Capsule

Microbiota can mislead antibodies

Unlike the response to many viral infections, most people do not produce antibodies capable of clearing HIV-1. Non-neutralizing antibodies that target HIV-1's envelope glycoprotein (Env) typically dominate the response, which is generated by B cells that cross-react with Env and the intestinal microbiota. Williams and group analyzed samples from individuals who had received a vaccine containing the Env protein, including the gp41 subunit. Most of the antibodies were non-neutralizing and targeted gp41. The antibodies also reacted to intestinal microbiota, suggesting that preexisting immunity to microbial communities skews vaccine-induced immune responses toward an unproductive target.

Science 2015;3 49: 10.1126/science.aab1253

Eitan Israeli

Capsule

NY-ESO-1-specific TCR-engineered T cells mediate sustained antigen-specific antitumor effects in myeloma

Despite recent therapeutic advances, multiple myeloma (MM) remains largely incurable. Rapoport and team report results of a phase I/II trial to evaluate the safety and activity of autologous T cells engineered to express an affinity-enhanced T cell receptor (TCR) recognizing a naturally processed peptide shared by the cancer-testis antigens NY-ESO-1 and LAGE-1. Twenty patients with antigen-positive MM received an average 2.4 × 109 engineered T cells 2 days after autologous stem cell transplant. Infusions were well tolerated without clinically apparent cytokine-release syndrome, despite high interleukin (IL)-6 levels. Engineered T cells expanded, persisted, trafficked to marrow and exhibited a cytotoxic phenotype. Persistence of engineered T cells in blood was inversely associated with NY-ESO-1 levels in the marrow. Disease progression was associated with loss of T cell persistence or antigen escape, in accordance with the expected mechanism of action of the transferred T cells. Encouraging clinical responses were observed in 16 of 20 patients (80%) with advanced disease, with a median progression-free survival of 19.1 months. NY-ESO-1–LAGE-1 TCR-engineered T cells were safe, trafficked to marrow and showed extended persistence that correlated with clinical activity against antigen-positive myeloma.

Nature Med 2015; 21: 914

Eitan Israeli

Capsule

Neutrophils promote Alzheimer's disease-like pathology and cognitive decline via LFA-1 integrin

Inflammation is a pathological hallmark of Alzheimer's disease, and innate immune cells have been shown to contribute to disease pathogenesis. In two transgenic models of Alzheimer's disease (5xFAD and 3xTg-AD mice), neutrophils extravasated and were present in areas with amyloid-β (Aβ) deposits, where they released neutrophil extracellular traps (NETs) and IL-17. Aβ42 peptide triggered the LFA-1 integrin high-affinity state and rapid neutrophil adhesion to integrin ligands. In vivo, LFA-1 integrin controlled neutrophil extravasation into the CNS and intraparenchymal motility. In transgenic Alzheimer's disease models, neutrophil depletion or inhibition of neutrophil trafficking via LFA-1 blockade reduced Alzheimer's disease-like neuropathology and improved memory in mice already showing cognitive dysfunction. Temporary depletion of neutrophils for 1 month at early stages of disease led to sustained improvements in memory. Transgenic Alzheimer's disease model mice lacking LFA-1 were protected from cognitive decline and had reduced gliosis. In humans with Alzheimer's disease, neutrophils adhered to and spread inside brain venules and were present in the parenchyma, along with NETs. These results demonstrate that neutrophils contribute to the disease's pathogenesis and cognitive impairment and suggest that the inhibition of neutrophil trafficking may be beneficial in Alzheimer's disease.

Nature Med 2015; 21: 880

Eitan Israeli

Capsule

The oral and gut microbiomes are perturbed in rheumatoid arthritis and partly normalized after treatment

Zhang et al. carried out metagenomic shotgun sequencing and a metagenome-wide association study (MGWAS) of fecal, dental and salivary samples from a cohort of individuals with rheumatoid arthritis (RA) and from healthy controls. Concordance was observed between the gut and oral microbiomes, suggesting overlap in the abundance and function of species at different body sites. Dysbiosis was detected in the gut and oral microbiomes of RA patients, but it was partially resolved after RA treatment. Alterations in the gut, dental or saliva microbiome distinguished individuals with RA from healthy controls, were correlated with clinical measures, and could be used to stratify individuals on the basis of their response to therapy. In particular, *Haemophilus* spp. were depleted in individuals with RA at all three sites and negatively correlated with levels of serum autoantibodies, whereas *Lactobacillus salivarius* was over-represented in individuals with RA at all three sites and was present in increased amounts in cases of very active RA. Functionally, the redox environment, transport and metabolism of iron, sulfur, zinc and arginine were altered in the microbiota of individuals with RA. Molecular mimicry of human antigens related to RA was also detectable. These results establish specific alterations in the gut and oral microbiomes in individuals with RA and suggest potential ways of using microbiome composition for prognosis and diagnosis.

