PNAS Plus Significance Statements

Differences between measured and reported volatile organic compound emissions from oil sands facilities in Alberta, Canada

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Validation of volatile organic compound (VOC) emission reports, especially from large industrial facilities, is rarely attempted. Given uncertainties in emission reports, their evaluation and validation will build confidence in emission inventories. It is shown that a top-down approach can provide measurement-based emission rates for such emission validation. Comparisons with emission reports from Alberta oil sands surface mining facilities revealed significant differences in VOC emissions between top-down emissions rates and reports. Comparison with VOC species emission reports using currently accepted estimation methods indicates that emissions were underestimated in the reports for most species. This exercise shows that improvements in the accuracy and completeness of emissions estimates from complex facilities would enhance their application to assessing the impacts of such emissions. (See pp. E3756–E3765.)

Mutant p53 perturbs DNA replication checkpoint control through TopBP1 and Treslin

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Mutant form of p53 (mutp53) proteins are expressed at high levels in many human cancers and can promote tumor cell growth. However, their mechanisms of action have not been fully understood. Elucidation of the mechanisms may identify new therapeutic strategies for treating many cancers that contain mutp53s. We describe a role for several hotspot mutp53s in reducing the checkpoint response to replication stress through interacting with TopBP1. This finding provides a rationale for a synthetic lethality strategy to treat mutp53-harboring cancer cells with inhibitors of another ATR activator, DNA2. We also find that certain mutp53s directly promote DNA replication by bridging the interaction between TopBP1 and Treslin. These results uncover mechanisms by which mutp53 enhances DNA replication. (See pp. E3766–E3775.)

Structure of Myo7b/USH1C complex suggests a general PDZ domain binding mode by MyTH4-FERM myosins

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MyTH4-FERM myosins (Myo7a, Myo7b, and Myo15a) regulate actin-bundle protrusion structures in various tissues, including brush border microvilli of intestines and stereocilia of inner ear hair cells. Mutations of the cargo binding MyTH4-FERM tandems of these myosins are frequently associated with human diseases, including hearing loss, vision defects, and digestive disorders, but with poorly understood mechanisms. In this work, we present the high-resolution crystal structure of Myo7b C-terminal MyTH4-FERM tandem (CMF) in complex with the USH1C PDZ3 domain. The structure, together with biochemical studies, indicates that binding to PDZ domain scaffold proteins is a general property of these myosins. The complex structure reported here also helps to explain why numerous mutations identified in Myo7a CMF can cause deafness and blindness in humans. (See pp. E3776–E3785.)

On the permeation of large organic cations through the pore of ATP-gated P2X receptors

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Unlike many ion channels whose pore conductances remain relatively stable over time, it is thought that prolonged ATP applications to P2X receptors cause a striking increase over time in the permeability of large molecules, a process dubbed pore dilation. However, this mechanism remains poorly understood and highly controversial. Here, we use different methods spanning single-channel recordings, photochemistry, molecular biology, and computations to show that contrary to longstanding view, rapid activation by ATP allows the stable passage of large cations through the P2X pore. We further discover that spermidine, a large natural cation known to modulate other ion channels, is able to transit through many P2X receptors, including those thought to be nondilating. Our data thus reveal an unacknowledged P2X-mediated signaling. (See pp. E3786–E3795.)

Epithelial EZH2 serves as an epigenetic determinant in experimental colitis by inhibiting TNFα-mediated inflammation and apoptosis

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TNFα is the key cytokine implicated in inflammatory bowel disease. However, TNFα is not always proinflammatory, because TNFα-activated NF-κB induces prosurvival proteins, including c-FLIP, to constrain caspase 8 activation. Here we report that epithelial EZH2 integrates the multifaceted effects of TNFα signaling to promote inflammation and apoptosis in colitis. EZH2 reduction directly stimulates TRAF2/5 expression to enhance TNFα-induced NF-κB signaling. More importantly, EZH2 deficiency up-regulates the expression of the E3 ligase ITCH to degrade the c-FLIP protein, thereby antagonizing the prosurvival role of NF-κB. Taken together, our results indicate that EZH2 serves as an epigenetic brake to modulate TNFα functions in colitis. Moreover, the data suggest that patients with lower levels of EZH2 might have a better response to anti-TNFα therapy. (See pp. E3796–E3805.)

Biliary epithelial injury-induced regenerative response by IL-33 promotes cholangiocarcinogenesis from peribiliary glands

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Death-driven compensatory proliferation to repair tissue defects is an important promoter of inflammation-associated carcinogenesis. Our work using a mouse model demonstrates that a biliary epithelial injury-induced regenerative response mediated by IL-33 accelerates development of extrahepatic cholangiocarcinoma (ECC) from peribiliary glands, an effect that was suppressed by anti–IL-33 treatment. Thus, IL-33 is a potential therapeutic target for ECC, and the mouse model reported in this study will enable identification of the mechanisms of biliary injury-based carcinogenesis. (See pp. E3806–E3815.)

