Capsule

Multiple dynamic representations in the motor cortex during sensorimotor learning

The mechanisms linking sensation and action during learning are poorly understood. Layer 2/3 neurons in the motor cortex might participate in sensorimotor integration and learning; they receive input from sensory cortex and excite deep layer neurons, which control movement. Huber et al. imaged activity in the same set of layer 2/3 neurons in the motor cortex over weeks, while mice learned to detect objects with their whiskers and report detection with licking. Spatially intermingled neurons represented sensory (touch) and motor behaviors (whisker movements and licking). With learning, the population-level representation of task-related licking strengthened. In trained mice, population-level representations were redundant and stable, despite dynamism of single-neuron representations. The activity of a subpopulation of neurons was consistent with touch driving licking behavior. These results suggest that ensembles of motor cortex neurons couple sensory input to multiple related motor programs during learning.

Nature 2012; 484: 473

Eitan Israeli

Capsule

IFITM3 restricts the morbidity and mortality associated with influenza

The 2009 H1N1 influenza pandemic showed the speed with which a novel respiratory virus can spread and the ability of a generally mild infection to induce severe morbidity and mortality in a subset of the population. Recent in vitro studies show that the interferon-inducible transmembrane (IFITM) protein family members potently restrict the replication of multiple pathogenic viruses. Both the magnitude and breadth of the IFITM proteins' in vitro effects suggest that they are critical for intrinsic resistance to such viruses, including influenza viruses. Using a knockout mouse model, Everitt and colleagues tested this hypothesis directly and found that IFITM3 is essential for defending the host against influenza A virus in vivo. Mice lacking *Ifitm3* display fulminant viral pneumonia when challenged with a normally low-pathogenicity influenza virus, mirroring the destruction inflicted by the highly pathogenic 1918 "Spanish" influenza. Similar increased viral replication is seen in vitro, with protection rescued by the re-introduction of *Ifitm3*. To test the role of IFITM3 in human influenza virus infection, the authors assessed the *IFITM3* alleles of individuals hospitalized with seasonal or pandemic influenza H1N1/09 viruses. They found that a statistically significant number of hospitalized subjects show enrichment for a minor *IFITM3* allele (SNP rs12252-C) that alters a splice acceptor site, and functional assays show the minor CC genotype IFITM3 has reduced influenza virus restriction in vitro. Together these data reveal that the action of a single intrinsic immune effector, IFITM3, profoundly alters the course of influenza virus infection in mice and humans.

Nature 2012; 484: 519

Eitan Israeli

Capsule

Selection of IgA-secreting cells in the gut

The gut needs to keep its trillions of microbial inhabitants contained. The immune system has evolved a multifaceted approach to this problem, which includes the production of large quantities of immunoglobulin A (IgA) in the intestinal mucosa. In a process that is not well understood, plasma cells that produce IgA specific for the gut microflora are selected in Peyer's patches in the gut. Kawamoto et al. used genetically manipulated mice to show that the inhibitory co-receptor, programmed cell death-1 (PD-1), is required for the proper selection of IgA-secreting cells in the gut. The effect of PD-1 deletion, however, was not intrinsic to the B cells that produce IgA. Instead, the absence of PD-1 affected the differentiation of T follicular helper cells, which provide important signals to B cells that help guide them as they develop the capacity to produce microflora-specific IgA. Mice deficient in PD-1 exhibited alterations in the composition in their microflora, which suggests that defective selection of IgA can perturb the careful balance that exists between the immune system and resident bacteria.

Science 2012; 336: 485

Eitan Israeli

Capsule

The American College of Rheumatology issues guidelines for management of lupus nephritis

To establish the 2012 lupus nephritis guidelines, investigators reviewed the medical literature from 1966 through 2010 for all evidence pertaining to "lupus kidney disease." Three panels of researchers were involved with reviewing the data and producing the recommendations, which include:

- Advising renal biopsy (in previously untreated patients with active nephritis)
- Adjunctive treatment (background therapy with hydroxychloroquine, ACE inhibitors, control of blood pressure to goal of 130/80 or lower for almost all SLE patients with nephritis)
- Induction of improvement in patients

with ISN Class III/IV lupus glomerulonephritis
with Class IV or IV/V plus cellular crescents
with Class V "pure membranous" lupus nephritis

