PNAS Plus Significance Statements

Randomly distributed embedding making short-term high-dimensional data predictable

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Making accurate forecast or prediction is a challenging task in the big data era, in particular for those datasets involving high-dimensional variables but short-term time series points, and these datasets are omnipresent in many fields. In this work, a model-free framework, named as "randomly distributed embedding" (RDE), is proposed to accurately predict future dynamics based on such short-term but high-dimensional data. The RDE framework creates the distribution information from the interactions among high-dimensional variables to compensate for the lack of time points in real applications. Instead of roughly predicting a single trial of future values, this framework achieves the accurate prediction by using the distribution information. (See pp. E9994–E10002.)

Faults and associated karst collapse suggest conduits for fluid flow that influence hydraulic fracturing-induced seismicity

Elwyn Galloway, Tyler Hauck, Hilary Corlett, Dinu Pană, and Ryan Schultz

Induced earthquakes can be caused by hydraulic fracturing (HF). However, the exact means by which stress changes are transferred to seismogenic faults are unknown. This paper provides evidence that a case of induced earthquakes in southern Alberta responded to increased pore pressure on a fault in hydraulic communication with the HF operation. Reflection-seismic and drill core data provide evidence that fluid flow along this fault caused strata underlying the target reservoir to dissolve, causing a karst collapse in the geological past. We suggest that seismogenic and hydraulically active faults are geologically rare and that the injection of fluid directly into them is even rarer, potentially explaining the small percentage of HF wells that cause induced earthquakes. (See pp. E10003–E10012.)

Distinct facial expressions represent pain and pleasure across cultures

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Humans often use facial expressions to communicate social messages. However, observational studies report that people experiencing pain or orgasm produce facial expressions that are indistinguishable, which questions their role as an effective tool for communication. Here, we investigate this counterintuitive finding using a new data-driven approach to model the mental representations of facial expressions of pain and orgasm in individuals from two different cultures. Using complementary analyses, we show that representations of pain and orgasm are distinct in each culture. We also show that pain is represented with similar face movements across cultures, whereas orgasm shows differences. Our findings therefore inform understanding of the possible communicative role of facial expressions of pain and orgasm, and how culture could shape their representation. (See pp. E10013–E10021.)

The structural basis for cancer drug interactions with the catalytic and allosteric sites of SAMHD1

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Nucleoside analog drugs are widely used to treat a variety of cancers and viral infections. With an essential role in regulating the nucleotide pool in the cell by degrading cellular nucleotides, SAMHD1 has the potential to decrease the cellular concentration of frequently prescribed nucleoside analogs and thereby decrease their clinical efficacy in cancer therapy. To improve future nucleoside analog treatments, it is important to understand SAMHD1 interactions with these drugs. Our work thoroughly examines the extent to which nucleotide analogs interact with the catalytic and allosteric sites of SAMHD1. This work contributes to the assessment of SAMHD1 as a potential therapeutic target for cancer therapy and the future design of SAMHD1 modulators that might improve the efficacy of existing therapies. (See pp. E10022–E10031.)

Molecular mechanism of activation of the immunoregulatory amidase NAAA

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There is a strong need for new analgesic and antiinflammatory medicines that are both effective and safe. Animal studies have shown that inhibition of

N-acylethanolamine acid amidase (NAAA)—an intracellular enzyme that degrades the lipid mediator palmitoylethanolamide—causes profound analgesic and antiinflammatory effects. To facilitate the discovery of drugs targeting this protein and to better understand its mechanism of action, we determined its 3D structure. Our results illustrate the sequential steps leading to the activation of NAAA at lipid membranes, and reveal how current inhibitors block this enzyme. (See pp. E10032–E10040.)

Meiosis-specific recombinase Dmc1 is a potent inhibitor of the Srs2 antirecombinase

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Here, we demonstrate that the antirecombinase Srs2 is unable to dismantle recombination intermediates containing the meiosis-specific recombinase Dmc1. Our work defines a function of Dmc1 as an inhibitor of the prototypical antirecombinase Srs2. Based on these findings, we propose that the presence of Dmc1 may help to prevent Srs2 from disruption of early meiotic recombination intermediates, which may in turn be anticipated to favor the formation of cross-over recombination products. (See pp. E10041–E10048.)

