PNAS Plus Significance Statements

An invertebrate smooth muscle with striated muscle myosin filaments

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All animals have the ability to move. In most animals, striated muscles move the body and smooth muscles the internal organs. In both muscles, contraction results from interaction between myosin and actin filaments. Based on vertebrate studies, smooth and striated muscles are thought to have different protein components and filament structures. We have studied muscle ultrastructure in the parasite *Schistosoma mansoni*, where we find that this view is not supported. This invertebrate possesses only smooth muscles, yet its myosin sequence and filament structure are identical to those of striated muscle, while its actin filaments are smooth muscle-like. Such "hybrid" muscles may be common in other invertebrates. This finding challenges the paradigm that smooth and striated muscles always have different components. (See pp. E5660–E5668.)

Direct link between metabolic regulation and the heat-shock response through the transcriptional regulator PGC-1α

Neri Minsky and Robert G. Roeder

In recent years an extensive effort has been made to elucidate the molecular pathways involved in metabolic signaling. Our study shows, surprisingly, a direct link between metabolic regulation and the heat-shock response, a highly conserved transcriptional program that is activated in the presence of various environmental stresses. Specifically, we demonstrate that peroxisome proliferator-activated receptor γ coactivator 1α, a critical and well-established inducible transcriptional coactivator of metabolic genes, acts as a direct transcriptional repressor of heat-shock factor 1, a key regulator of the heat-shock/stress response and a factor more recently demonstrated to be necessary for cancer initiation and survival. Thus, our findings have possible implications both for our understanding of the full scope of metabolically regulated target genes in vivo and, conceivably, for therapeutics. (See pp. E5669–E5678.)

A respiratory chain controlled signal transduction cascade in the mitochondrial intermembrane space mediates hydrogen peroxide signaling

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Both the mitochondrial respiratory chain and reactive oxygen species (ROS) control numerous physiological and pathological cellular responses. ROS such as hydrogen peroxide (H_2O_2) are thought to initiate signaling by broadly and nonspecifically redox-modifying signaling molecules, suggesting that H_2O_2 signaling may be distinct from other signal transduction pathways. Here, we provide evidence suggesting that H_2O_2 signaling is under control of what appears to be a typical signal transduction cascade that connects the respiratory chain to the mitochondrial intermembrane space-localized conserved Syk pathway and results in a focused signaling response in diverse cell types. The results thus reveal a mechanism that allows the respiratory chain to communicate with the remainder of the cell in response to ROS. (See pp. E5679–E5688.)

Consequences of zygote injection and germline transfer of mutant human mitochondrial DNA in mice

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Therapies for Leber hereditary optic neuropathy (LHON), in common with all disorders caused by mutated mtDNA, are inadequate, in part because of the absence of suitable animal models. To test a potential therapy, we introduced mutant human NADH ubiquinone oxidoreductase subunit 4 DNA directly into mitochondria of mouse zygotes to generate transgenic LHON mice. This mutation in mice caused the hallmark visual loss and optic neuropathy seen in LHON patients. We reversed the blindness by gene therapy with the wild-type allele. To our knowledge, this is the first description of a mouse model with the same genotype and phenotype as the human counterpart disorder. This innovative technology has implications not only for creating mouse models of mutant mtDNA but also for treating the mitochondrial dysfunction with gene therapy. (See pp. E5689–E5698.)

Activation of cyclic GMP-AMP synthase by self-DNA causes autoimmune diseases

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The immune system detects microbial DNA in the cytosol of infected cells and mounts effective antimicrobial responses, including the production of type-I interferons. However, when self-DNA enters or accumulates in the cytosol, it can cause autoimmune diseases. Mutations of the exonuclease Trex1 in humans have been linked to autoimmune diseases including Aicardi–Goutieres Syndrome (AGS) and systemic lupus erythematosus (SLE). In mice, genetic deletion of Trex1 or the lysosomal nuclease DNaseII leads to lethal autoimmune diseases. Here we show that cyclic GMP-AMP synthase (cGAS) activation by self-DNA is responsible for the lethal autoimmune diseases in these models. These results provide the proof-of-concept that inhibition of cGAS may be an effective therapy for some autoimmune diseases such as AGS and SLE. (See pp. E5699–E5705.)

Mutation of the ER retention receptor KDELR1 leads to cell-intrinsic lymphopenia and a failure to control chronic viral infection

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Chaperones in the endoplasmic reticulum (ER) are essential for protein folding and for the maintenance of an efficient secretory pathway. These chaperones can also accompany their substrates during transit from the ER to the Golgi. The prototypical mammalian KDEL receptor (KDELR1) functions by returning chaperones and other proteins to the ER. We show that a recessive missense mutation of *Kdelr1* in mice is associated with low numbers of lymphocytes in the blood (lymphopenia), reduced expression of the T-cell receptor, and compromised antiviral immunity. (See pp. E5706–E5714.)