- Maintaining improvement in patients responsive to induction therapy (with azathioprine or mycophenolate mofetil)
- Changing therapies in patients not adequately responsive to induction therapy
- Identifying vascular disease in SLE patients with renal abnormalities
- Treating nephritis in pregnant patients

Despite the availability of new therapeutics, studies have shown an increase in the incidence of end-stage renal disease from lupus over the past twenty years, with specific increases in young patients, African Americans, and in the southern U.S. "We look forward to seeing a reduction in these trends with implementation of these guidelines as part of high-quality, comprehensive care for SLE patients," said Dr. Hahn. The authors acknowledge that the guidelines are limited by the absence of agreed terms for remission, flare and response, and limited data to inform recommendations for steroid dosing and tapering of immunosuppressive therapies. Dr. Hahn concludes, "Ongoing evaluation and expansion of the guidelines is necessary to further improve outcomes for patients with SLE and nephritis."

Arthritis Care Res May 3, 2012 (DOI: 10.1002/acr.21664)

Eitan Israeli

Capsule

Osteoprotection by semaphorin 3A

The bony skeleton is maintained by local factors that regulate bone-forming osteoblasts and bone-resorbing osteoclasts, in addition to hormonal activity. Osteoprotegerin protects bone by inhibiting osteoclastic bone resorption, but no factor has yet been identified as a local determinant of bone mass that regulates both osteoclasts and osteoblasts. Hayashi and team show that semaphorin 3A (Sema3A) exerts an osteoprotective effect by both suppressing osteoclastic bone resorption and increasing osteoblastic bone formation. The binding of Sema3A to neuropilin-1 (Nrp1) inhibited receptor activator of nuclear factor-κB ligand (RANKL)-induced osteoclast differentiation by inhibiting the immunoreceptor tyrosine-based activation motif (ITAM) and RhoA signaling pathways. In addition, Sema3A and Nrp1 binding stimulated osteoblast and inhibited adipocyte differentiation through the canonical Wnt/β-catenin signaling pathway. The osteopenic phenotype in *Sema3a*$^{-/-}$ mice was recapitulated by mice in which the Sema3A-binding site of Nrp1 had been genetically disrupted. Intravenous Sema3A administration in mice increased bone volume and expedited bone regeneration. Thus, Sema3A is a promising new therapeutic agent in bone and joint diseases.

Nature 2012; 485: 69

Eitan Israeli

Capsule

Pathogen-induced human T_H17 cells produce IFNγ or IL-10 and are regulated by IL-1β

Interleukin (IL)-17-producing CD4+ T helper cells (TH17) have been extensively investigated in mouse models of autoimmunity. However, the requirements for differentiation and the properties of pathogen-induced human TH17 cells remain poorly defined. Using an approach that combines the in vitro priming of naive T cells with the ex vivo analysis of memory T cells, Zielinski et al. describe two types of human TH17 cells with distinct effector function and differentiation requirements. Candida albicans-specific TH17 cells produced IL-17 and interferon-gamma (IFNγ), but no IL-10, whereas Staphylococcus aureus-specific TH17 cells produced IL-17 and could produce IL-10 upon restimulation. IL-6, IL-23 and IL-1β contributed to TH17 differentiation induced by both pathogens, but IL-1β was essential in C. albicans-induced TH17 differentiation to counteract the inhibitory activity of IL-12 and to prime IL-17/IFNγ double-producing cells. In addition, IL-1β inhibited IL-10 production in differentiating and in memory TH17 cells, whereas blockade of IL-1β in vivo led to increased IL-10 production by memory TH17 cells. We also show that, after restimulation, TH17 cells transiently downregulated IL-17 production through a mechanism that involved IL-2-induced activation of STAT5 and decreased expression of ROR-γt. Taken together these findings demonstrate that by eliciting different cytokines, C. albicans and S. aureus prime TH17 cells that produce either IFNγ or IL-10, and identify IL-1β and IL-2 as pro- and anti-inflammatory regulators of TH17 cells both at priming and in the effector phase.

