Capsule

Curbing the other side of the brain

The two hemispheres of the brain are connected via the corpus callosum; however, this pathway and its function are still not fully understood. Palmer et al. used a combination of optogenetic, calcium-imaging, and electrophysiological methods to investigate the cellular mechanism of inter-hemispheric inhibition of the firing frequency of neocortical layer 5 pyramidal neurons in rats in vivo and in vitro. They discovered that this form of inhibition involved interneurons in the top layers of the cortex that suppressed active dendritic currents synergistically recruited by back-propagating action potentials. This mechanism depended upon a γ-aminobutyric acid type B receptor-mediated mechanism acting on specific ion channels in the dendrites of pyramidal neurons.

Science 2012; 335: 989

Eitan Israeli

Capsule

Mice completely lacking immunoproteasomes show major changes in antigen presentation

The importance of immunoproteasomes to antigen presentation has been unclear because animals totally lacking immunoproteasomes had not been available. Having now developed mice lacking the three immunoproteasome catalytic subunits, Kincaid et al. found that the dendritic cells of these mice had defects in presenting several major histocompatibility complex (MHC) class I epitopes. During viral infection in vivo, the presentation of a majority of MHC class I epitopes was markedly reduced in immunoproteasome-deficient animals compared with wild-type animals, whereas presentation of MHC class II peptides was unaffected. According to mass spectrometry, the repertoire of MHC class I-presented peptides was ~50% different from that in wild-type mice, and these differences were sufficient to stimulate robust transplant rejection of wild-type cells in mutant mice. These results indicated that immunoproteasomes were more important in antigen presentation than previously thought.

Nature Immunol 2012; 13: 129

Eitan Israeli

Capsule

Biomarkers toward diagnosing multiple sclerosis

Identification of biomarkers contributing to disease diagnosis, classification or prognosis could be of considerable utility. For example, primary methods to diagnose multiple sclerosis (MS) include magnetic resonance imaging and detection of immunological abnormalities in cerebrospinal fluid. Tossberg et al. determined whether gene expression differences in blood discriminated MS subjects from comparator groups, and identified panels of ratios that performed with varying degrees of accuracy depending upon complexity of comparator groups. High levels of overall accuracy were achieved by comparing MS with homogeneous comparator groups. Overall accuracy was compromised when MS was compared with a heterogeneous comparator group. Results, validated in independent cohorts, indicate that gene expression differences in blood accurately exclude or include a diagnosis of MS and suggest that these approaches may provide clinically useful prediction of MS.

Genes Immun 2012; 13: 146

Eitan Israeli

Capsule

TNFα-converting enzyme (TACE) intracellular trafficking

The cytokine tumor necrosis factor (TNF) is a major driver of inflammation and contributes to the immune pathology seen in a variety of diseases, including inflammatory bowel disease, rheumatoid arthritis, and sepsis. Soluble TNF is produced by cleavage of its ectodomain by the ADAM family metalloprotease, TNFα-converting enzyme (TACE). However, the molecular regulation of TACE is not understood. Adrain and collaborators (*Science* 2012: 335: 225) and McIlwain et al. (p. 229) now show that the rhomboid family member iRhom2 interacts with TACE in macrophages and is required for its proper intracellular trafficking and activation. In the absence of iRhom2, TACE was not released from the endoplasmic reticulum, and active protease did not reach the cell surface. Because of an inability to produce TNF, iRhom2-deficient mice were more resistant to lipopolysaccharide-induced septic shock but could not adequately control a *Listeria monocytogenes* infection.

Eitan Israeli

Capsule

New cardiac invasive technology

A new technology whereby pertinent information collected during the catheterization procedure is sent directly to the I Pad was developed by Prof. Ran Kornowski at Israel's Rabin Medical Center. This application presents the entire catheterization process on the screen, enabling the cardiologist to explain the procedure to the patient and family in a simple visual manner. The cardiac catheterization procedure provides relevant online information on the patient's heart and the condition of the arteries, necessary for the cardiologist to accurately perform the procedure.

Israel High-Tech & Investment Report, January 2012

Capsule

Therapeutic blockade of PD-L1 and LAG-3 rapidly clears established blood-stage *Plasmodium infection*

Infection of erythrocytes with *Plasmodium* species induces clinical malaria. Parasite-specific CD4+ T cells correlate with lower parasite burdens and severity of human malaria and are needed to control blood-stage infection in mice. However, the characteristics of CD4+ T cells that determine protection or parasite persistence remain unknown. Butler et al. show that infection of humans with *Plasmodium falciparum* resulted in higher expression of the inhibitory receptor PD-1 associated with T cell dysfunction. In vivo blockade of the PD-1 ligand PD-L1 and the inhibitory receptor LAG-3 restored CD4+ T cell function, amplified the number of follicular helper T cells and germinal-center B cells and plasmablasts, enhanced protective antibodies, and rapidly cleared blood-stage malaria in mice. Thus, chronic malaria drives specific T cell dysfunction, and proper function can be restored by inhibitory therapies to enhance parasite control.

