Capsule

Broad defects in the energy metabolism of leukocytes underlie immunoparalysis in sepsis

The acute phase of sepsis is characterized by a strong inflammatory reaction. At later stages in some patients, immunoparalysis may be encountered and is associated with a poor outcome. By transcriptional and metabolic profiling of human patients with sepsis, Cheng et al. found that a shift from oxidative phosphorylation to aerobic glycolysis was an important component of initial activation of host defense. Blocking metabolic pathways with metformin diminished cytokine production and increased mortality in systemic fungal infection in mice. In contrast, in leukocytes rendered tolerant by exposure to lipopolysaccharide or after isolation from patients with sepsis and immunoparalysis, a generalized metabolic defect at the level of both glycolysis and oxidative metabolism was apparent, which was restored after recovery of the patients. Finally, the immunometabolic defects in humans were partially restored by therapy with recombinant interferon-γ, which suggested that metabolic processes might represent a therapeutic target in sepsis.

Nature Immunol 2016; 17: 406

Eitan Israeli

Capsule

Variation in microbiome LPS immunogenicity contributes to autoimmunity in humans

According to the hygiene hypothesis, the increasing incidence of autoimmune diseases in Western countries may be explained by changes in early microbial exposure, leading to altered immune maturation. Vatanen et al. followed gut microbiome development from birth until age 3 in 222 infants in Northern Europe, where early-onset autoimmune diseases are common in Finland and Estonia but are less prevalent in Russia. The authors found that *Bacteroides* species are lowly abundant in Russians but dominate in Finnish and Estonian infants. Therefore, their lipopolysaccharide (LPS) exposures arose primarily from *Bacteroides* rather than from *Escherichia coli*, which is a potent innate immune activator. They show that *Bacteroides* LPS is structurally distinct (4–5 acyl chains) from *E. coli* LPS (6 acyl chains) and inhibits innate immune signaling and endotoxin tolerance; furthermore, unlike LPS from *E. coli*, *B. dorei* LPS does not decrease incidence of autoimmune diabetes in non-obese diabetic mice. Early colonization by immunologically silencing microbiota may thus preclude aspects of immune education.

Cell 2016; 165: 842

Eitan Israeli

Capsule

Apoptotic epithelial cells control the abundance of Treg cells at barrier surfaces

Epithelial tissues continually undergo apoptosis. Commensal organisms that inhabit the epithelium influence tissue homeostasis, in which regulatory T cells (Treg cells) have a central role. However, the physiological importance of epithelial cell apoptosis and how the number of Treg cells is regulated are both incompletely understood. Nakahashi-Oda et al. found that apoptotic epithelial cells negatively regulated the commensal-stimulated proliferation of Treg cells. Gut commensals stimulated CX3CR1+CD103-CD11b+ dendritic cells (DCs) to produce interferon-beta (IFNβ), which augmented the proliferation of Treg cells in the intestine. Conversely, phosphatidylserine exposed on apoptotic epithelial cells suppressed IFNβ production by the DCs via inhibitory signaling mediated by the cell-surface glycoprotein CD300a and thus suppressed Treg cell proliferation. These findings reveal a regulatory role for apoptotic epithelial cells in maintaining the number of Treg cell and tissue homeostasis.

Nature Immunol 2016; 17: 441

Eitan Israeli

Capsule

A window into Alzheimer's disease

Alzheimer's disease (AD) involves the accumulation of amyloid-β (Aβ) plaques and tau tangles in the brain. The cognitive and pathological results of Aβ deposition in patients with AD have been well studied, owing to the availability of PET (positron emission tomography) imaging ligands. Brier et al. used newly available PET imaging agents for tau to explore the relationship between tau pathology and Aβ pathology in patients with early AD. Overall, tau imaging provided a more robust predictor of disease status than Aβ imaging. Whereas Aβ imaging is a good marker of early AD, tau imaging is a more robust predictor of disease progression.

Sci Transl Med 2016; 8: 338a66

Eitan Israeli

Capsule

A recipe for intestinal IgA

Our guts are teeming with microbes, some friendly and others not. Plasma cells in the gut secrete immunoglobulin A (IgA), which helps to keep the peace with resident commensal bacteria and fights pathogens. B cell isotype switching to IgA occurs in lymphoid tissues called Peyer's patches. Reboldi et al. studied the cellular processes that guide B cells toward making IgA in mice. B cells took an unexpected journey from Peyer's patches follicles to the intestinal mucosa to interact with specialized IgA-triggering dendritic cells. The B cells then migrated back to the follicles to become IgA-producing B cells.