Entropic contribution to enhanced thermal stability in the thermostable P450 CYP119

Zhuo Liu, Sara Lemmonds, Juan Huang, Madhusudan Tyagi, Liang Hong, and Nitin Jain

Understanding the thermodynamic factors responsible for enhanced stability of thermophilic cytochrome P450 enzymes is significant in their development as efficient catalysts for high-temperature monooxygenation reactions. These factors are usually inferred from structural comparison with mesophilic P450s and invoke rigidifying enthalpic interactions as primary thermodynamic determinants for thermostability. Using the thermophilic P450 CYP119 as an example, the present work, however, questions this enthalpy-driven notion of P450 thermostability and provides strong experimental evidence that their thermostability may actually be entropy-driven due to increased flexibility in the folded state relative to mesophilic P450s and that this flexibility is partitioned effectively between functional activity and thermal stability. This represents a major paradigm shift in understanding the basis of thermostability in thermophilic P450s. (See pp. E10049–E10058.)

Swi5–Sfr1 stimulates Rad51 recombinase filament assembly by modulating Rad51 dissociation

Chih-Hao Lu, Hsin-Yi Yeh, Guan-Chin Su, Kentaro Ito, Yumiko Kurokawa, Hiroshi Iwasaki, Peter Chi, and Hung-Wen Li

In DNA homologous recombination, recombinase-coated single-stranded DNA filament formation is the first committed step and is subject to tight regulation. Stabilization of nucleoprotein filament by accessory proteins can be achieved by enhancing filament formation, reducing filament disassembly, or both. However, the mechanism of regulation is not understood by conventional biochemical methods. This is a study of the mechanism of how accessory proteins stimulate filament assembly by applying single-molecule methods that allow us to monitor the binding of Rad51 on DNA in mouse and fission yeast. Our results show that the Swi5–Sfr1 complex demonstrates the evolutionarily conserved stimulation of Rad51 filament assembly by stabilizing Rad51 on DNA, allowing both the formation of the stable nucleus and the reduction of Rad51 dissociation. (See pp. E10059–E10068.)

mTOR inhibitors lower an intrinsic barrier to virus infection mediated by IFITM3

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Gene delivery by virus-like particles holds enormous therapeutic potential to correct inherited genetic disorders and to prevent infectious disease. However, cells express antiviral factors that prevent virus infection and, consequently, limit the success of gene therapy. Here, we reveal the mechanism by which the drug rapamycin improves lentivirus-mediated gene delivery. Rapamycin treatment led to degradation of IFITM3, a broad and potent antiviral protein which inhibits virus entry into cells. IFITM3 is selectively cleared from endosomes, the sites where viral and cellular membranes fuse, and is sorted for disposal in lysosomes. While revealing an immunosuppressive function with clinical benefits, we caution that rapamycin use in humans may facilitate infection by pathogenic viruses like Influenza A virus. (See pp. E10069–E10078.)

Mitosis-specific MRN complex promotes a mitotic signaling cascade to regulate spindle dynamics and chromosome segregation

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The Mre11–Rad50–Nbs1 (MRN) complex is well known for participating in DNA damage response pathways and mediating the ATM-dependent phosphorylation signaling cascade. Hypomorphic mutations in the human MRN complex have been identified in autosomal recessive genetic diseases, ataxia-telangiectasia–like disorder, and Nijmegen breakage syndrome. Here, we show that MRN forms a mitosis-specific complex with a protein, MMAP, which mediates a mitotic signaling cascade between PLK1 and KIF2A. We demonstrate that the assembly of this complex is crucial for normal spindle dynamics during mitosis. Thus, our study describes a signaling cascade in which PLK1-dependent phosphorylation promotes the assembly of the MRN–MMAP–PLK1–KIF2A complex, leading to mitotic spindle turnover and chromosome alignment. (See pp. E10079–E10088.)