Nature Immunol 2012; 13: 188

Eitan Israeli

Capsule

IgE+ memory B cells and plasma cells generated through a germinal-center pathway

Immunoglobulin E (IgE) antibodies are pathogenic in asthma and allergic diseases, but the in vivo biology of IgE-producing (IgE+) cells is poorly understood. A model of the differentiation of IgE+ B cells proposes that IgE+ cells develop through a germinal-center IgG1+ intermediate and that IgE memory resides in the compartment of IgG1+ memory B cells. Talay et al. used a reporter mouse expressing green fluorescent protein associated with membrane IgE transcripts (IgE-GFP) to assess in vivo IgE responses. In contrast to the IgG1-centered model of IgE switching and memory, the authors found that IgE+ cells developed through a germinal-center IgE+ intermediate to form IgE+ memory B cells and plasma cells. These studies delineate a new model for the in vivo biology of IgE switching and memory.

Nature Immunol 2012 13: 396

Eitan Israeli

Capsule

Death of cells for development

Cell death is critical for animal development and for the promotion of gastrulation, as well as for sculpting tissues. Although cell death by apoptosis is essential in some invertebrates, genes promoting apoptosis in the mouse are not required for viability. This surprising observation prompted investigations by Blum et al., who discovered a non-apoptotic developmental cell death process mediated by a polyglutamine-repeat protein in the nematode worm *Caenorhabditis elegans*. This form of cell death is morphologically similar to cell death occurring during vertebrate development, particularly cell death accompanying polyglutamine-dependent neurodegeneration.

Science 2012; 335: 970

Eitan Israeli

Capsule

Living in the liver: hepatic infections

The liver has vital metabolic and clearance functions that involve the uptake of nutrients, waste products and pathogens from the blood. In addition, its unique immunoregulatory functions mediated by local expression of co-inhibitory receptors and immunosuppressive mediators help to prevent inadvertent organ damage. However, these tolerogenic properties render the liver an attractive target site for pathogens. Although most pathogens that reach the liver via the blood are eliminated or controlled by local innate and adaptive immune responses, some pathogens (such as hepatitis viruses) can escape immune control and persist in hepatocytes, causing substantial morbidity and mortality worldwide. Protzer and co-workers review the current knowledge of the mechanisms of liver targeting by pathogens and describe the interplay between pathogens and host factors that promote pathogen elimination and maintain organ integrity or that allow pathogen persistence.

Nature Rev Immunol 2012; 12: 201

Eitan Israeli

Capsule

An epigenetic blockade of cognitive functions in the neurodegenerating brain

Cognitive decline is a debilitating feature of most neurodegenerative diseases of the central nervous system, including Alzheimer's disease. The causes leading to such impairment are only poorly understood and effective treatments are slow to emerge. Graff et al. show that cognitive capacities in the neurodegenerating brain are constrained by an epigenetic blockade of gene transcription that is potentially reversible. This blockade is mediated by histone deacetylase 2, which is increased by Alzheimer's disease-related neurotoxic insults in vitro, in two mouse models of neurodegeneration and in patients with Alzheimer's disease. Histone deacetylase 2 associates with and reduces the histone acetylation of genes important for learning and memory, which show a concomitant decrease in expression. Importantly, reversing the build-up of histone deacetylase 2 by short hairpin RNA-mediated knockdown unlocks the repression of these genes, reinstates structural and synaptic plasticity, and abolishes neurodegeneration-associated memory impairments. These findings advocate for the development of selective inhibitors of histone deacetylase 2 and suggest that cognitive capacities following neurodegeneration are not entirely lost, but merely impaired by this epigenetic blockade.

Nature 2012; 483: 222

Eitan Israeli

Capsule

The sirtuin SIRT6 regulates lifespan in male mice

The significant increase in human lifespan during the past century confronts us with great medical challenges. To meet these challenges, the mechanisms that determine healthy aging must be understood and controlled. Sirtuins are highly conserved deacetylases that have been shown to regulate lifespan in yeast, nematodes and fruit flies. However, the role of sirtuins in regulating worm and fly lifespan has recently become controversial. Moreover, the role of the seven mammalian sirtuins, SIRT1 to SIRT7 (homologues of the yeast sirtuin Sir2), in regulating lifespan is unclear. Kanfi et al. show that male, but not female, transgenic mice overexpressing *Sirt6* have a significantly longer lifespan than wild-type mice. Gene expression analysis revealed significant differences between male *Sirt6*-transgenic mice and male wild-type mice: transgenic males displayed lower serum levels of insulin-like growth factor 1 (IGF1), higher levels of IGF-binding protein 1 and altered phosphorylation levels of major components of IGF1 signaling, a key pathway in the regulation of lifespan. This study shows the regulation of mammalian lifespan by a sirtuin family member and has important therapeutic implications for age-related diseases.