Nature 2012; 484: 514

Eitan Israeli

Capsule

Restoration of vision after transplantation of photoreceptors

Cell transplantation is a potential strategy for treating blindness caused by the loss of photoreceptors. Although transplanted rod-precursor cells are able to migrate into the adult retina and differentiate to acquire the specialized morphological features of mature photoreceptor cells, the fundamental question remains whether transplantation of photoreceptor cells can actually improve vision. Pearson et al. provide evidence of functional rod-mediated vision after photoreceptor transplantation in adult *Gnat*1$^{-/-}$ mice, which lack rod function and are a model of congenital stationary night blindness. The authors show that transplanted rod precursors form classic triad synaptic connections with second-order bipolar and horizontal cells in the recipient retina. The newly integrated photoreceptor cells are light-responsive with dim-flash kinetics similar to adult wild-type photoreceptors. By using intrinsic imaging under scotopic conditions they demonstrate that visual signals generated by transplanted rods are projected to higher visual areas, including V1. Moreover, these cells are capable of driving optokinetic head tracking and visually guided behavior in the *Gnat1*$^{-/-}$ mouse under scotopic conditions. Together, these results demonstrate the feasibility of photoreceptor transplantation as a therapeutic strategy for restoring vision after retinal degeneration.

Nature 2012; 485: 99

Eitan Israeli

Capsule

Prions also interact with components of the miRNA pathway

MicroRNAs (miRNAs) are small non-coding RNAs that, when part of a miRNA-induced silencing complex (miRISC), repress the expression of fully or partially complementary mRNAs. Argonaute (Ago) proteins bind miRNAs and form the heart of the silencing machinery. Intriguingly, plasma membrane-associated forms of the human prion protein (PrP^C), which is associated with neurodegenerative diseases in humans, also interact with components of the miRNA pathway. Gibbings et al. show that a transmembrane form of PrP^C exposes an AGO anchor sequence in the cytoplasm and that this repeat binds AGO1 and AGO2. These PrPC-AGO complexes are found on vesicles in cells that resemble multivesicular bodies (MVBs). During miRNA maturation, AGO protein bound to miRNA must be transferred from the RISC-loading complex (RLC) to the miRISC-silencing complex. PrP^C binds components of both the RLC and the miRISC but seems to do so in distinct cellular locations. PrP^C promotes the association of AGO with the miRISC and/or the stability of this complex. Indeed, PrP^C is required for effective miRNA silencing of a number of target mRNAs. PrP^C may do this through subcellular trafficking, as it seems to increase the interaction between MVBs and AGO-rich structures, such as P or GW bodies, thereby promoting shuttling of AGO between the RISC-loading complex and the miRNA-induced silencing complex.

Nat Struct Mol Biol 2012; 19, 10.1038/nsmb.227

Eitan Israeli

Capsule

Natural blood pressure gauge

Endothelial cells line blood vessels and, by interacting with smooth muscle, can help to control blood flow. Sonkusare and collaborators describe how signaling in endothelial cells controls contraction of surrounding smooth muscle cells, which provides an important mechanism for control of blood pressure. A calcium-sensitive fluorescent protein was expressed in endothelial cells of mouse arteries to image small changes in calcium concentration that appear to represent opening of single TRPV4 ion channels and consequent influx of calcium into the cell. Clustering of the channels allowed cooperative activation of a handful of channels, which appeared to produce a sufficient calcium signal to open another set of calcium-sensitive potassium channels. The resulting depolarization of the endothelial cells then passes an electrical connection to smooth muscle cells through gap junctions.

Science 2012; 336: 597

Eitan Israeli

Capsule

NLRP10 is a NOD-like receptor essential to initiate adaptive immunity by dendritic cells

NLRs (nucleotide-binding domain leucine-rich-repeat-containing receptors, NOD-like receptors) are a class of pattern recognition receptors (PRR) that respond to host perturbation from either infectious agents or cellular stress. The function of most NLR family members has not been characterized and their role in instructing adaptive immune responses remains unclear. NLRP10 (also known as PYNOD, NALP10, PAN5 and NOD8) is the only NLR lacking the putative ligand-binding leucine-rich-repeat domain and has been postulated to be a negative regulator of other NLR members, including NLRP3. Eisenbarth and team did not find evidence that NLRP10 functions through an inflammasome to regulate caspase-1 activity nor that it regulates other inflammasomes. Instead, *Nlrp10*–/– mice had a profound defect in helper T cell-driven immune responses to a diverse array of adjuvants, including lipopolysaccharide, aluminium hydroxide and complete Freund's adjuvant. Adaptive immunity was impaired in the absence of NLRP10 because of a dendritic cell (DC) intrinsic defect in emigration from inflamed tissues, whereas upregulation of DC co-stimulatory molecules and chemotaxis to CCR7-dependent and independent ligands remained intact. The loss of antigen transport to the draining lymph nodes by a subset of migratory DCs resulted in an almost absolute loss in naive $CD4^+$ T cell priming, highlighting the critical link between diverse innate immune stimulation, NLRP10 activity and the immune function of mature DCs.