XBP1s activation can globally remodel N-glycan structure distribution patterns

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Diverse polysaccharides are installed on specific asparagine residues as glycoproteins traverse the endoplasmic reticulum and Golgi. These N-glycan structures comprise the N-glycome, which coats cell surfaces, regulates cell–cell and cell–matrix interactions, and has functional consequences for immune system function and beyond. Our understanding of how intracellular signaling regulates the molecular architecture of the N-glycome remains immature. We show that the transcription factor XBP1s alters N-glycan structures displayed on endogenous membrane-associated and secreted glycoproteins, coincident with XBP1s-induced changes in

N-glycosylation–related transcripts. These results establish a role for the unfolded protein response in defining the global composition of the N-glycome–providing a mechanism for transducing internal stress to an external signal, a phenomenon with implications for both normal biology and pathology. (See pp. E10089–E10098.)

Noncanonical autophagy at ER exit sites regulates procollagen turnover

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Type I collagen, a major component of bone, skin, and other connective tissues, is synthesized in the endoplasmic reticulum (ER) and passes through the secretory pathway. Rerouting of its procollagen precursor to a degradative pathway is crucial for reducing intracellular buildup in pathologies caused by defects in procollagen folding and trafficking. Here, we identify an autophagy pathway initiated at ER exit sites (ERESs). Procollagen proteins following this pathway accumulate at ERESs modified with ubiquitin, LC3, p62, and other autophagy machinery. Modified ERESs carrying procollagen are then engulfed by lysosomes through a microautophagy-like mechanism, not involving conventional, double-membrane autophagosomes. Procollagen homeostasis thus involves a noncanonical mode of autophagy initiated at ERESs, which might also be important in degradation of other secretory proteins. (See pp. E10099–E10108.)

Human leukemia mutations corrupt but do not abrogate GATA-2 function

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GATA-2 functions in stem and progenitor cells to control blood cell development, and its mutations cause blood diseases (immunodeficiency, myelodysplasia, and myeloid leukemia). How GATA-2 mutations cause these diseases is unclear. We innovated a genetic complementation assay to analyze functional ramifications of GATA-2 disease mutations. The activities of GATA-2 and mutants were quantified in blood progenitor cells from mice engineered to express a low level of GATA-2 due to deletion of an essential *Gata2* enhancer. Unexpectedly, the mutants were not only competent to induce myeloid cells, but their activities exceeded that of GATA-2. These results transform the current paradigm that disease mutations are solely inhibitory, and ectopically low GATA-2 levels/activity constitute the disease mechanism. (See pp. E10109–E10118.)

Differential regulation of PD-L1 expression by immune and tumor cells in NSCLC and the response to treatment with atezolizumab (anti–PD-L1)

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Programmed death-ligand 1 (PD-L1) expression on tumor cells and tumor-infiltrating immune cells is regulated by distinct mechanisms and has nonredundant roles in regulating anticancer immunity, and PD-L1 on both cell types is important for predicting best response to atezolizumab in non-small cell lung cancer. (See pp. E10119–E10126.)

iNOS promotes $CD24^+CD133^+$ liver cancer stem cell phenotype through a TACE/ADAM17-dependent Notch signaling pathway

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$CD24^+CD133^+$ liver cancer stem cells (LCSCs) express higher levels of the inducible nitric oxide synthase (iNOS) and possess self-renewal and tumor growth properties. iNOS is associated with more aggressive hepatocellular carcinoma (HCC), leading to the upregulation of Notch1 signaling. The activation of Notch1 by iNOS/NO is dependent on cGMP/PKG-mediated activation of TACE and upregulation of iRhom-2. The expression of iNOS, CD24, and CD133 correlates with the expression of activated TACE and Notch signaling in more aggressive human HCC. These findings have implications for understanding how LCSCs are regulated in the setting of chronic inflammation, where signals to upregulate iNOS are often present. Targeting iNOS could have therapeutic benefit in HCC. (See pp. E10127–E10136.)

