Capsule

Antiviral immunity via RIG-I-mediated recognition of RNA bearing 5'-diphosphates

Mammalian cells possess mechanisms to detect and defend themselves from invading viruses. In the cytosol, the RIG-I-like receptors (RLRs), RIG-I (retinoic acid-inducible gene I, encoded by *DDX58*) and MDA5 (melanoma differentiation-associated gene 5, encoded by *IFIH1*) sense atypical RNAs associated with virus infection. Detection triggers a signaling cascade via the adaptor MAVS that culminates in the production of type I interferons (IFN-α and β), which are key antiviral cytokines. RIG-I and MDA5 are activated by distinct viral RNA structures and much evidence indicates that RIG-I responds to RNAs bearing a triphosphate (ppp) moiety in conjunction with a blunt-ended, base-paired region at the 5'-end. Goubau et al. show that RIG-I also mediates antiviral responses to RNAs bearing 5'-diphosphates (5'pp). Genomes from mammalian reoviruses with 5'pp termini, 5'pp-RNA isolated from yeast L-A virus, and base-paired 5'pp-RNAs made by in vitro transcription or chemical synthesis, all bind to RIG-I and serve as RIG-I agonists. Furthermore, a RIG-I-dependent response to 5'pp-RNA is essential for controlling reovirus infection in cultured cells and in mice. Thus, the minimal determinant for RIG-I recognition is a base-paired RNA with 5'pp. Such RNAs are found in some viruses but not in uninfected cells, indicating that recognition of 5'pp-RNA, like that of 5'ppp-RNA, acts as a powerful means of self/non-self-discrimination by the innate immune system.

Nature 2014; 514: 372

Eitan Israeli

Capsule

Closing the loop on neuroprosthetic control

Patients paralyzed from a spinal cord injury may soon be able to move their legs more naturally. Current neuromodulation devices cause leg movement by electrically stimulating the spinal cord, but they require constant monitoring and adjustment. Wenger and colleagues created a closed-loop system that auto-tunes the device. The authors stimulated the spinal cords of paralyzed rats and then mapped their leg movements while they walked or climbed stairs, creating integrated feedback and feed-forward models for continuous stepping control.

Sci Transl Med 2014; 6: 255ra133

Eitan Israeli

Capsule

Inflammatory caspases are innate immune receptors for intracellular LPS

The murine caspase-11 non-canonical inflammasome responds to various bacterial infections. Caspase-11 activation-induced pyroptosis, in response to cytoplasmic lipopolysaccharide (LPS), is critical for endotoxic shock in mice. The mechanism underlying cytosolic LPS sensing and the responsible pattern recognition receptor are unknown. Shi et al. show that human monocytes, epithelial cells and keratinocytes undergo necrosis upon cytoplasmic delivery of LPS. LPS-induced cytotoxicity was mediated by human caspase-4 that could functionally complement murine caspase-11. Human caspase-4 and the mouse homologue caspase-11 (caspase-4/11) and also human caspase-5, directly bound to LPS and lipid A with high specificity and affinity. LPS associated with endogenous caspase-11 in pyroptotic cells. Insect-cell purified caspase-4/11 underwent oligomerization upon LPS binding, resulting in activation of the caspases. Underacylated lipid IVa and lipopolysaccharide from *Rhodobacter sphaeroides* (LPS-RS) could bind to caspase-4/11 but failed to induce their oligomerization and activation. LPS binding was mediated by the CARD domain of the caspase. Binding-deficient CARD-domain point mutants did not respond to LPS with oligomerization or activation and failed to induce pyroptosis upon LPS electroporation or bacterial infections. The function of caspase-4/5/11 represents a new mode of pattern recognition in immunity and also an unprecedented means of caspase activation.

Nature 2014; 514: 187

Eitan Israeli

Capsule

Beware of T cells that don't know how to stop

During an infection, T cells divide extensively and secrete proteins that can severely damage tissues. But T cells know when to stop – they express proteins on their surface such as CTLA4, which put on the brakes. Kuehn et al. report genetic evidence of the importance of CTLA4 in humans. They identified six patients with mutations in one copy of *CTLA4*. Patients presented with symptoms of an overzealous immune response, with immune cells infiltrating their organs. The findings support the idea that CTLA4 tells the immune system when enough is enough.