Mapping of histone modifications in episomal HBV cccDNA uncovers an unusual chromatin organization amenable to epigenetic manipulation

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Chronic hepatitis B virus (HBV) infection is maintained by the persistence of episomal HBV closed circular DNA (cccDNA) in infected hepatocytes. Current therapeutic regimes have no or limited impact on cccDNA, and the development of cccDNA-targeted therapies is complicated by our limited understanding of cccDNA regulation. We present a novel approach and first detailed analysis to our knowledge of cccDNA chromatin from de novo infected cells and infected liver tissue and reveal general features of cccDNA chromatin organization, and features that are unique to each source of cccDNA. We show that cccDNA chromatin is modulated by innate immunity and manipulated with an epigenetic agent, thereby establishing the importance of chromatin for cccDNA regulation and as a potential target for therapy of chronic HBV infection. (See pp. E5715–E5724.)

Remodeling nuclear architecture allows efficient transport of herpesvirus capsids by diffusion

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The nucleus is structured into chromatin and interchromatin compartments. Its sieve-like architecture permits individual proteins to rapidly diffuse while large macromolecular assemblies are corralled in the interchromatin. Herpesvirus capsids assemble in the nucleus and have to access the nuclear periphery for exit. It was hypothesized that nuclear herpesvirus capsids recruit filamentous actin and molecular motor protein to overcome nuclear entrapment. Here we use "ring-sheet" microscopy to track nuclear capsids with high spatiotemporal resolution. We report that nuclear herpesvirus capsids do not use directed motility. Instead, virus infection changes nuclear architecture, which allows capsids to reach the nuclear membranes by diffusion. Our findings illustrate a pathway for very large macromolecular assemblies to cross the nucleoplasm without directed motility. (See pp. E5725–E5733.)

Melanopsin-driven increases in maintained activity enhance thalamic visual response reliability across a simulated dawn

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Irradiance-dependent ("luxotonic") changes in baseline firing were first described in neurones of the early visual system decades ago. However, the origin and function (if any) of this visual response is still poorly understood. Here we address both questions by recording electrophysiological activity in mouse dorsal lateral geniculate nucleus over a simulated dawn. First, we show that in the photopic regime luxotonic activity becomes increasingly driven by inner-retinal melanopsin photoreceptors as irradiance increases. Then, that irradiance-dependent increases in activity apply not only to baseline firing but also to the amplitude of fast visual responses, producing increases in signal: noise across the simulated dawn, revealing a function for luxotonic activity and a new way in which inner retinal photoreceptors support conventional vision. (See pp. E5734–E5743.)

Calcineurin mediates homeostatic synaptic plasticity by regulating retinoic acid synthesis

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Chronic reduction of synaptic activity in neural networks leads to compensatory changes at both excitatory and inhibitory synapses, a phenomenon known as homeostatic synaptic plasticity. Postsynaptic activity/Ca^{2+}-dependent regulation of retinoic acid (RA) synthesis is critically involved in homeostatic synaptic plasticity; however, the signaling molecule that gates RA synthesis in response to Ca^{2+} level changes remains unknown. Using pharmacologic and genetic manipulations, we show that calcineurin (CaN) activity, which is regulated by postsynaptic Ca^{2+} levels, directly controls RA synthesis. Inhibiting CaN activity or genetic ablation of CaN leads to homeostatic modulation of synaptic transmission in an RA signaling-dependent manner. These findings uncover the molecular mechanism by which activity regulates synaptic strength through RA synthesis. (See pp. E5744–E5752.)

Drosophila TRPA1 isoforms detect UV light via photochemical production of H_2O_2

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Discovering new light-sensing mechanisms and cell types are of considerable interest to researchers across disciplines. Understanding how cells sense light is one of the most fundamental problems in biology. In addition, optogenetics has become a critical research tool and discovery of new light-sensing mechanisms may expand the existing toolbox. In this work, we described our discovery of a dTRPA1-dependent photochemical pathway that is sufficient to confer UV sensitivity to light-insensitive cells. We also discovered a group of neuroendocrine cells that express these isoforms endogenously and can sense UV. These findings demonstrate a new cell type that can sense strong UV and the potential of exploiting dTRPA1 channel as an optogenetic tool. (See pp. E5753–E5761.)