Nature Med 2015; 21: 895

Eitan Israeli

Capsule

Connecting β-amyloid, memory, and sleep

One of the risk factors for developing Alzheimer's disease is poor sleep quality. People consolidate memories while they sleep, suggesting how disrupted sleep could contribute to the cognitive decline seen in individuals with Alzheimer's disease. Mander and colleagues scanned the brains of healthy older adults for the presence of β-amyloid (Aβ), which is elevated in Alzheimer's disease, and found that it correlated with poor non-rapid eye movement slow-wave sleep quality. They then performed memory retention tests before and after sleep and found that subjects consolidated memories more poorly after a bad night of sleep. A computational model based on these findings suggests that Aβ disrupts people's ability to form memories through its detrimental effects on sleep.

Nat Neurosci 2015; 7: 1051

Eitan Israeli

Capsule

Out-of-register axons control output

A neuron integrates synaptic inputs and fires action potentials from its axon initial segment (AIS), a specialized membrane region on neuronal axons that also forms synapses with other axons. Stimulating neurons chronically can cause the AIS to move distally along the axon, but do its associated synapses move with it? Wefelmeyer et al. used optogenetics and imaging to show that in the rat hippocampus, synapses of chandelier interneurons on pyramidal neurons do not move with the AIS. Nor is there a change in the number of synapses or their architecture. Computational modeling revealed that neurons with distal AIS and proximal synapses have weaker and delayed action potentials. Such AIS plasticity may be a homeostatic mechanism for neurons to avoid becoming overexcited.

Proc Natl Acad Sci USA 2015; 10.1073/pnas.1502902112

Eitan Israeli

Capsule

VSV-EBOV rapidly protects macaques against infection with the 2014/15 Ebola virus outbreak strain

The latest Ebola virus (EBOV) epidemic spread rapidly through Guinea, Sierra Leone, and Liberia, creating a global public health crisis and accelerating the assessment of experimental therapeutics and vaccines in clinical trials. One of those vaccines is based on recombinant vesicular stomatitis virus expressing the EBOV glycoprotein (VSV-EBOV), a live-attenuated vector with marked preclinical efficacy. Marzi et al. provide the preclinical proof that VSV-EBOV completely protects macaques against lethal challenge with the West African EBOV-Makona strain. Complete and partial protection was achieved with a single dose given as late as 7 and 3 days before challenge, respectively. This indicates that VSV-EBOV may protect humans against EBOV infections in West Africa with relatively short time to immunity, promoting its use for immediate public health responses.

Science 2015; 349: 739

Eitan Israeli

Capsule

Cell type-specific glial networks

Glial cells respond to neurotransmitters when nerve cells communicate with each other. Glial cells themselves release gliotransmitters that regulate neural synaptic transmission. Martín et al. studied this reciprocal relationship in a brain region called the dorsal striatum, which has two types of experimentally identifiable neurons and two types of synapses. Subpopulations of glial cells selectively responded to the activity of one specific type of neuron. In turn, these specifically activated glial cells signaled only to the same type of neurons but not the other, indicating that glial-nerve signaling is largely cell-type specific.

Science 2015; 349: 730

Eitan Israeli

Capsule

Snail1-induced partial epithelial-to-mesenchymal transition drives renal fibrosis in mice and can be targeted to reverse established disease

Progressive kidney fibrosis contributes greatly to end-stage renal failure, and no specific treatment is available to preserve organ function. During renal fibrosis, myofibroblasts accumulate in the interstitium of the kidney, leading to massive deposition of extracellular matrix and organ dysfunction. The origin of myofibroblasts is manifold, but the contribution of an epithelial-to-mesenchymal transition (EMT) undergone by renal epithelial cells during kidney fibrosis is still debated. Grande et al. show that the reactivation of *Snai1* (encoding snail family zinc finger 1, known as Snail1) in mouse renal epithelial cells is required for the development of fibrosis in the kidney. Damage-mediated Snail1 reactivation induces a partial EMT in tubular epithelial cells that, without directly contributing to the myofibroblast population, relays signals to the interstitium to promote myofibroblast differentiation and fibrogenesis and to sustain inflammation. The authors also show that Snail1-induced fibrosis can be reversed in vivo and that obstructive nephropathy can be therapeutically ameliorated in mice by targeting Snail1 expression. These results reconcile conflicting data on the role of the EMT in renal fibrosis and provide avenues for the design of novel anti-fibrotic therapies.