Science 2014; 345: 1623

Eitan Israeli

Capsule

Preventing vascular scarring after surgery

The endothelium that lines blood vessels can undergo a change called the endothelial-to-mesenchymal transition (EndMT), which can cause vessel "scarring." Such scarring limits the success of surgical procedures that require blood vessel grafting, including, for example, heart transplantation or coronary bypass surgery. Chen et al. found that mice lacking FGFR1 in endothelial cells showed increased EndMT after blood vessel grafting. Moreover, arteries from patients who had rejected heart transplants had lower levels of FGFR1 than those from normal individuals. Thus, enhancing FGFR1 activity could limit vascular scarring in heart disease patients undergoing surgery.

Sci Signal 2014; 7: ra90

Eitan Israeli

Capsule

The early spread and epidemic ignition of HIV-1 in human populations

Thirty years after the discovery of HIV-1, the early transmission, dissemination and establishment of the virus in human populations remain unclear. Using statistical approaches applied to HIV-1 sequence data from central Africa, Faria et al. show that from the 1920s Kinshasa (in what is now the Democratic Republic of Congo) was the focus of early transmission and the source of pre-1960 pandemic viruses elsewhere. Location and dating estimates were validated using the earliest HIV-1 archival sample, also from Kinshasa. The epidemic histories of HIV-1 group M and non-pandemic group O were similar until ~1960, after which group M underwent an epidemiological transition and outpaced regional population growth. These results reconstruct the early dynamics of HIV-1 and emphasize the role of social changes and transport networks in the establishment of this virus in human populations. Thus, around 1960, rail links promoted the spread of the virus to mining areas in south-eastern Congo and beyond. Ultimately, HIV crossed the Atlantic in Haitian teachers returning home. From those early events, a pandemic was born.

Science 2014; 346: 56

Eitan Israeli

Capsule

Mapping human drug targets in the cell

To understand both the beneficial and the side effects of a drug, one would need to know its full binding profile to all cellular proteins. Savitski and colleagues take significant steps toward meeting this daunting challenge. They monitored the unfolding or "melting" of over 7000 human proteins and measured how small-molecule binding changes individual melting profiles. As a proof of principle, over 50 targets were identified for an inhibitor known to bind a broad spectrum of kinases. Two cancer drugs, vemurafib and alectinib, are known to have a side effect of photosensitivity. The thermal profiling approach identified drug-protein interactions responsible for these side effects.

Science 2014; 346: 10.1126/science.1255784

Eitan Israeli

Capsule

Teaching tolerance stops the bleeding

People with hemophilia A lack a clotting factor [factor VIII (FVIII)] that stops wounds from bleeding. Regular infusions of FVIII can help, but up to 30% of patients make antibodies that attack this treatment. To prevent this, Sherman et al. developed a way to teach the immune system to tolerate FVIII, rather than make antibodies against it. For 2 months, the researchers fed mice leaves from plants engineered to produce fragments of FVIII. The fragments, safely encapsulated in plant cells, entered the area of the gut where immune cells reside and reduced the immune response to FVIII. Treated mice made fewer antibodies against FVIII, suggesting that teaching (immune) tolerance may allow FVIII to stick around and do its job.

Blood 2014; 123: 10

Eitan Israeli

Capsule

Immune cells and bugs make a sugary coat

Epithelial cells line the intestinal tract and help to keep the peace between our immune system and our trillions of gut microbes. Such peacekeeping requires glycosylated proteins (proteins with attached carbohydrate chains) present on the epithelial cell surface, but how glycosylation occurs is unclear. Goto et al. found that fucosylation (a type of glycosylation) of gut epithelial cells in mice requires gut. This process also requires innate lymphoid cells there, which produce the cytokines interleukin-22 and lymphotoxin, presumably in response to microbial signals. These cytokines signal epithelial cells to add fucose to membrane proteins, which allows the détente between microbes and immune cells to continue.

Science 2014; 345: 10.1126/science.1254009

Eitan Israeli

Capsule

Illuminating brain stimulation therapy

Stroke, the disruption in blood supply to the brain, affects approximately 15 million people worldwide each year. With few treatment options, strokes leave one-third of their sufferers permanently disabled. One promising therapy is magnetic stimulation of the brain but it is relatively non-specific. To determine which cell types may promote recovery Cheng and group engineered mice to express light-activated protein receptors in their neurons. They then used light to activate specific neurons and found that while stimulating neurons in the ipsilesional primary motor cortex had no effect on healthy mice, it did help mice recover after stroke. Stimulating neurons in a targeted manner may be a promising therapy for stroke patients and cause fewer side effects.