Histone methylation regulator PTIP is required to maintain normal and leukemic bone marrow niches

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Osteoclasts play an essential role in bone homeostasis. Understanding how osteoclast differentiation is regulated is important in the context of pathological bone conditions and the hematopoietic stem cell (HSC) niche. We show that PTIP directly promotes chromatin changes required for *Pparγ* expression, a transcription factor essential for osteoclastogenesis. Deletion of PTIP disrupts the integrity of the bone marrow (BM) niche, leading to a reduction of HSCs in the BM. Furthermore, a PTIP-deficient BM microenvironment decreases the number of acute myeloid leukemia-initiating cells in the BM and increases survival upon transplantation. Taken together, our data identify PTIP as an epigenetic regulator of osteoclastogenesis that is required for the integrity of the BM niche to sustain both normal hematopoiesis and leukemia. (See pp. E10137–E10146.)

$MmpL8_{MAB}$ controls *Mycobacterium abscessus* virulence and production of a previously unknown glycolipid family

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One major defense mechanism of mycobacteria relies mainly on the synthesis and transport of specialized lipids, processes that reside in the cell wall. Among the transporters, Mycobacterial membrane protein Large (MmpL) plays an essential role. We describe the role of MmpL8 ($MmpL8_{MAB}$) in the survival of *Mycobacterium abscessus* within eukaryotic hosts. We show that its absence slows the contact between *M. abscessus* and the host cell cytosol, an essential element in its resistance to the cell

bactericidal mechanisms. The absence of $MmpL8_{MAB}$ leads to reduced production of a previously unknown glycolipid: a glycosyl diacylated nonadecyl diol (GDND). The glycolipid seems unique to the *Mycobacterium chelonae* complex, supporting the view that GDND might represent a typical signature of *M. abscessus* infection. (See pp. E10147–E10156.)

Interplay between coronavirus, a cytoplasmic RNA virus, and nonsense-mediated mRNA decay pathway

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Coronaviruses (CoVs) are important pathogens for humans and domestic animals. The development of effective countermeasures against CoVs requires an understanding of the host pathways that regulate viral gene expression and the viral subversion mechanisms. However, little is known about how the stability of viral mRNAs is controlled. We show that the nonsense-mediated decay (NMD) pathway, which primarily targets aberrant cellular mRNAs for degradation, also induced the degradation of CoV mRNAs that are of cytoplasmic origin. Our study further suggests the importance of CoV-induced inhibition of the NMD pathway, mediated by a viral protein, for efficient CoV replication. The present study highlights an interplay between the NMD pathway and CoVs that modulates viral replication by controlling the stability of viral mRNAs. (See pp. E10157–E10166.)

Dopaminergic basis for signaling belief updates, but not surprise, and the link to paranoia

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To survive in changing environments animals must use sensory information to form accurate representations of the world. Surprising sensory information might signal that our current beliefs about the world are inaccurate, motivating a belief update. Here, we investigate the neuroanatomical and neurochemical mechanisms underlying the brain's ability to update beliefs following informative sensory cues. Using multimodal brain imaging in healthy human participants, we demonstrate that dopamine is strongly related to neural signals encoding belief updates, and that belief updating itself is closely related to the expression of individual differences in paranoid ideation. Our results shed new light on the role of dopamine in making inferences and are relevant for understanding psychotic disorders such as schizophrenia, where dopamine function is disrupted. (See pp. E10167–E10176.)

Activity-dependent bulk endocytosis proteome reveals a key presynaptic role for the monomeric GTPase Rab11

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The maintenance of neurotransmission by synaptic vesicle (SV) recycling is critical to brain function. The dominant SV recycling mode during intense activity is activity-dependent bulk endocytosis (ADBE), suggesting it will perform a pivotal role in neurotransmission. However, the role of ADBE is still undetermined, due to the absence of identified molecules specific for this process. The determination of the bulk endosome proteome (a key ADBE organelle) revealed that it has a unique molecular signature and identified a role for Rab11 in presynaptic function. This work provides the molecular inventory of ADBE, a resource that will be of significant value to researchers wishing to modulate neurotransmission during intense neuronal activity in both health and disease. (See pp. E10177–E10186.)