Nature Med 2015; 21: 989

Eitan Israeli

Capsule

Commensal bacteria direct selective cargo sorting to promote symbiosis

Mucosal immunity protects a host from intestinal inflammation and infection and is profoundly influenced by symbiotic bacteria. Zhang and team report that in mice, symbiotic bacteria directed selective cargo sorting in Paneth cells to promote symbiosis through Nod2, a cytosolic bacterial sensor, and the multifunctional protein kinase LRRK2, both encoded by inflammatory bowel disease (IBD)-associated genes. Commensals recruited Nod2 onto lysozyme-containing dense core vesicles (DCVs), which was required for DCV localization of LRRK2 and a small GTPase, Rab2a. Deficiency of Nod2, LRRK2 or Rab2a or depletion of commensals resulted in lysosomal degradation of lysozyme. Thus, commensal bacteria and host factors orchestrate the lysozyme-sorting process to protect the host from enteric infection, implicating Paneth cell dysfunction in IBD pathogenesis.

Nature Immunol 2015; 16: 918

Eitan Israeli

Capsule

Trichuris suis soluble products induce Rab7b expression and limit TLR4 responses in human dendritic cells

Inflammatory immune disorders such as inflammatory bowel disease and multiple sclerosis are major health problems. Currently, the intestinal whipworm *Trichuris suis* is being explored in clinical trials to reduce inflammation in these diseases; however, the mechanisms by which the parasite affects the host immune system are not known. Klaver et al. determined the effects of *T. suis* soluble products (SPs) on Toll-like receptor-4 (TLR4)-stimulated human dendritic cells (DCs) using Illumina bead chip gene arrays. Pathway analysis of lipopolysaccharide-stimulated DCs with or without *T. suis* treatment showed that co-stimulation with *T. suis* SPs resulted in a downregulation of both the myeloid differentiation primary response gene 88-dependent and the TIR-domain-containing adaptor-inducing interferon-β-dependent signaling pathways triggered by TLR4. These data were verified using quantitative real-time PCR of several key genes within these pathways and/or defining their protein levels. In addition, *T. suis* SPs induce Rab7b, a negative regulator of TLR4 signaling that interferes with its trafficking, which coincided with a reduced surface expression of TLR4. These data indicate that the mechanism by which *T. suis* SPs reduce inflammatory responses is through suppression of both TLR4 signaling and surface expression on DCs.

Genes Immunity 2015; 16: 378

Eitan Israeli

Capsule

The way to a broken heart

Mice lacking cardiac myosin binding protein C (MYBC) develop defective hearts that are twice the normal size. MYBC is a component of contractile thick filaments in the cardiac muscle. Jiang and collaborators found that the heart cells in mice lacking MYBC divided one extra time shortly after birth – when normal mouse heart cells would have stopped dividing. This caused the mice to have more myocytes with single nuclei, which compromise heart function. This unanticipated role of a structural protein in regulating how muscle cells divide may be important in different types of cardiomyopathy in human patients.

Proc Natl Acad Sci USA 2015; 112: 9046

Eitan Israeli

Capsule

Hydrogels cozy up to inflamed tissues

Inflammation drives many chronic conditions. Directing potent drugs to the site of inflammation is highly desirable for improving treatment. Zhang et al. designed a hydrogel that self-assembles and delivers hydrophobic anti-inflammatory drugs directly to inflamed colon cells. Dexamethasone-loaded hydrogel enemas administered to a genetic mouse model of ulcerative colitis – a type of inflammatory bowel disease – relieved inflammation more effectively than free dexamethasone. In tissue samples from these patients, as well as in a chemically induced mouse model of colitis, hydrogel microfibers preferentially attached to inflamed tissue.

Sci Transl Med 2015; 7: 300ra128

Eitan Israeli

Capsule

TH17 cells promote microbial killing and innate immune sensing of DNA via interleukin 26

Interleukin 17-producing helper T cells (TH17 cells) play a major role in protecting against infections and in mediating autoimmune diseases, yet the mechanisms involved are incompletely understood. Meller and co-researchers found that interleukin 26 (IL-26), a human TH17 cell-derived cytokine, is a cationic amphipathic protein that kills extracellular bacteria via membrane-pore formation. Furthermore, TH17 cell-derived IL-26 formed complexes with bacterial DNA and self-DNA released by dying bacteria and host cells. The resulting IL-26-DNA complexes triggered the production of type I interferon by plasmacytoid dendritic cells via activation of Toll-like receptor 9, but independently of the IL-26 receptor. These findings provide insights into the potent antimicrobial and pro-inflammatory function of TH17 cells by showing that IL-26 is a natural human antimicrobial that promotes immune sensing of bacterial and host cell death.

