Capsule

How the brain sorts and routes messages

How do higher brain areas communicate with each other? Do they send out all computations equally to all target areas and leave the recipient to extract the needed and relevant information? Or does the transmitting region package and route computations differentially to distinct target areas, depending on the content? Ciocchi et al. found that the ventral hippocampus routes anxiety-related information preferentially to the prefrontal cortex and goal-related information preferentially to the nucleus accumbens. Hippocampal neurons with multiple projections were more involved in a variety of behavioral tasks and in memory consolidation.

Science 2015; 348: 560

Eitan Israeli

Capsule

Targeting the MLL complex in castration-resistant prostate cancer

Resistance to androgen deprivation therapies and increased androgen receptor (AR) activity are major drivers of castration-resistant prostate cancer (CRPC). Although prior work has focused on targeting AR directly, co-activators of AR signaling, which may represent new therapeutic targets, are relatively underexplored. Malik et al. demonstrate that the mixed-lineage leukemia protein (MLL) complex, a well-known driver of MLL fusion-positive leukemia, acts as a co-activator of AR signaling. AR directly interacts with the MLL complex via the menin-MLL subunit. Menin expression is higher in CRPC than in both hormone-naive prostate cancer and benign prostate tissue, and high menin expression correlates with poor overall survival of individuals diagnosed with prostate cancer. Treatment with a small-molecule inhibitor of menin-MLL interaction blocks AR signaling and inhibits the growth of castration-resistant tumors in vivo in mice. Taken together, this work identifies the MLL complex as a crucial co-activator of AR and a potential therapeutic target in advanced prostate cancer.

Nature Med 2015; 21: 344

Eitan Israeli

Capsule

Myocardial healing requires Reg3β-dependent accumulation of macrophages in the ischemic heart

Cardiac healing after myocardial ischemia depends on the recruitment and local expansion of myeloid cells, particularly macrophages. Holger Lörchner et al. identified Reg3β as an essential regulator of macrophage trafficking to the damaged heart. Using mass spectrometry-based secretome analysis, they found that dedifferentiating cardiomyocytes releases Reg3β in response to the cytokine OSM, which signals through Jak1 and Stat3. Loss of Reg3β led to a large decrease in the number of macrophages in the ischemic heart, accompanied by increased ventricular dilatation and insufficient removal of neutrophils. This defect in neutrophil removal, in turn, caused enhanced matrix degradation, delayed collagen deposition and increased susceptibility to cardiac rupture. These data indicate that OSM, acting through distinct intracellular pathways, regulates both cardiomyocyte dedifferentiation and cardiomyocyte-dependent regulation of macrophage trafficking. Release of OSM from infiltrating neutrophils and macrophages initiates a positive feedback loop in which OSM-induced production of Reg3β in cardiomyocytes attracts additional OSM-secreting macrophages. The activity of the feedback loop controls the degree of macrophage accumulation in the heart, which is instrumental in myocardial healing.

Nature Med 2015; 21: 353

Eitan Israeli

Capsule

Immunogenetics of mice and men

Species undergo different selective forces, and those that drive immunity are of special interest because they may affect studies of human health. Webb and co-researchers investigated the differences between human and mouse for 456 protein-coding gene families involved in innate immunity. Of these, 2 genes in humans and 35 genes in mice exhibited signatures of positive selection. Examining the evolutionary distance between mice and humans, they further identified many genes likely to be under positive selection in the primate and murid lineages. These changes, for the most part, appear to have been fixed within humans and mice, respectively, demonstrating the different evolutionary trajectories that immune genes have taken during evolution.

Mol Biol Evol 2015,10.1093/molbev/msv051

Eitan Israeli

Capsule

A CRISPR view of genes responsible for tumor metastasis

Large tumors metastasize more often than small tumors. Is this simply because large tumors release a greater number of malignant cells into the circulation? Or is it because the genetic changes in tumor cells that drive them to proliferate rapidly are the same as those that promote their metastatic behavior? To explore this question, Chen and group designed a screen based on a genome-editing technology called CRISPR-Cas9 to identify genes that, when inactivated, enhance tumor growth, lung metastasis, or both in mice. The small set of inactivated genes found in metastatic lesions largely overlapped with the set found in late-stage primary tumors, implying that functional loss of these genes drives both growth and metastasis.