Science 2016; 352: 10.1126/science.aaf4822

Eitan Israeli

Capsule

Antibiotics: a double-edged sword

Patients undergoing allogeneic hematopoietic stem cell transplantation often receive antibiotics for infections, which unfortunately also kill intestinal bacteria. These symbiotic bacteria in the gut do not normally cause disease and are thought to suppress inflammation. Shono and colleagues examined the records of 857 transplant patients and found that certain antibiotics were linked to the development of graft-versus-host disease (GVHD), which can cause severe intestinal inflammation. In a mouse model these antibiotics appeared to select for bacteria that consume intestinal mucus, damaging this important protective layer and exacerbating GVHD.

Sci Transl Med 2016; 8: 339a71

Eitan Israeli

Capsule

Another pathway to cancer resistance

Therapies targeting the tumor microenvironment show promise for treating cancer. For example, antibodies targeting colony-stimulating factor-1 receptor (CSF-1R) inhibit protumorigenic macrophages and regress tumors in mouse models of glioblastoma multiforme (GBM), a deadly form of brain cancer. Quail et al. found that although CSR-1R blockade prolonged survival in mouse models of GBM, more than 50% of tumors eventually recurred. Recurrence was correlated with elevated PI3-K activity in tumors, driven by macrophage-secreted IGF-1. Blocking PI3-K and IGF-1 signaling in rebounding tumors prolonged survival. Thus, tumors can acquire resistance to therapy through intrinsic changes and through changes in their microenvironment.

Science 2016; 352, p. 10.1126/science.aad3018

Eitan Israeli

"We all have our time machines. Some take us back, they're called memories. Some take us forward, they're called dreams"

Jeremy Irons (1948), British stage, film and TV actor. After receiving classical training at the Bristol Old Vic Theatre School, Irons began his acting career on stage in 1969 and has since appeared in many West End theater productions, movies and BBC television series

Capsule

A prostaglandin barrier to inflammation

Blood-borne bacterial infections and severe trauma can send the immune system into overdrive, causing it to pump out inflammatory mediators, sometimes at lethal doses. Duffin et al. report on a role for prostaglandins in keeping systemic inflammation in check. They found that systemic inflammation correlates with decreased production of the prostaglandin E2 (PGE2). Blocking PGE2 signaling in mice led to severe inflammation associated with the translocation of gut bacteria. PGE2 acts on innate lymphoid cells, which produce interleukin-22, a secreted protein that helps promote intestinal integrity.

Science 2016; 351: 1333

Eitan Israeli

Capsule

Dissolving away cholesterol

Atherosclerosis-driven cardiovascular disease is one of the most common causes of death worldwide. Existing therapies do not treat all patients effectively. Cyclodextrin, a common FDA-approved substance, is already used as a solubilizing agent to improve drug delivery. Zimmer and colleagues found that cyclodextrin solubilizes cholesterol, removes it from plaques, dissolves cholesterol crystals, and successfully treated atherosclerosis in a mouse model. Because cyclodextrin is already known to be safe in humans, this drug is now a candidate for testing in patients with atherosclerosis.

Sci Trans Med 2016; 8: 333ra50

Eitan Israeli

Capsule

An antibody to block viral fusion

A small fraction of HIV-1-infected individuals develop broad and potent antibodies that bind the HIV-1 envelope protein (Env). These antibodies recognize a limited set of conserved epitopes on Env, such as Env's host receptor-binding site. Kong and fellow-scientists now report a neutralizing antibody isolated from an HIV-1-infected individual that binds to the fusion peptide of Env. This is unexpected because viruses often try to mask such key components of their cell entry machinery from antibody attack. Crystal structures of the antibody bound to the fusion peptide and to Env itself define the epitope, provide insight into the specific mechanism of antibody binding, and may inform HIV-1 vaccine design.

Science 2016; 352: 828

Eitan Israeli

Capsule

Linking neurodegeneraton and immune cells

The expansion of a repetitive DNA sequence in the *C9orf72* gene is the major genetic cause of amyotrophic lateral sclerosis and frontotemporal dementia. Although the expansion decreases *C9orf72* expression, most research has focused on the toxic RNA and protein products it creates in neurons. O'Rourke et al. found that C9orf72 unexpectedly plays a key role in innate immune cells. Loss of *C9orf72* in mice led to macrophage and microglial dysfunction and age-related neuroinflammation. This raises the possibility of a "dual-effect" disease mechanism, in which toxic byproducts in neurons are combined with microglial dysfunction from decreased *C9orf72* expression, together promoting neurodegeneration.