Nature 2012; 484L510

Eitan Israeli

Capsule

Commensal microflora help to regulate the numbers and functions of natural killer T (NKT) cells in the colon and lung in mice

Epidemiological studies have suggested that the increase in the incidence of asthma and other inflammatory diseases seen in many parts of the world may be due to a reduced exposure to microbes during early childhood. Olszak and co-workers show that commensal microflora help to regulate the numbers and functions of natural killer T (NKT) cells in the colon and lung in mice. Germ-free mice had elevated numbers of NKT cells in these tissues and were more susceptible to chemically induced colitis and allergic asthma. Neonatal recolonization of germ-free mice with microflora prevented enhanced colitis and asthma sensitivity; however, exposure of adult mice to these conditions was not effective. Thus, early exposure to microbes has important, lasting effects on the immune system's sensitivity to inflammation.

Science 2012; 336: 489

Eitan Israeli

Capsule

B cell receptor signal transduction in the GC is short-circuited by high phosphatase activity

Germinal centers (GCs) generate memory B and plasma cells, which are essential for long-lived humoral immunity. GC B cells with high affinity B cell receptors (BCRs) are selectively expanded. To enable this selection, BCRs of such cells are thought to signal differently from those with lower affinity. Khalil et al. show that, surprisingly, most proliferating GC B cells did not demonstrate active BCR signaling. Rather, spontaneous and induced signaling was limited by increased phosphatase activity. Accordingly, both SH2 domain-containing phosphatase-1 (SHP-1) and SH2 domain-containing inositol 5 phosphatase were hyperphosphorylated in GC cells and remained co-localized with BCRs after ligation. Furthermore, SHP-1 was required for GC maintenance. Intriguingly, GC B cells in the cell cycle G_2 period regained responsiveness to BCR stimulation. These data have implications for how higher affinity B cells are selected in the GC.

Science 2012; 336: 1178

Eitan Israeli

Capsule

Aspirin helps to control metabolism, polarity, autophagy, and the restraint of cell proliferation

The protein kinase AMPK (adenosine monophosphate-activated protein kinase) directly monitors cellular energy stores as reflected by changes in cellular concentrations of AMP, adenosine diphosphate (ADP), and adenosine triphosphate (ATP). Through phosphorylation of its targets, it helps to control metabolism, polarity, autophagy, and the restraint of cell proliferation. Activation of AMPK is also proposed to be beneficial for the treatment of diseases, including cancer and diabetes. Hawley et al. report that AMPK can be activated by high concentrations of salicylate, a compound derived from the very commonly used drug aspirin. In mice, salicylate promoted fatty acid and carbohydrate metabolism in an AMPK-dependent fashion

Science 2012; 336: 918

Eitan Israeli

Capsule

Cancer cells need more glycine

To better characterize metabolic properties of cancer cells, Jain et al. systematically measured the concentrations of hundreds of metabolites in cell culture medium in which 60 different cancer cell lines were growing. The fastest growing cancer cells tended to consume glycine, whereas more slowly growing cells excreted some glycine. The rapidly growing cancer cells appeared to need glycine for synthesis of purine nucleotides required for continued synthesis of DNA. Interfering with glycine metabolism slowed growth of the rapidly proliferating cancer cells. Thus, an increased dependence on glycine by rapidly growing cancer cells could potentially provide a target for therapeutic intervention.