Proc Natl Acad Sci USA 2014; 10.1073/pnas.1404109111

Eitan Israeli

Capsule

Interleukin-22 alleviates metabolic disorders and restores mucosal immunity in diabetes

The connection between an altered gut microbiota and metabolic disorders such as obesity, diabetes and cardiovascular disease is well established. Defects in preserving the integrity of the mucosal barriers can result in systemic endotoxemia that contributes to chronic low grade inflammation, which further promotes the development of metabolic syndrome. Interleukin (IL)-22 exerts essential roles in eliciting antimicrobial immunity and maintaining mucosal barrier integrity within the intestine. Wang et al. investigated the connection between IL-22 and metabolic disorders. They found that the induction of IL-22 from innate lymphoid cells and CD4+ T cells is impaired in obese mice under various immune challenges, especially in the colon during infection with *Citrobacter rodentium*. While innate lymphoid cell populations are largely intact in obese mice, the upregulation of IL-23, a cytokine upstream of IL-22, is compromised during the infection. Consequently, these mice are susceptible to *C. rodentium* infection, and both exogenous IL-22 and IL-23 are able to restore the mucosal host defense. Importantly, they further unveiled unexpected functions of IL-22 in regulating metabolism. Mice deficient in IL-22 receptor and fed with a high fat diet are prone to developing metabolic disorders. Strikingly, administration of exogenous IL-22 in genetically obese leptin-receptor-deficient (*db*/*db*) mice and mice fed a high fat diet reverses many of the metabolic symptoms, including hyperglycemia and insulin resistance. IL-22 shows diverse metabolic benefits, as it improves insulin sensitivity, preserves gut mucosal barrier and endocrine functions, decreases endotoxemia and chronic inflammation, and regulates lipid metabolism in liver and adipose tissues. In summary, they identified the IL-22 pathway as a novel target for therapeutic intervention in metabolic diseases.

Nature 2014; 514: 237

Eitan Israeli

Capsule

Progranulin protects against amyloid β deposition and toxicity in Alzheimer's disease mouse models

Haploinsufficiency of the progranulin (PGRN) gene (*GRN*) causes familial frontotemporal lobar degeneration (FTLD) and modulates an innate immune response in humans and in mouse models. *GRN* polymorphism may be linked to late-onset Alzheimer's disease (AD). However, the role of PGRN in AD pathogenesis is unknown. Minami et al. show that PGRN inhibits amyloid β (Aβ) deposition. Selectively reducing microglial expression of PGRN in AD mouse models impaired phagocytosis, increased plaque load threefold and exacerbated cognitive deficits. Lentivirus-mediated PGRN overexpression lowered plaque load in AD mice with aggressive amyloid plaque pathology. Aβ plaque load correlated negatively with levels of hippocampal PGRN, showing the dose-dependent inhibitory effects of PGRN on plaque deposition. PGRN also protected against Aβ toxicity. Lentivirus-mediated PGRN overexpression prevented spatial memory deficits and hippocampal neuronal loss in AD mice. The protective effects of PGRN against Aβ deposition and toxicity have important therapeutic implications. The authors propose enhancing PGRN as a potential treatment for PGRN-deficient FTLD and AD.

Nature Med 2014; 20: 1157

Eitan Israel

Capsule

Regulation of astrocyte activation by glycolipids drives chronic CNS inflammation

Astrocytes have complex roles in health and disease, thus it is important to study the pathways that regulate their function. Mayo and co-researchers report that lactosylceramide (LacCer) synthesized by β-1,4-galactosyltransferase 6 (B4GALT6) is upregulated in the central nervous system (CNS) of mice during chronic experimental autoimmune encephalomyelitis (EAE), a model of multiple sclerosis (MS). LacCer acts in an autocrine manner to control astrocyte transcriptional programs that promote neurodegeneration. In addition, LacCer in astrocytes controls the recruitment and activation of microglia and CNS-infiltrating monocytes in a non-cell autonomous manner by regulating production of the chemokine CCL2 and granulocyte-macrophage colony-stimulating factor (GM-CSF), respectively. The authors also detected high *B4GALT6* gene expression and LacCer concentrations in CNS MS lesions. Inhibition of LacCer synthesis in mice suppressed local CNS innate immunity and neurodegeneration in EAE and interfered with the activation of human astrocytes in vitro. Thus, B4GALT6 regulates astrocyte activation and is a potential therapeutic target for MS and other neuroinflammatory disorders.

Nature Med 2014; 20: 1147

Eitan Israeli

Capsule

Mutant protein in tumors hits the DEK

Cancer genome sequencing projects have uncovered a multitude of mutations in human tumors. Understanding whether and how these mutations contribute to tumor development and progression could ultimately lead to new therapies. Theurillat et al. studied the protein product of a gene that is recurrently mutated in prostate cancer. Normally this protein helps attach a biochemical tag to cellular proteins that marks them for degradation. The new work shows that the tumor-associated mutant protein loses this tagging ability, which results in the stabilization of a handful of cellular proteins that would otherwise be degraded. One of the most intriguing of these proteins was DEK, which helps prostate cancer cells invade into surrounding tissue.

