responsible for inhibition did not overlap. Scientists can uncover new pathways of immune system regulation and new means for manipulating immune responses by comparing the molecular functions of these viral and cellular FLIPs.

Hydrophobic plug functions as a gate in voltage-gated proton channels

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Voltage-gated proton (Hv1) channels play important roles in various physiological processes, such as the innate immune response. However, the mechanism by which this channel closes and opens its proton permeation pathways is unknown, due to the lack of structural information about the closed and open states of the channel. This study (pp. E273–E282) uses both simulation and experimental approaches to develop models of the closed and open states of the Hv1 channel. These models suggest a mechanism for how the channel closes and opens. The models also suggest a mechanism explaining why a blocker only binds to the open state of the channel. These structural models will be essential for future investigations of this channel and the development of new pharmacological blockers.

Mutation of the palmitoylation site of estrogen receptor α in vivo reveals tissue-specific roles for membrane versus nuclear actions

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The in vivo roles of plasma membrane-associated estrogen receptor (ER)α, including cross-talk with nuclear ERα, are poorly understood. We created a mouse with a point mutation of the palmitoylation site of ERα (C451A-ERα) to obtain membrane-specific loss of function. A complementary mouse lacking the ERα activation function AF-2 (ERα-AF2^0) provided selective loss of function of nuclear ERα actions. Physiologic studies revealed critical requirements for membrane receptors in ovarian function and thereby in fertility, and in vascular physiology. In contrast, nuclear ERα actions mediate uterine responses to estrogen and genome-wide analysis indicates that membrane-to-nuclear receptor cross-talk in vivo is quite modest in uterus. These findings (pp. E283–E290) demonstrate for the first time critical tissue-specific roles for membrane versus nuclear actions of a steroid hormone receptor in vivo.

Foveal analysis and peripheral selection during active visual sampling

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Picking up visual information from our environment in a timely manner is the starting point of adaptive visual-motor behavior. Humans and other animals with foveated visual systems extract visual information through a cycle of brief fixations interspersed with gaze shifts. Object identification typically requires foveal analysis (limited to a small region of central vision). In addition, the next fixation location needs to be selected using peripheral vision. How does the brain coordinate these two tasks on the short time scale of individual fixations? We show that the uptake of information for foveal analysis and peripheral selection occurs in parallel and independently. These results (pp. E291–E299) provide important theoretical constraints on models of eye movement control in a variety of visual-motor domains.