Nature Immunol 2015; 16: 970

Eitan Israeli

Capsule

Gut microbes make T cells keep the peace

Our guts harbor trillions of microbial inhabitants, some of which regulate the types of immune cells that are present in the gut. For instance, *Clostridium* species of bacteria induce a type of T cell that promotes tolerance between the host and its microbial contents. Ohnmacht et al. and Sefik et al. (*Science* 2015; 349: 989 and 993) characterized a population of gut regulatory T cells in mice, which required gut microbiota to survive. Multiple bacterial species of the microbiota could induce transcription factor-expressing regulatory T cells that helped maintain immune homeostasis. Mice engineered to lack these transcription factors exhibited enhanced susceptibility to colonic inflammation and had elevated amounts of pro-inflammatory molecules associated with allergies.

Eitan Israeli

Capsule

Antigen-specific NK cell memory in rhesus macaques

Natural killer (NK) cells have traditionally been considered non-specific components of innate immunity, but recent studies have shown features of antigen-specific memory in mouse NK cells. However, it has remained unclear whether this phenomenon also exists in primates. Reeves et al. found that splenic and hepatic NK cells from $SHIV_{SF162P3}$-infected and SIV_{mac251}-infected macaques specifically lysed Gag- and Env-pulsed dendritic cells in an NKG2-dependent fashion, in contrast to NK cells from uninfected macaques. Moreover, splenic and hepatic NK cells from Ad26-vaccinated macaques efficiently lysed antigen-matched but not antigen-mismatched targets 5 years after vaccination. These data demonstrate that robust, durable, antigen-specific NK cell memory can be induced in primates after both infection and vaccination, and this finding could be important for the development of vaccines against HIV-1 and other pathogens.

Nature Immunol 2015; 16: 927

Eitan Israeli

Capsule

Structural integration in hypoxia-inducible factors

The hypoxia-inducible factors (HIFs) coordinate cellular adaptations to low oxygen stress by regulating transcriptional programs in erythropoiesis, angiogenesis and metabolism. These programs promote the growth and progression of many tumors, making HIFs attractive anticancer targets. Transcriptionally active HIFs consist of HIF-α and ARNT (also called HIF-1β) subunits. Wu et al. describe crystal structures for each of mouse HIF-2α-ARNT and HIF-1α-ARNT heterodimers in states that include bound small molecules and their hypoxia response element. A highly integrated quaternary architecture is shared by HIF-2α-ARNT and HIF-1α-ARNT, wherein ARNT spirals around the outside of each HIF-α subunit. Five distinct pockets are observed that permit small-molecule binding, including PAS domain encapsulated sites and an interfacial cavity formed through subunit heterodimerization. The DNA-reading head rotates, extends and cooperates with a distal PAS domain to bind hypoxia response elements. HIF-α mutations linked to human cancers map to sensitive sites that establish DNA binding and the stability of PAS domains and pockets.

Nature 2015; 524: 303

Eitan Israeli

Capsule

A tale of two asthmas

Classifying diseases according to symptoms is rapidly becoming an outmoded practice. Targeted therapeutics have shown that sets of symptoms can be caused by different pathogenic mechanisms. Choy et al. demonstrate that asthma can be divided into three immunological clusters – T_H2-high, T_H17-high, and T_H2-T_H17-low. The T_H2-high and T_H17-high clusters inversely correlate in a mouse model of asthma, whereby neutralizing one signature promoted the other. Combination therapies targeting both pathways might better treat asthmatic individuals.

Sci Transl Med 2015; 7: 301ra129

Eitan Israeli

Capsule

Meta-analysis of shared genetic architecture across ten pediatric autoimmune diseases

Genome-wide association studies (GWASs) have identified hundreds of susceptibility genes, including shared associations across clinically distinct autoimmune diseases. Li and colleagues performed an inverse $\chi 2$ meta-analysis across ten pediatric-age-of-onset autoimmune diseases (pAIDs) in a case-control study including more than 6035 cases and 10,718 shared population-based controls. The authors identified 27 genome-wide significant loci associated with one or more pAIDs, mapping to *in silico*-replicated autoimmune-associated genes (including IL2RA) and new candidate loci with established immun-o regulatory functions such as *ADGRL2*, *TENM3*, *ANKRD30A*, *ADCY7* and *CD40LG*. The pAID-associated single-nucleotide polymorphisms (SNPs) were functionally enriched for deoxyribonuclease (DNase)-hypersensitivity sites, expression quantitative trait loci (eQTLs), microRNA (miRNA)-binding sites and coding variants. We also identified biologically correlated, pAID-associated candidate gene sets on the basis of immune cell expression profiling and found evidence of genetic sharing. Network and protein-interaction analyses demonstrated converging roles for the signaling pathways of type 1, 2 and 17 helper T cells (T_H1, T_H2 and T_H17), JAK-STAT, interferon and interleukin in multiple autoimmune diseases.

Nature Med 2015; 21: 1018

Eitan Israeli