Science 2014; 345: 85

Eitan Israeli

Capsule

Continuous requirement for the TCR in regulatory T cell function

Foxp3+ regulatory T cells (T_{reg} cells) maintain immunological tolerance, and their deficiency results in fatal multi-organ autoimmunity. Although heightened signaling via the T cell antigen receptor (TCR) is critical for the differentiation of T_{reg} cells, the role of TCR signaling in T_{reg} cell function remains largely unknown. Levine et al. demonstrated that inducible ablation of the TCR resulted in T_{reg} cell dysfunction that could not be attributed to impaired expression of the transcription factor Foxp3, decreased expression of T_{reg} cell signature genes or altered ability to sense and consume interleukin 2 (IL-2). Instead, TCR signaling was required for maintaining the expression of a limited subset of genes comprising 25% of the activated T_{reg} cell transcriptional signature. These results reveal a critical role for the TCR in the suppressor capacity of T_{reg} cells.

Nature Immunol 2014; 15: 1070

Eitan Israeli

Capsule

Induction of the nuclear receptor PPAR-γ by the cytokine GM-CSF is critical for the differentiation of fetal monocytes into alveolar macrophages

Tissue-resident macrophages constitute heterogeneous populations with unique functions and distinct gene-expression signatures. While it has been established that they originate mostly from embryonic progenitor cells, the signals that induce a characteristic tissue-specific differentiation program remain unknown. Schneider and team found that the nuclear receptor PPAR-γ determined the perinatal differentiation and identity of alveolar macrophages (AMs). In contrast, PPAR-γ was dispensable for the development of macrophages located in the peritoneum, liver, brain, heart, kidneys, intestine and fat. Transcriptome analysis of the precursors of AMs from newborn mice showed that PPAR-γ conferred a unique signature, including several transcription factors and genes associated with the differentiation and function of AMs. Expression of PPAR-γ in fetal lung monocytes was dependent on the cytokine GM-CSF. Therefore, GM-CSF has a lung-specific role in the perinatal development of AMs through the induction of PPAR-γ in fetal monocytes.

Nature Immunol 2014; 15: 1026

Eitan Israeli

Capsule

Artificial sweeteners induce glucose intolerance by altering the gut microbiota

Non-caloric artificial sweeteners (NAS) are among the most widely used food additives worldwide, regularly consumed by lean and obese individuals alike. NAS consumption is considered safe and beneficial owing to their low caloric content, yet supporting scientific data remain sparse and controversial. Suez et al. from the Weizmann Institute of Science demonstrated that consumption of commonly used NAS formulations drives the development of glucose intolerance through induction of compositional and functional alterations to the intestinal microbiota. These NAS-mediated deleterious metabolic effects are abrogated by antibiotic treatment and are fully transferrable to germ-free mice upon fecal transplantation of microbiota configurations from NAS-consuming mice, or of microbiota anerobically incubated in the presence of NAS. The authors identified NAS-altered microbial metabolic pathways that are linked to host susceptibility to metabolic disease and demonstrated similar NAS-induced dysbiosis and glucose intolerance in healthy human subjects. These results link NAS consumption, dysbiosis and metabolic abnormalities, thereby calling for a reassessment of massive NAS usage.

Nature 2014; 514: 181

Eitan Israeli

Capsule

Chaperone-mediated autophagy regulates T cell responses through targeted degradation of negative regulators of T cell activation

Chaperone-mediated autophagy (CMA) targets soluble proteins for lysosomal degradation. Valdor et al. found that CMA was activated in T cells in response to engagement of the T cell antigen receptor (TCR), which induced expression of the CMA-related lysosomal receptor LAMP-2A. In activated T cells, CMA targeted the ubiquitin ligase Itch and the calcineurin inhibitor RCAN1 for degradation to maintain activation-induced responses. Consequently, deletion of the gene encoding LAMP-2A in T cells caused deficient in vivo responses to immunization or infection with *Listeria monocytogenes*. Impaired CMA activity also occurred in T cells with age, which negatively affected their function. Restoration of LAMP-2A in T cells from old mice resulted in enhancement of activation-induced responses. These findings define a role for CMA in regulating T cell activation through the targeted degradation of negative regulators of T cell activation.

Nature Immunol 2014; 15: 1046

Eitan Israeli