Science 2016; 351: 1324

Eitan Israeli

Capsule

High fat diet enhances stemness and tumorigenicity of intestinal progenitors

Little is known about how pro-obesity diets regulate tissue stem and progenitor cell function. Beyaz et al. show that high-fat diet (HFD)-induced obesity augments the numbers and function of *Lgr5* +intestinal stem cells of the mammalian intestine. Mechanistically, a HFD induces a robust peroxisome proliferator-activated receptor delta (PPAR-δ) signature in intestinal stem cells and progenitor cells (non-intestinal stem cells), and pharmacological activation of PPAR-δ recapitulates the effects of a HFD on these cells. Like a HFD, ex vivo treatment of intestinal organoid cultures with fatty acid constituents of the HFD enhances the self-renewal potential of these organoid bodies in a PPAR-δ-dependent manner. Notably, HFD- and agonist-activated PPAR-δ signaling endow organoid-initiating capacity to progenitors, and enforced PPAR-δ signaling permits these progenitors to form in vivo tumors after loss of the tumor suppressor *Apc*. These findings highlight how diet-modulated PPAR-δ activation alters not only the function of intestinal stem and progenitor cells, but also their capacity to initiate tumors.

Nature 2016; 531: 53

Eitan Israeli

"I'm willing to admit that I may not always be right, but I am never wrong"

Samuel Goldwyn (1879-1974), Jewish Polish American film producer, most known for being the founding contributor and executive of several motion picture studios in Hollywood

Capsule

Lens regeneration using endogenous stem cells with gain of visual function

The repair and regeneration of tissues using endogenous stem cells represents an ultimate goal in regenerative medicine. Currently, the only treatment for cataracts, the leading cause of blindness worldwide, is to extract the cataractous lens and implant an artificial intraocular lens. However, this procedure poses notable risks of complications. Lin et al. isolated lens epithelial stem/progenitor cells (LECs) in mammals and showed that *Pax6* and *Bmi1* are required for LEC renewal. The authors designed a surgical method of cataract removal that preserves endogenous LECs and achieves functional lens regeneration in rabbits and macaques, as well as in human infants with cataracts. This method differs conceptually from current practice, as it preserves endogenous LECs and their natural environment maximally, and regenerates lenses with visual function. This approach demonstrates a novel treatment strategy for cataracts and provides a new paradigm for tissue regeneration using endogenous stem cells.

Nature 2016; 531: 323

Eitan Israeli

"Would the boy you were be proud of the man you are?"

Laurence J. Peter (1919-1990), Canadian educator and "hierarchiologist" best known for the formulation of the Peter Principle, whereby "In a hierarchy every employee tends to rise to his level of incompetence." The Peter Principle became one of the most profound principles of management from the University of Southern California

Capsule

Antibodies block Ebola virus entry

The recent Ebola virus outbreak in West Africa illustrates the need for both an effective vaccine and therapies to treat infected individuals. Corti et al. isolated two monoclonal antibodies from a survivor of the 1995 Kikwit outbreak and demonstrated their therapeutic efficacy in Ebola virus-infected macaques. In fact, one antibody protected macaques when it was given up to 5 days after infection. Misasi et al. solved the crystal structures of fragments of the two antibodies bound to the Ebola virus glycoprotein (GP), which mediates viral cell entry. The two antibodies targeted different regions of GP, but in both cases blocked steps required for viral entry.

Science 2016; 351: 1339 & 1343

Eitan Israeli

Capsule

Adjuvant dependent innate and adaptive immune signatures of risk of SIV_{mac251} acquisition

A recombinant vaccine containing Aventis Pasteur's canarypox vector (ALVAC)-HIV and gp120 alum decreased the risk of HIV acquisition in the RV144 vaccine trial. The substitution of alum with the more immunogenic MF59 adjuvant is under consideration for the next efficacy human trial. Vaccari et al. found that an ALVAC-simian immunodeficiency virus (SIV) and gp120 alum (ALVAC-SIV + gp120) equivalent vaccine, but not an ALVAC-SIV + gp120 MF59 vaccine, was efficacious in delaying the onset of SIV_{mac251} in rhesus macaques, despite the higher immunogenicity of the latter adjuvant. Vaccine efficacy was associated with alum-induced, but not with MF59-induced, envelope (Env)-dependent mucosal innate lymphoid cells (ILCs) that produce interleukin (IL)-17, as well as with mucosal IgG to the gp120 variable region 2 (V2) and the expression of 12 genes, 10 of which are part of the RAS pathway. The association between RAS activation and vaccine efficacy was also observed in an independent efficacious SIV-vaccine approach. Whether RAS activation, mucosal ILCs and antibodies to V2 are also important hallmarks of HIV-vaccine efficacy in humans will require further studies.

Nature Med 2016; 22: 762

Eitan Israeli

"America has been called a melting pot, but it seems better to call it a mosaic, for in it each nation, people, or race which has come to its shores has been privileged to keep its individuality, contributing at the same time its share to the unified pattern of a new nation

King Baudouin of Belgium (1930-1993)