Science 2012; 336: 1040

Eitan Israeli

Capsule

AMPK regulates NADPH homeostasis to promote tumor cell survival during energy stress

Overcoming metabolic stress is a critical step for solid tumor growth. However, the underlying mechanisms of cell death and survival under metabolic stress are not well understood. A key signalling pathway involved in metabolic adaptation is the liver kinase B1 (LKB1) AMP-activated protein kinase (AMPK) pathway. Energy stress conditions that decrease intracellular ATP levels below a certain level promote AMPK activation by LKB1. Previous studies showed that LKB1-deficient or AMPK-deficient cells are resistant to oncogenic transformation and tumorigenesis, possibly because of the function of AMPK in metabolic adaptation. However, the mechanisms by which AMPK promotes metabolic adaptation in tumor cells are not fully understood. Jeon et al. show that AMPK activation, during energy stress, prolongs cell survival by redox regulation. Under these conditions, NADPH generation by the pentose phosphate pathway is impaired, but AMPK induces alternative routes to maintain NADPH and inhibit cell death. The inhibition of the acetyl-CoA carboxylases ACC1 and ACC2 by AMPK maintains NADPH levels by decreasing NADPH consumption in fatty acid synthesis and increasing NADPH generation by means of fatty acid oxidation. Knockdown of either ACC1 or ACC2 compensates for AMPK activation and facilitates anchorage-independent growth and solid tumor formation in vivo, whereas the activation of ACC1 or ACC2 attenuates these processes. Thus AMPK, in addition to its function in ATP homeostasis, has a key function in NADPH maintenance, which is critical for cancer cell survival under energy stress conditions, such as glucose limitations, anchorage-independent growth and solid tumor formation in vivo.

Nature 2012; 485: 661

Eitan Israeli

Capsule

Actin filaments are recognized as danger signals

Besides responding to infections, the immune system can also recognize tissue injury in the absence of any infectious agents. Examples of this include antitumor immunity and responses to transplanted organs. During these "sterile" responses, the immune system is triggered by so-called DAMPs, danger-associated molecular patterns. These include intracellular contents such as ATP and HMGB1 that are released upon cell damage or death. The C-type lectin DNGR-1 (Clec9a) is a receptor expressed by certain subsets of dendritic cells that is required for the presentation of antigens derived from necrotic cells to T cells. What it recognizes on dying cells, however, has remained a mystery. After a rather challenging hunt, Zhang et al. and Ahrens et al. (*Immunity* 2012; 36: 635; 646) report that DNGR-1 recognized actin filaments. Monomeric actin, or G-actin, was not recognized by DNGR-1, and actin-binding proteins such as spectrin enhanced DNGR-1 recognition of actin. The identification of F-actin as a ligand for DNGR-1 reinforces the idea that molecules that normally play a housekeeping role in healthy cells are able to activate the immune system when released into the extracellular milieu. Although this often triggers a controlled immune response that promotes tissue repair, alterations in this response could drive inflammation and contribute to disease processes.

Eitan Israeli

Capsule

Disease-promoting and -protective genomic loci on mouse chromosomes 3 and 19 control the incidence and severity of autoimmune arthritis

Proteoglycan (PG)-induced arthritis (PGIA) is a murine model of rheumatoid arthritis. Arthritis-prone BALB/c mice are 100% susceptible, whereas the major histocompatibility complex-matched DBA/2 strain is completely resistant to PGIA. To reduce the size of the disease-suppressive loci for sequencing and to find causative genes of arthritis, Glant et al. created a set of BALB/c.DBA/2-congenic/subcongenic strains carrying DBA/2 genomic intervals overlapping the entire *Pgia26* locus on chromosome 3 (chr3) and *Pgia23/Pgia12* loci on chr19 in the arthritis-susceptible BALB/c background. Upon immunization of these sub-congenic strains and their wild-type (BALB/c) littermates, we identified a major *Pgia26a* sub-locus on chr3 that suppressed disease onset, incidence and severity via controlling the complex trait of T cell responses. The region was reduced to 3 Mbp (11.8 Mbp with flanking regions) in size and contained gene(s) influencing the production of a number of pro-inflammatory cytokines. Additionally, two independent loci (*Pgia26b* and *Pgia26c*) suppressed the clinical scores of arthritis. The *Pgia23* locus (~3 Mbp in size) on chr19 reduced arthritis susceptibility and onset, and the *Pgia12* locus (6 Mbp) associated with low arthritis severity. Thus, we have reached the critical sizes of arthritis-associated genomic loci on mouse chr3 and chr19, which are ready for high throughput sequencing of genomic DNA.

Genes Immunity 2012; 13: 336

Eitan Israeli