Chronic social stress-induced hyperglycemia in mice couples individual stress susceptibility to impaired spatial memory

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Stress-associated mental disorders and diabetes pose an enormous socio-economic burden. Glucose dysregulation occurs with both psychosocial and metabolic stress. While cognitive impairments are common in metabolic disorders such as diabetes and are accompanied by hyperglycemia, a causal role for glucose has not been established. We show that chronic social defeat (CSD) stress induces lasting peripheral and central hyperglycemia and impaired glucose metabolism in a subgroup of mice. Animals exhibiting hyperglycemia early post-CSD display spatial memory impairments that can be rescued by the antidiabetic empagliflozin. We demonstrate that individual stress vulnerability to glucose homeostasis can be identified early after insult and that stress-induced hyperglycemia directly impinges on cognitive integrity. Our findings further bridge the gap between stress-related pathologies and metabolic disorders. (See pp. E10187–E10196.)

Long noncoding RNA GM12371 acts as a transcriptional regulator of synapse function

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Neuronal functions of long noncoding RNAs (lncRNAs) are poorly understood. Here we describe identification and function of lncRNA GM12371 in regulating synaptic transmission, synapse density, and dendritic arborization in primary hippocampal neurons. GM12371 expression is regulated by cAMP signaling and is critical for the activity regulated synaptic transmission. Importantly, GM12371 is associated with transcriptionally active chromatin and regulates expression of several genes involved in neuronal growth and development. Taken together, these results suggest that GM12371 acts as a transcriptional regulator of synapse function. (See pp. E10197–E10205.)

The brain's hemodynamic response function rapidly changes under acute psychosocial stress in association with genetic and endocrine stress response markers

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Understanding how stress predisposes for psychopathology requires the identification of physiological stress-regulatory

mechanisms with pathogenic potential. Here, we applied fMRI to investigate the interaction between acute psychosocial stress and the brain's hemodynamic response function (HRF). The HRF models how local neural activity elicits cerebral blood flow changes, spanning several biophysical processes including neurovascular coupling (NVC). Stress replicably shifted the HRF peak in temporal, insular, and prefrontal brain regions, moderated by functional variants of *KCNJ2*, a protein involved in NVC. Hippocampal HRF markers correlated with the cortisol response and genetic variants that reflect transcriptional responses to glucocorticoids and the risk for depression. We suggest that acute psychosocial stress modulates hemodynamic response properties which could lead to previously undescribed endophenotypes of stress-related disorders. (See pp. E10206–E10215.)

DSCAM promotes self-avoidance in the developing mouse retina by masking the functions of cadherin superfamily members

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Cell adhesion molecules (CAMs) provide highly specific cell-surface recognition signals by which developing neurons interact with specific partners. However, these CAMs are common between neurons of the same type, and without a mechanism of self-avoidance or of homotypic avoidance, developing neurons will excessively adhere with themselves. This self-avoidance can be promoted by extreme molecular diversity, such as that of *Dscam1* (Down syndrome cell adhesion molecule 1) in flies, which gives neurons distinct barcodes. Mouse *Dscam*, on the other hand, promotes self-avoidance without molecular diversity. Here, we provide evidence that DSCAM can functionally interact with other CAMs, called cadherins and protocadherins, to act like a general "nonstick" signal. Through this "adhesive masking" mechanism, DSCAM allows neurons to develop their appropriate shapes, positions, and connections. (See pp. E10216–E10224.)

MRI-based assessment of function and dysfunction in myelinated axons

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Blood-oxygen-level-dependent (BOLD) fMRI has proven to be extremely powerful for studying brain function, but is essentially limited to applications in gray matter. This work investigates the underlying mechanisms responsible for MRI-based signal changes in myelinated axonal fibers of perfused bullfrog sciatic nerves. Simultaneous in-magnet recording of compound action potentials (CAPs) and MRI data acquisition reveal that the diffusion fMRI response is linearly proportional to the number of electrical impulses. Increased restricted diffusion fraction (from diffusion basis spectrum imaging) could be related to submyelinic vacuole formation observed by electron microscopy of perfused nerves fixed resting or undergoing stimulation. Microstructural changes and osmotically driven redistribution of tissue water play a crucial role in the observed diffusion fMRI response in myelinated fibers. (See pp. E10225–E10234.)

