PNAS Plus Significance Statements

Structural basis for the recruitment of glycogen synthase by glycogenin

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The body stores excess blood glucose as glycogen, a sugary substance that contains up to 55,000 glucose molecules joined together as a chain, mostly in liver and muscle cells. Conversion of glucose to glycogen and glycogen to glucose in these cells plays an important role in regulating blood glucose levels. Glycogen ensures that we don't run out of fuel during prolonged exercise. To make glycogen from blood sugar, cells need two enzymes: glycogenin and glycogen synthase. Glycogenin kick starts the process by first linking to itself a string of glucose residues and then recruiting glycogen synthase to elaborate this "seed" glycogen particle. Here (pp. E2831–E2840), we describe the molecular details of how these two enzymes come together and begin to make glycogen.

Cep164 triggers ciliogenesis by recruiting Tau tubulin kinase 2 to the mother centriole

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The primary cilium is an organelle typically found on postmitotic vertebrate cells. Cilia serve as antennae to receive signals from extracellular space and thus play important roles in both development and disease. Understanding the mechanisms controlling their formation (ciliogenesis) is of great importance. Ciliogenesis is known to depend on basal bodies, but although major steps have been described at a morphological level, the underlying mechanism and its regulation remain poorly understood. In our study (pp. E2841–E2850), we characterized Cep164, a key component of basal bodies that is crucial for ciliogenesis. We show that one major function of Cep164 is to recruit a protein kinase, TTBK2, to basal bodies. Once localized correctly, TTBK2 then functions in distal appendage assembly and primary cilia formation.

Two miRNA clusters, *miR-34b/c* and *miR-449*, are essential for normal brain development, motile ciliogenesis, and spermatogenesis

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Most of the single miRNA gene knockouts display no developmental phenotype. Here, we report that simultaneous inactivation of two functionally overlapping miRNAs, *miR-34b/c* and *miR-449*, led to a sexually dimorphic partial perinatal lethality, growth retardation and sterility. Multiple underlying developmental defects, including underdevelopment of the basal forebrain structures, a lack of motile cilia in trachea and oviduct, severely disrupted spermatogenesis and oligoasthenoteratozoospermia, result from the dysregulation of ∼240 target genes that are mainly involved in three major cellular functions, including cell fate control, brain development and microtubule dynamics. This study (pp. E2851–E2857) provides physiological evidence demonstrating an essential role of *miR-34b/c* and *miR-449* in normal brain development, motile ciliogenesis and spermatogenesis.

The *Tn7* transposition regulator TnsC interacts with the transposase subunit TnsB and target selector TnsD

Ki Young Choi, Jeanelle M. Spencer, and Nancy L. Craig

DNA cut-and-paste transposons are discrete DNA segments that move from place to place within genomes via excision from a donor site by double-strand DNA breaks and insertion into a target site. These events are mediated by nucleoprotein complexes whose assembly regulates and coordinates breakage and joining. Multiple protein–protein and protein–DNA interactions are involved in assembly of these nucleoprotein complexes. The nucleoprotein complexes that mediate the movement of the bacterial transposon Tn7 are particularly elaborate, requiring four Tn7-encoded proteins. Here (pp. E2858–E2865) we define specific protein–protein interactions between the central regulator of Tn7 transposition, TnsC, and both the transposase that carries out the chemical steps of transposition and the target-selecting protein.

Positron emission tomography probe demonstrates a striking concentration of ribose salvage in the liver

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The saccharide ribose is naturally present in food and circulates in the blood. Previous studies suggest that cells internalize ribose directly from the extracellular space, but how, why, and where this occurs in the body are not well understood. Here (pp. E2866–E2874), we developed a new PET probe to monitor this process in vivo. Using this probe and [^{14}C]ribose, we show that ribose salvage is concentrated in the liver. We identify that solute carrier family 2, member 2 is one of potentially several ribose transporters. We demonstrate that ribose salvage is down-regulated during metabolic syndrome. This work raises the possibility that ribose is an important sugar for whole-body metabolism.

Oligotyping analysis of the human oral microbiome

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The human body, including the mouth, is home to a diverse assemblage of microbial organisms. Although high-throughput sequencing of 16S rRNA genes provides enormous amounts of census data, accurate identification of taxa in these large datasets remains problematic because widely used computational approaches do not resolve closely related but distinct organisms. We used a computational approach that relies on information theory to reanalyze the human oral microbiome. This analysis (pp. E2875–E2884) revealed organisms differing by as little as a single rRNA nucleotide, with dramatically different distributions across habitats or individuals. Our information theory-based approach in combination with habitat analysis demonstrates the potential to deconstruct entire microbiomes, detect previously unrecognized diversity, and provide deep insight into microbial communities in health and disease.

Transcription factor induction of human oligodendrocyte progenitor fate and differentiation

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Transplantation of human myelinogenic cells represents a realizable strategy for treatment of congenital and acquired demyelinating diseases. Although generation of undifferentiated neural stem and progenitors is feasible, the induction of myelinogenic cell fate remains a significant challenge. In this paper (pp. E2885–E2894), we describe, to our knowledge, the first comprehensive study of transcription factor expression and function by purified neural and oligodendrocyte progenitors obtained directly from human brain tissue. We have identified those transcription factors capable of regulating oligodendrocyte progenitor fate and establish that among these, only SOX10 was capable of comprehensively inducing oligodendrocyte fate both in vitro and following transplantation into a model of human leukodystrophy. Thus, viral and pharmacologic approaches to increasing SOX10 expression likely will improve the outcome of human transplant therapy.

Activity-dependent dendritic spine neck changes are correlated with synaptic strength

Roberto Araya, Tim P. Vogels, and Rafael Yuste

Dendritic spines are the main recipients of excitatory information in the brain, and though it is accepted that they must serve an essential function in neural circuits, their precise role remains ill-defined. Here (pp. E2895–E2904), using minimal synaptic stimulation, we show that spine neck length correlates inversely with synaptic efficacy. In addition, we discovered a previously unidentified form of spine plasticity following a spike timing-dependent plasticity protocol, characterized by rapid shortening of spine neck length and concomitant increases in synaptic strength. These results provide new insights for our understanding of synaptic plasticity, and could provide an explanation for the presence of thousands of long-necked spines in the dendrites of pyramidal neurons, whose somatic synaptic contribution would otherwise be small or negligible.

Impaired functional communication between the L-type calcium channel and mitochondria contributes to metabolic inhibition in the *mdx* heart

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Duchenne muscular dystrophy (DMD) is a fatal X-linked disease that results in cardiomyopathy and heart failure. The cardiomyopathy is characterized by cytoskeletal protein disarray, contractile dysfunction, and reduced energy production. The mechanisms for altered energy metabolism are not yet fully clarified. The L-type Ca^{2+} channel regulates excitation and contraction in the heart, and can regulate mitochondrial function via the movement of cytoskeletal proteins. Here (pp. E2905–E2914), we find that myocytes from the murine model of DMD (*mdx*) exhibit impaired communication between the L-type Ca^{2+} channel and the mitochondria that results in poor energy production. Morpholino oligomer therapy targeting dystrophin or block of the mitochondrial voltage-dependent anion channel (VDAC) "rescues" metabolic function, indicating that impaired communication between the L-type Ca^{2+} channel and VDAC contributes to the cardiomyopathy.