Cell 2015; 10.1016/j.cell.2015.02.038

Eitan Israeli

Capsule

Changing shape to destroy RNA

Clustered regularly interspaced short palindromic repeats (CRISPRs) together with CRISPR-associated (Cas) proteins form an adaptive immune system that helps bacteria and archaea defend themselves against invading viruses and plasmids. CRISPR RNAs (crRNAs) target CRISPR-Cas protein complexes to the invaders, bringing about their destruction. Taylor et al. used cryo-electron microscopy to determine the structure of a 12-subunit CRISPR-Cas protein complex with crRNA from *Thermus thermophilus*, in the presence and absence of single-stranded target RNA. Binding to the target RNA causes a change in shape of the CRISPR-Cas complex which results in target recognition and destruction.

Science 2015; 348: 581

Eitan Israeli

Capsule

Fatty acid carbon is essential for dNTP synthesis in endothelial cells

The metabolism of endothelial cells during vessel sprouting remains poorly studied. Schoors et al. report that endothelial loss of CPT1A, a rate-limiting enzyme of fatty acid oxidation (FAO), causes vascular sprouting defects due to impaired proliferation, not migration, of human and murine endothelial cells. Reduction of FAO in endothelial cells did not cause energy depletion or disturb redox homeostasis, but impaired de novo nucleotide synthesis for DNA replication. Isotope labeling studies in control endothelial cells showed that fatty acid carbons substantially replenished the Krebs cycle, and were incorporated into aspartate (a nucleotide precursor), uridine monophosphate (a precursor of pyrimidine nucleoside triphosphates) and DNA. CPT1A silencing reduced these processes and depleted endothelial cell stores of aspartate and deoxyribonucleoside triphosphates. Acetate (metabolized to acetyl-CoA, thereby substituting for the depleted FAO-derived acetyl-CoA) or a nucleoside mix rescued the phenotype of CPT1A-silenced endothelial cells. Finally, CPT1 blockade inhibited pathological ocular angiogenesis in mice, suggesting a novel strategy for blocking angiogenesis.

Nature 2015; 520: 192

Eitan Israeli

Capsule

Distinct plasma immune signatures in ME/CFS are present early in the course of illness

Myalgic encephalomyelitis/chronic fatigue syndrome is a disabling disorder that may affect up to 4 million people in the United States alone. Distinct features include fatigue, memory and concentration deficits, sleep disturbances, headache, joint and muscle pain, post-exertional malaise, and gastrointestinal and immune system dysfunction lasting for 6 months or more. Until now no validated laboratory marker to help confirm the diagnosis existed. Hornig et al. report distinct alterations in plasma immune signatures early in the course of ME/CFS (n=52) compared to healthy controls (n=348) that were not present in subjects with longer duration of illness (n=246). In early disease lasting less than 3 years they found prominent activation of pro-inflammatory (interleukin (IL)-1α, IL-8, IL-12p40, IL-17A, tumor necrosis factor-alpha (TNFα), TNF-related apoptosis-inducing ligand (TRAIL), chemokine ligand (CCL)-2, monocyte chemoattractant protein 1 (MCP1), stem cell factor (SCF), resistin and anti-inflammatory cytokines (IL-1RA, IL-4, IL-13) as well as dissociation of intercytokine regulatory networks (especially CD40 ligand). They found a stronger relationship of cytokine alterations with illness duration than with measures of illness severity. Their findings suggest that immunopathology of ME/CFS is not static.

Sci Advances 2015; 1: e1400121

Mojca Bizjak

Capsule

A role for macrophages in Rett syndrome

Mutations in meningeal macrophages may contribute to the generation of Rett syndrome. Scientists previously implicated microglia, a macrophage subset in the brain, in the pathogenesis of the neurodegenerative disease Rett syndrome. To better understand how microglia and other types of macrophages might contribute to the development of the disease, Cronk et al. examined MECP2-deficient mice. Multiple types of macrophages express MECP2 in normal mice, and several of these populations, including microglia, are lost in MECP2-deficient mice. MECP2 regulated a pro-inflammatory gene expression signature in macrophages. When the authors selectively re-expressed MECP2 in macrophages, they were able to extend the lives of MECP2-deficient mice, which suggests that macrophages probably contribute to disease pathogenesis.

Immunity 2015; 42: 679

Eitan Israeli

Capsule

Branch-specific dendritic Ca2+ spikes cause persistent synaptic plasticity

The brain has an extraordinary capacity for memory storage, but how it stores new information without disrupting previously acquired memories remains unknown. Cichon and team show that different motor learning tasks induce dendritic Ca2+ spikes on different apical tuft branches of individual layer V pyramidal neurons in the mouse motor cortex. These task-related, branch-specific Ca2+spikes cause long-lasting potentiation of post-synaptic dendritic spines active at the time of spike generation. When somatostatin-expressing interneurons are inactivated, different motor tasks frequently induce Ca2+ spikes on the same branches. On those branches, spines potentiated during one task are depotentiated when they are active seconds before Ca2+ spikes induced by another task. Concomitantly, increased neuronal activity and performance improvement after learning one task are disrupted when another task is learned. These findings indicate that dendritic branch-specific generation of Ca2+ spikes is crucial for establishing long-lasting synaptic plasticity, thereby facilitating information storage associated with different learning experiences.

