PNAS Plus Significance Statements

Stratospheric ozone over the United States in summer linked to observations of convection and temperature via chlorine and bromine catalysis

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Stratospheric ozone is one of the most delicate aspects of habitability on the planet. Removal of stratospheric ozone over the polar regions in winter/spring has established the vulnerability of ozone to halogen catalytic cycles. Elevated ClO concentrations engendered, in part, by heterogeneous catalytic conversion of inorganic chlorine to free radical form on ubiquitous sulfate–water aerosols, govern the rate of ozone removal. We report here observations of the frequency and depth of penetration of convectively injected water vapor into the stratosphere, triggered by severe storms that are specific to the central United States in summer, and model their effect on lower stratospheric ozone. This effect implies, with observed temperatures, increased risk of ozone loss over the Great Plains in summer. (See pp. E4905–E4913.)

Modeling gene regulation from paired expression and chromatin accessibility data

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Chromatin plays a critical role in the regulation of gene expression. Interactions among chromatin regulators, sequence-specific transcription factors, and *cis*-regulatory sequence elements are the main driving forces shaping context-specific chromatin structure and gene expression. However, because of the large number of such interactions, direct data on them are often missing in most cellular contexts. The purpose of the present work is to show that, by modeling matched expression and accessibility data across diverse cellular contexts, it is possible to recover a significant portion of the information in the missing data on binding locations and chromatin states and to achieve accurate inference of gene regulatory relations. (See pp. E4914–E4923.)

Mitochondrial dysfunction induced by a SH2 domain-targeting STAT3 inhibitor leads to metabolic synthetic lethality in cancer cells

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The transcription factor STAT3 is involved in multiple oncogenic signaling pathways and is an attractive therapeutic target. This study shows that a potent inhibitor of STAT3 interferes with mitochondrial activity and protein homeostasis, leading to a synthetic lethality effect in glucose-depleted cancer cells. These findings provide a rationale for novel strategies based on the use of STAT3 inhibitors for cancer treatment. (See pp. E4924–E4933.)

Neurog2 and *Ascl1* together regulate a postmitotic derepression circuit to govern laminar fate specification in the murine neocortex

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Projection neurons of the neocortex represent a diverse neuronal population that can be conveniently classified into three broad categories based on axon projection patterns: corticothalamic, subcerebral, and callosal. These neuronal subtypes are known to be specified postmitotically by a cortical derepression circuit involving the key transcription factors Tbr1, Fezf2, Satb2, and Ctip2. However, projection neuron identities are also known to be determined at the progenitor cell level, but the molecular mechanisms are poorly understood. Here we reveal that the proneural genes *Neurog2* and *Ascl1*, which are together expressed in neocortical progenitors, cooperate to regulate the expression of components of the cortical derepression circuit to specify corticothalamic and subcerebral identities while repressing a callosal fate. (See pp. E4934–E4943.)

Probabilistic model predicts dynamics of vegetation biomass in a desert ecosystem in NW China

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The temporal dynamics of vegetation biomass are of vital importance for evaluating the sustainability of arid and semiarid ecosystems. Field observations indicate that soil moisture and plant biomass fluctuate stochastically with the occurrence of rainfall events. Based on long-term field observations, we find that the dynamics of the vegetation biomass can be quantified by their analytically derived time-dependent probability distribution. This allows for the study of the impact of climate change scenarios on vegetation cover and plant water resource competition. It is found that in a restored desert ecosystem in northwest (NW) China, the growing season leaf biomass is expected to increase by nearly 25% compared to the present. (See pp. E4944–E4950.)

Transposon mutagenesis identifies chromatin modifiers cooperating with *Ras* in thyroid tumorigenesis and detects *ATXN7* as a cancer gene

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Mutations of RAS are believed to be early events in thyroid tumorigenesis but are insufficient to induce transformation. A forward genetic screen with transposons engineered to integrate randomly into the mouse Ras-mutant thyroid cell genome and to disrupt genes at their insertion sites resulted in tumors that phenocopied human RAS-driven, poorly differentiated thyroid cancers. Analysis of the transposon-integration sites revealed recurrent mutations of chromatin modifiers and PI3K pathway genes, consistent with mutations seen in human advanced thyroid cancers. These human cancers have a high mutation burden, which confounds distinctions between driver and passenger mutations. This unbiased screen for genes selected during tumorigenesis provides strong functional support for genetic disruptions in these pathways in RAS-induced thyroid tumor progression. (See pp. E4951–E4960.)