Nature 2012; 483: 218

Eitan Israeli

Capsule

Sound the alarm after infection

When small protein fragments or nucleic acids derived from an invading pathogen are detected by pattern recognition receptors on immune cells, the innate immune response is triggered. This event activates cells of the adaptive immune system, and together, both responses clear the infection. Infections also induce the release of "danger-associated molecular patterns," or alarmins, from the host as a result of tissue damage. Whether these are also important for the ensuing immune response is less clear. Bonilla et al. report that the alarmin, interleukin-33, is required for optimal cytotoxic $CD8^+$ T cell responses and antiviral immunity in mice. In virus-infected mice deficient in IL-33 or its receptor, IL-33 is essential for signaling $CD8^+$ T cells to expand, produce multiple cytokines and acquire cytotoxic capabilities. These results showed that endogenous material, independently of pathogen-derived molecules, are also required for antiviral immunity.

Science 2012; 335: 984

Eitan Israeli

Capsule

Skin infection generates non-migratory memory CD8+ T_{RM} cells providing global skin immunity

Protective T cell memory has long been thought to reside in blood and lymph nodes, but recently the concept of immune memory in peripheral tissues mediated by resident memory T (T_{RM}) cells was proposed. Jiang et al. show in mice that localized vaccinia virus (VACV) skin infection generates long-lived non-recirculating CD8+ skin T_{RM} cells that reside within the entire skin. These skin T_{RM} cells are potent effector cells, and are superior to circulating central memory T (T_{CM}) cells at providing rapid long-term protection against cutaneous re-infection. The authors found that CD8+ T cells are rapidly recruited to skin after acute VACV infection. CD8+ T cell recruitment to skin is independent of CD4+ T cells and interferon-gamma, but requires the expression of E- and P-selectin ligands by CD8+ T cells. Using parabiotic mice, they further show that circulating CD8+ T_{CM} and CD8+ skin T_{RM} cells are both generated after skin infection; however, CD8+ T_{CM} cells recirculate between blood and lymph nodes whereas T_{RM} cells remain in the skin. Cutaneous CD8+ T_{RM} cells produce effector cytokines and persist for at least 6 months after infection. Mice with CD8+ skin T_{RM} cells rapidly cleared a subsequent re-infection with VACV whereas mice with circulating T_{CM} but no skin T_{RM} cells showed greatly impaired viral clearance, indicating that T_{RM} cells provide superior protection. Finally, the authors show that T_{RM} cells generated as a result of localized VACV skin infection reside not only in the site of infection, but also populate the entire skin surface and remain present for many months. Repeated re-infections lead to progressive accumulation of highly protective T_{RM} cells in non-involved skin. These findings have important implications for understanding protective immune memory at epithelial interfaces with the environment, and suggest novel strategies for vaccines that protect against tissue tropic organisms.

Nature 2012; 483: 227

Eitan Israeli

Capsule

Structure and dynamics of the M3 muscarinic acetylcholine receptor

Acetylcholine, the first neurotransmitter to be identified, exerts many of its physiological actions via activation of a family of G protein-coupled receptors (GPCRs) known as muscarinic acetylcholine receptors (mAChRs). Although the five mAChR subtypes (M1–M5) share a high degree of sequence homology, they show pronounced differences in G protein coupling preference and the physiological responses they mediate. Unfortunately, despite decades of effort, no therapeutic agents endowed with clear mAChR subtype selectivity have been developed to exploit these differences. Kruse et al. describe the structure of the $G_{q/11}$-coupled M3 mAChR ('M3 receptor', from rat) bound to the bronchodilator drug tiotropium and identify the binding mode for this clinically important drug. This structure, together with that of the $G_{i/o}$-coupled M2 receptor, offers possibilities for the design of mAChR subtype-selective ligands. Importantly, the M3 receptor structure allows a structural comparison between two members of a mammalian GPCR subfamily displaying different G protein coupling selectivities. Furthermore, molecular dynamics simulations suggest that tiotropium binds transiently to an allosteric site en route to the binding pocket of both receptors. These simulations offer a structural view of an allosteric binding mode for an orthosteric GPCR ligand and provide additional opportunities for the design of ligands with different affinities or binding kinetics for different mAChR subtypes. These findings not only offer insights into the structure and function of one of the most important GPCR families, but may also facilitate the design of improved therapeutics targeting these critical receptors.