Nature 2015; 520: 180

Eitan Israeli

Capsule

Complex archaea that bridge the gap between prokaryotes and eukaryotes

The origin of the eukaryotic cell remains one of the most contentious puzzles in modern biology. Recent studies have provided support for the emergence of the eukaryotic host cell from within the archaeal domain of life, but the identity and nature of the putative archaeal ancestor remains a subject of debate. Spang and colleagues describe the discovery of 'Lokiarchaeota', a novel candidate archaeal phylum, which forms a monophyletic group with eukaryotes in phylogenomic analyses, and whose genomes encode an expanded repertoire of eukaryotic signature proteins suggestive of sophisticated membrane remodeling capabilities. These results provide strong support for hypotheses in which the eukaryotic host evolved from a bona fide archaeon, and demonstrate that many components that underpin eukaryote-specific features were already present in that ancestor. This provided the host with a rich genomic 'starter-kit' to support the increase in the cellular and genomic complexity that is characteristic of eukaryotes.

Nature 2015; 521: 173

Eitan Israeli

Capsule

Methyl-C binding may explain Rett late onset

Girls with Rett syndrome develop normally for the first 1 or 2 years of life before suffering from progressive neurological problems, perhaps due to mutations in methyl-CpG-binding protein 2 (MeCP2). Chen et al. analyzed the binding of MeCP2 to genomic DNA in the mouse brain and found that before birth MeCP2 binds predominantly to methylated CG sequences. After birth, there is an increase in the genome of methylated C in a non-CG context (mCH). MeCP2 binds to many of these mCH sites, which are enriched in genes with neuronal functions. MeCP2 binding modulates the transcription of these genes, some of which are implicated in Rett syndrome, potentially explaining the late onset of the disease.

Proc Natl Acad Sci USA 2015; doi/10.1073/pnas.1505909112

Eitan Israeli

Capsule

Extra dividends from measles vaccine

Vaccination against measles has many benefits, not only lifelong protection against this potentially serious virus. Mina and collaborators analyzed data collected since mass vaccination began in high income countries when measles was common. Measles vaccination is associated with less mortality from other childhood infections. Measles is known to cause transient immunosuppression, but close inspection of the mortality data suggests that it disables immune memory for 2 to 3 years. Vaccination thus does more than safeguard children against measles; it also stops other infections taking advantage of measles-induced immune damage.

Science 2015; 348: 694

Eitan Israeli

Capsule

Early T cells keep autoimmunity at bay

A major challenge faced by the immune system is to react to foreign substances, such as microbes, while simultaneously tolerating the self. Upsetting this balance leads to autoimmunity. Regulatory T cells (Tregs) are a subset of immune cells that help to maintain this balance. Yang and team found that murine Treg cells generated very early in life are distinct from those generated in older animals and play an especially important role in keeping autoimmunity in. These changes are due to differences in the way Tregs develop in the thymus in newborn versus adult mice.

Science 2015; 348: 589

Eitan Israeli

Capsule

Sleeping while awake

Sleep deprivation affects our behavior and performance. Bernardi and co-workers demonstrate the connection between task-specific performance decrease and local sleep in relevant parts of the human brain. During 24 hours of wakefulness, individuals participated in driving simulations and executive function exercises. Their task-related abilities, such as visuomotor control and response inhibition, were tested alongside electroencephalography (EEG) recordings and functional magnetic resonance imaging (fMRI). Local EEG theta waves, normally observed during sleep, coincided with times of slower movements, visual inaccuracies, and decreased impulse control. The fMRI scans exposed cognitive fatigue in the form of regional neuronal disconnections in the task-relevant brain areas in addition to the general deficiencies.

J Neurosci 2015; 35: 4487

Eitan Israeli

Capsule

Seeing stress signaling in living mice

Stress activates the eIF2α-ATF4 pathway to reduce global protein production while enhancing targeted gene expression, which helps cells adapt and survive. Activation of this pathway is associated with various pathologies, such as tissue fibrosis after injury. Chaveroux et al. developed transgenic mice in which the activation of this pathway could be monitored at the whole-animal level and at the tissue and cellular level. Activation was tissue-specific, depending on the initiating stress. Chemically induced liver fibrosis correlated with activation of the eIF2α-ATF4 pathway by a specific kinase.

Sci Signal 2015; 8: rs5

Eitan Israeli