Estrogen receptor β, a regulator of androgen receptor signaling in the mouse ventral prostate

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Prostate cancer is an androgen receptor (AR)-dependent disease. Goals in treatment of prostate cancer include keeping low Gleason grades low and preventing development of the lethal disease castration-resistant metastatic prostate cancer. The present study revealed that ERβ modulates AR signaling by repressing AR driver RORc and increasing AR corepressor DACH1/2. Loss of ERβ resulted in up-regulation of genes whose expression is associated with poor prognosis in prostate cancer accompanied by down-regulation of tumor-suppressive or tumor-preventive genes. Treatment of mice with an ERβ agonist resulted in the nuclear import of PTEN and repression of AR signaling. ERβ may be a promising target for treating early stage prostate cancer to prevent cancer progression. (See pp. E3816–E3822.)

The SP100 component of ND10 enhances accumulation of PML and suppresses replication and the assembly of HSV replication compartments

Pei Xu and Bernard Roizman

Nuclear domain 10 (ND10) bodies are both sensors and responders to many viruses that infect human cells. The key components of ND10 bodies are PML and SP100. Their importance in innate immune responses to infection is underscored by the observation that numerous viruses have evolved means to degrade, disperse, or at least inactivate PML and SP100. This report focuses on SP100, which, along with PML, is degraded by a viral E3 ligase in HSV-1–infected cells. The question posed here is the function of SP100 and PML in the course of HSV infection. The results indicate that the function of SP100 is different than, but complementary to, that of PML and ranks high in the cellular defense mechanisms against infection. (See pp. E3823–E3829.)

Astrocytes locally translate transcripts in their peripheral processes

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Cellular compartments are specialized for particular functions. In astrocytes, the peripheral, perisynaptic processes contain proteins specialized for reuptake of neurotransmitters and ions, and have been shown to alter their morphology in response to activity. Regulated transport of a specific subset of nuclear-derived mRNAs to specific compartments is thought to support the specialization of these compartments and allow for local regulation of translation. In neurons, local translation near activated synapses is thought to generate the proteins needed for the synaptic alterations that constitute memory. We demonstrate that astrocytes also have sequence-dependent local translation in their peripheral processes, including transcripts with roles in regulating synapses, and identify one mechanism regulating this translation. These findings suggest local translation in astrocyte processes may play a role in synapse modulation. (See pp. E3830–E3838.)

Early immune responses are independent of RGC dysfunction in glaucoma with complement component C3 being protective

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Exactly how high intraocular pressure (IOP) initiates glaucoma is unknown. Immune responses occur early in glaucoma, but whether they are induced by high IOP or occur secondarily to retinal ganglion cell (RGC) dysfunction and molecular changes in neurons and glia remains unknown. This paper addresses these relationships and provides a deeper understanding of this very common neurodegeneration. Overall, our data suggest that early immune responses are independent of RGC dysfunction and thus are triggered as a more direct result of high IOP. Furthermore, early immune responses by astrocytes that involve complement C3 and EGFR signaling are beneficial. (See pp. E3839–E3848.)

Endocrine network essential for reproductive success in *Drosophila melanogaster*

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Endocrine networks are the foundation of estrous cycles in most vertebrates. However, hormones regulating reproduction in invertebrates often are examined in isolation rather than as part of an emergent endocrine context. Here we show that a highly conserved endocrine network consisting of ecdysone, ecdysis triggering hormone, and juvenile hormone interact in *Drosophila melanogaster* to promote reproductive success. These findings provide a foundation for future studies on the endocrine regulation of reproduction in invertebrates. (See pp. E3849–E3858.)

Brain networks for confidence weighting and hierarchical inference during probabilistic learning

Florent Meyniel and Stanislas Dehaene

What has been learned must sometimes be unlearned in a changing world. Yet knowledge updating is difficult since our world is also inherently uncertain. For instance, a heatwave in winter is surprising and ambiguous: does it denote an infrequent fluctuation in normal weather or a profound change? Should I trust my current knowledge, or revise it? We propose that humans possess an accurate sense of confidence that allows them to evaluate the reliability of their knowledge, and use this information to strike the balance between prior knowledge and current evidence. Our functional MRI data suggest that a frontoparietal network implements this confidence-weighted learning algorithm, acting as a statistician that uses probabilistic information to estimate a hierarchical model of the world. (See pp. E3859–E3868.)