Nature 2012; 482: 552

Eitan Israeli

Capsule

Treatment of stroke with a PSD-95 inhibitor in the gyrencephalic primate brain

All attempts at treating strokes by pharmacologically reducing the human brain's vulnerability to ischemia have failed, leaving stroke as a leading cause of death, disability and massive socioeconomic loss worldwide. Over decades, research has failed to translate over 1000 experimental treatments from discovery in cells and rodents to use in humans, a scientific crisis that gave rise to the prevailing belief that pharmacological neuroprotection is not feasible or practicable in higher-order brains. To provide a strategy for advancing stroke therapy, Cook et al. used higher-order gyrencephalic non-human primates, which bear genetic, anatomic and behavioral similarities to humans and tested neuroprotection by PSD-95 inhibitors – promising compounds that uncouple postsynaptic density protein PSD-95 from neurotoxic signaling pathways. The authors show that stroke damage can be prevented in non-human primates in which a PSD-95 inhibitor is administered after stroke onset in clinically relevant situations. This treatment reduced infarct volumes as gauged by magnetic resonance imaging and histology, preserved the capacity of ischemic cells to maintain gene transcription in genome-wide screens of ischemic brain tissue, and significantly preserved neurological function in neurobehavioral assays. The degree of tissue neuroprotection by magnetic resonance imaging corresponded strongly to the preservation of neurological function, supporting the intuitive but unproven dictum that integrity of brain tissue can reflect functional outcome. These findings establish that tissue neuroprotection and improved functional outcome after stroke is unequivocally achievable in gyrencephalic non-human primates treated with PSD-95 inhibitors.

Nature 2012; 483: 213

Eitan Israeli

Capsule

Dysfunction of lipid sensor GPR120 leads to obesity in both mouse and human

Free fatty acids provide an important energy source as nutrients, and act as signaling molecules in various cellular processes. Several G protein-coupled receptors have been identified as free fatty acid receptors important in physiology as well as in several diseases. GPR120 (also known as O3FAR1) functions as a receptor for unsaturated long chain free fatty acids and has a critical role in various physiological homeostasis mechanisms such as adipogenesis, regulation of appetite, and food preference. Ichimura et al. show that GPR120-deficient mice fed a high fat diet develop obesity, glucose intolerance and fatty liver with decreased adipocyte differentiation and lipogenesis and enhanced hepatic lipogenesis. Insulin resistance in such mice is associated with reduced insulin signaling and enhanced inflammation in adipose tissue. The authors show that in humans, *GPR*120 expression in adipose tissue is significantly higher in obese individuals than in lean controls. *GPR*120 exon sequencing in obese subjects reveals a deleterious non-synonymous mutation (p.R270H) that inhibits GPR120 signaling activity. Furthermore, the p.R270H variant increases the risk of obesity in European populations. Overall, this study demonstrates that the lipid sensor GPR120 has a key role in sensing dietary fat and, therefore, in the control of energy balance in both humans and rodents.

Nature 2012; 483: 350

Eitan Israeli

Capsule

Co-evolution in multidimensional trait space favors escape from parasites and pathogens

Almost all species are subject to continuous attack by parasites and pathogens. Because parasites and pathogens tend to have shorter generation times and often experience stronger selection due to interaction than their victims do, it is frequently argued that they should evolve more rapidly and thus maintain an advantage in the evolutionary race between defense and counter-defense. This prediction generates an apparent paradox: how do victim species survive and even thrive in the face of a continuous onslaught of more rapidly evolving enemies? One potential explanation is that defense is physiologically, mechanically or behaviorally easier than attack, so that evolution is less constrained for victims than for parasites or pathogens. Another possible explanation is that parasites and pathogens have enemies themselves and that victim species persist because parasites and pathogens are regulated from the top down and thus generally have only modest demographic impacts on victim populations. Gilman and co-authors explore a third possibility: that victim species are not as evolutionarily impotent as conventional wisdom holds, but instead have unique evolutionary advantages that help to level the playing field. The authors use quantitative genetic analysis and individual-based simulations to show that victims can achieve such an advantage when co-evolution involves multiple traits in both the host and the parasite.

Nature 2012; 483: 328

Eitan Israeli

Capsule

The role of interleukin-2 during homeostasis and activation of the immune system

Interleukin-2 (IL-2) signals influence various lymphocyte subsets during differentiation, immune responses and homeostasis. As discussed in this review by Boyman et al., stimulation with IL-2 is crucial for the maintenance of regulatory T (T_{Reg}) cells and for the differentiation of $CD4^+$ T cells into defined effector T cell subsets following antigen-mediated activation. For $CD8^+$ T cells, IL-2 signals optimize both effector T cell generation and differentiation into memory cells. IL-2 is presented in soluble form or bound to dendritic cells and the extracellular matrix. Use of IL-2 – either alone or in complex with particular neutralizing IL-2-specific antibodies – can amplify $CD8^+$ T cell responses or induce the expansion of the T_{Reg} cell population, thus favoring either immune stimulation or suppression.

Nature Rev Immunol 2012: 12: 180

Eitan Israeli