An Exportin-1–dependent microRNA biogenesis pathway during human cell quiescence

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Quiescence is a growth-arrested cellular state; genes involved in this process are finely regulated by several factors, including miRNAs. During miRNA biogenesis, Exportin-5 transports miRNA precursors from the nucleus to the cytoplasm. In this study, we demonstrated the existence of an alternative miRNA biogenesis pathway in quiescent primary human cells. This pathway involves the repression of Exportin-5 expression by autophagy and miRNAs and the 2,2,7-trimethylguanosine-cap modification of specific primary miRNAs (pri-miRNAs), which signal their export to the cytoplasm by Exportin-1. We further showed that these pri-miRNAs are processed rapidly in the cytoplasm by a small isoform of Drosha. Collectively, these results reveal an alternative mechanism of miRNA biogenesis that will expand our understanding of miRNA regulation in normal or disease-related cells. (See pp. E4961–E4970.)

Treatment with diphenyl–pyrazole compound anle138b/c reveals that α-synuclein protects melanoma cells from autophagic cell death

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People with Parkinson's disease, the second most common neurodegenerative disorder, have a lower risk and decreased incidence of cancer with the one exception being melanoma. The fact that, compared with other malignancies, melanoma occurs more frequently in patients with Parkinson's disease and vice versa and that there is an association between a history of melanoma and an increased prevalence of prodromal markers of Parkinson's disease prompted us to explore the possibility of an inverse biological link between these two diseases. The findings of our study suggest that α-synuclein, one of the key regulators in Parkinson's disease, although toxic to dopaminergic neurons, is protective for advanced melanoma cells. (See pp. E4971–E4977.)

Reconstitution of a minimal machinery capable of assembling periplasmic type IV pili

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Type IV pili (Tfp) define a group of multipurpose filamentous nanomachines widespread in Bacteria and Archaea. Tfp biogenesis is a complex process relying on machines composed of up to 15 conserved proteins. Here, to improve our limited understanding of the molecular mechanisms of filament assembly, we have reconstituted in a nonpiliated heterologous host a minimal machinery capable of building Tfp. We show that eight proteins are sufficient to promote filament assembly and that they form a macromolecular complex at the cytoplasmic membrane, which we have purified and characterized biochemically. Our results contribute to a better mechanistic understanding of the functioning of filamentous nanomachines nearly ubiquitous in prokaryotes. (See pp. E4978–E4986.)

High-mobility group box-1 as an autocrine trophic factor in white matter stroke

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Ischemic stroke in white matter induces degeneration of oligodendrocytes (OLs) and myelin. How ischemia leads to white matter degeneration remains elusive, and there is therefore no specific treatment to prevent ischemic white matter damage. Here we provide evidence that HMGB1 released from ischemic OLs may provide TLR2-dependent autocrine trophic effects on neighboring OLs. Injection of an HMGB1 inhibitor exacerbated the structural and functional outcomes in a focal white matter stroke model, suggesting a function for HMGB1 as an endogenous trophic factor for OLs and myelin sheath under ischemia. Thus, our study identified HMGB1 as a stress-induced signal that maintains structural and functional integrity of the white matter and provides a target for therapeutic development in white matter stroke. (See pp. E4987–E4995.)

Dynamic changes in murine forebrain miR-211 expression associate with cholinergic imbalances and epileptiform activity

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Acute traumatic stress increases the sensitivity to develop epileptic seizures in certain people. It is therefore important to discover physiological mechanisms that avoid epilepsy. To test if rapidly inducible microRNAs (miRs) could mediate such protection, we combined mouse engineering, RNA sequencing, electric recording of brain activity, and learning tests. We discovered that miR-211, originating from an epilepsy-related genomic locus, may be involved, and therefore engineered mice produce a drug-suppressible excess of brain miR-211. In these mice, suppressing miR-211 excess to the original expression levels in normal brains led to electrically recorded epilepsy and hypersensitivity to epilepsy-inducing compounds; it also modified acetylcholine receptor composition. The functional impact of miR-211 dynamics on seizure threshold may enable future development of miR-211–directed therapeutics. (See pp. E4996–E5005.)

Chemical probes to potently and selectively inhibit endocannabinoid cellular reuptake

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Suitable chemical tools have been instrumental in the discovery and characterization of the endocannabinoid system. However, the lack of potent and selective inhibitors for endocannabinoid transport has prevented the molecular characterization of this process. Current uptake inhibitors are poorly bioavailable to the central nervous system (CNS) and weakly selective because they also inhibit fatty acid amide hydrolase (FAAH), the major anandamide-degrading enzyme. Few studies have addressed the uptake inhibition of 2-arachidonoyl glycerol (2-AG), which is the major endocannabinoid. Here, we report a highly potent and selective endocannabinoid reuptake inhibitor. Our data indicate that endocannabinoid transport across the membrane can be targeted, leading to general antiinflammatory and anxiolytic effects in mice. (See pp. E5006–E5015.)