Cbln2 and Cbln4 are expressed in distinct medial habenula-interpeduncular projections and contribute to different behavioral outputs

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Cerebellins are important neurexin ligands that remain poorly understood. Two critical questions in particular remain unanswered: do different cerebellins perform distinct functions, and do these functions act in the initial establishment of synapses or in rendering nascent synapses capable of normal synaptic transmission? Here we report that in mice, two homologous cerebellins, Cbln2 and Cbln4, are expressed in different types of neurons of the medial habenula (MHb), and that these neurons project to distinct target neurons in the interpeduncular nucleus. Ablation of Cbln2 or Cbln4 from the MHb impairs distinct behaviors, but only ablation of Cbln2 affects synapse numbers. Our data show that different cerebellins perform distinct functions that involve synaptic information processing but not initial synapse formation. (See pp. E10235–E10244.)

p38α MAPK signaling drives pharmacologically reversible brain and gastrointestinal phenotypes in the SERT Ala56 mouse

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Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by communication and social behavior deficits, repetitive behaviors, and medical comorbidities, including gastrointestinal dysfunction. No pharmacologic treatments are available that ameliorate core symptoms. Genetic variants in the serotonin transporter (SERT) are linked to ASD. Here we demonstrate that administration of a CNS-penetrant p38α MAPK antagonist normalizes multiple physiological and behavioral perturbations reminiscent of ASD in adult, SERT Ala56 mice. Conditional genetic manipulations validate a requirement for 5-HT neuron p38α MAPK signaling in establishing perturbations observed in SERT Ala56 mice. Our findings suggest that p38α MAPK may be a potential target for treatment of adults with ASD, particularly in relation to traits driven by elevated SERT activity and diminished 5-HT signaling. (See pp. E10245–E10254.)

Translating biased signaling in the ghrelin receptor system into differential in vivo functions

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Obesity is a major health threat of the twenty-first century, impacting individual patients and healthcare expenditure. Due to safety concerns, few antiobesity treatments with only moderate effect remain on the market. The ghrelin receptor is an attractive target for the development of novel antiobesity drugs, since ghrelin increases both fat accumulation and food intake. However, ghrelin also modulates a variety of additional physiological functions. Thus, drugs targeting the ghrelin receptor may induce unacceptable side effects and have limited clinical use. We demonstrate that biased ligands, which selectively activate

only a subset of the molecular signaling pathways, may be powerful tools to obtain drugs that efficaciously reduce body weight without inducing adverse effects by selectively modulating appetite and energy expenditure. (See pp. E10255–E10264.)

Quantitative and functional posttranslational modification proteomics reveals that TREPH1 plays a role in plant touch-delayed bolting

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Plants respond to a delicate force signal, such as a light touch, similar to animal neural systems, as demonstrated by thigmotropism, thigmonastic movement, and thigmomorphogenesis. To understand the force-signaling networks, we applied stable isotope labeling in *Arabidopsis* (SILIA)-based quantitative posttranslational modification proteomics to assess protein phosphorylation changes in *Arabidopsis* subjected to 40-second cotton-swab touch, identified 4,895 nonredundant phosphopeptides, 579 of which are previously unreported phosphosites derived from 509 phosphoprotein groups, and identified 24 TOUCH-REGULATED PHOSPHOPROTEIN (TREPH) groups. Molecular biological, genetic, and bioinformatic analyses revealed that the previously uncharacterized TREPH1 protein is required for the bolting-delay aspect of the *Arabidopsis* touch response. These studies suggest that protein phosphorylation and the TREPH1 protein are critical for the mechanotransduction pathway leading to an aspect of plant thigmomorphogenesis. (See pp. E10265–E10274.)

Bottom trawl fishing footprints on the world's continental shelves

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We conducted a systematic, high-resolution analysis of bottom trawl fishing footprints for 24 regions on continental shelves and slopes of five continents and New Zealand. The proportion of seabed trawled varied >200-fold among regions (from 0.4 to 80.7% of area to a depth of 1,000 m). Within 18 regions, more than two-thirds of seabed area remained untrawled during study periods of 2–6 years. Relationships between metrics of total trawling activity and footprint were strong and positive, providing a method to estimate trawling footprints for regions where high-resolution data are not available. Trawling footprints were generally smaller in regions where fisheries met targets for exploitation rates, implying collateral environmental benefits of effective fisheries management. (See pp. E10275–E10282.)