Capsule

Why rapamycin is a good immunosuppressant

Recipients of organ transplants receive the immunosuppressant rapamycin to prevent rejection. Rapamycin targets mTORC1, a ubiquitous kinase-containing complex that promotes cell growth and proliferation. So and co-authors discovered why lymphocytes are particularly sensitive to rapamycin. Lymphocytes used one mTORC1 effector to mediate both cell growth and proliferation, unlike other cell types in which these processes are mediated by two different effectors. Phosphorylation of this effector by mTORC1 triggers cell growth and proliferation, and was more sensitive to disruption by rapamycin in lymphocytes.

Sci Signal 2016; 9: ra57

Eitan Israel

Capsule

At risk by association

Soon genetics may routinely tell clinicians whether certain drugs put patients at risk of developing heart disease or cancer. Scott et al. inspected six genes that encode targets of various drugs for type 2 diabetes or obesity to identify genetic variations linked to metabolic traits such as fasting glucose levels. Using two cohorts totaling more than 50,000 individuals, the authors landed on a variant in GLPR1 – which encodes glucagon-like peptide-1 receptor, a target for certain drugs frequently used in the clinic – and compared it against disease outcomes. In more than 200,000 patients (some with heart disease, some controls) the GLPR1 variant proved protective against coronary artery disease and was not associated with cancers or neurological diseases.

Sci Transl Med 2016; 8: 341ra76

Eitan Israeli

Capsule

Making cardiac cells from fibroblasts

Reprogramming non-cardiac cells into functional cardiomyocytes without any genetic manipulation could open up new avenues for cardiac regenerative therapies. Cao and team identified a combination of nine small molecules that could epigenetically activate human fibroblasts, efficiently reprogramming them into chemically induced cardiomyocytes (ciCMs). The ciCMs contracted uniformly and resembled human cardiomyocytes. This method may be adapted for reprogramming multiple cell types and have important implications in regenerative medicine.

Science 2016; 352: 1216

Eitan Israeli

Capsule

Immune activation in context

Dendritic cells (DCs) initiate protective immunity upon binding molecules derived from microbes or released from dying cells. Zanoni et al. examined how microbial and endogenous signals interact to shape the course of the ensuing immune response. They found that oxPAPC, an oxidized phospholipid released from dying cells, binds to a protein called caspase-11 in DCs, activating an inflammatory program in these cells. Whereas caspase-11 binding to oxPAPC and bacterial lipopolysaccharide causes DCs to produce the cytokine interleukin-1 (IL-1) and undergo cell death, binding to oxPAPC alone triggers DCs to secrete IL-1 and induce strong adaptive immunity. Thus, context-dependent signals can shape the ensuing immune response.

Science 2016; 352: 1232

Eitan Israeli

Capsule

An essential role for the IL-2 receptor in T_{reg} cell function

Regulatory T cells (T_{reg} cells), which have abundant expression of the interleukin 2 receptor (IL-2R), are reliant on IL-2 produced by activated T cells. This feature indicates a key role for a simple network based on the consumption of IL-2 by T_{reg} cells in their suppressor function. However, congenital deficiency in IL-2R results in reduced expression of the T_{reg} cell lineage-specification factor Foxp3, which has confounded experimental efforts to understand the role of IL-2R expression and signaling in the suppressor function of T_{reg} cells. Using genetic gain- and loss-of-function approaches, Chinen et al. found that capture of IL-2 was dispensable for the control of $CD4^+$ T cells but was important for limiting the activation of $CD8^+$ T cells, and that IL-2R-dependent activation of the transcription factor STAT5 had an essential role in the suppressor function of T_{reg} cells separable from signaling via the T cell antigen receptor.

Nature Immunol 2016; 17: 1322

Eitan Israeli

"Life is like a game of cards. The hand you are dealt is determinism; the way you play it is free will"

Jawaharlal Nehru (1889-1964), first Prime Minister of India and a central figure in Indian politics before and after independence. Under the tutelage of Mahatma Gandhi, he is considered the architect of the modern Indian nation-state: a sovereign, socialist, secular, and democratic republic

Capsule

Disaggregating proteins ameliorate disease

A variety of debilitating neurodegenerative diseases are caused by the defective folding of particular proteins. A case in point is amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease), which can be caused by the misfolding of superoxide dismutase 1 (SOD1). The misfolded proteins aggregate in the cytosol of motor neurons, eventually causing their death, and thereby the progressive paralysation characteristic of the disease. Nagy et al. found that overexpression of an Hsp110 protein in motor neurons improved the survival of SOD1 mutant mouse models of ALS. Hsp110 proteins are part of a cytosolic protein disaggregation machinery. Thus, increasing the disaggregation capacity of the cytosol can help to alleviate the progression of a neurodegenerative disease.

Proc Natl Acad Sci USA 2016; 113: 5424

Eitan Israeli

Capsule

Engineering T cells to treat autoimmunity

Autoimmune diseases such as lupus and rheumatoid arthritis lack therapies that specifically target only the disease-causing cells. Inspired by the clinical success of using chimeric antigen receptor T cells to treat certain types of cancers, Ellebrecht et al. asked whether a similar approach might also work against antibody-driven autoimmune diseases. They engineered T cells to express chimeric receptors consisting of the disease-causing autoantigen desmoglein 3 fused to signaling domains that activate T cells. When given to diseased mice, the engineered T cells targeted and killed B cells that express antibodies targeting desmoglein 3, hinting that such a strategy may be an effective way to treat antibody-driven autoimmune diseases.

Science 2016; 353: 179

Eitan Israeli

"People who think they know everything are a great annoyance to those of us who do"

Isaac Asimov (1920-1992), American author, professor of biochemistry at Boston University, known for his works on science fiction and popular science

Capsule

CARD9 impacts colitis by altering gut microbiota metabolism of tryptophan into aryl hydrocarbon receptor ligands

Complex interactions between the host and the gut microbiota govern intestinal homeostasis but remain poorly understood. Lamas and co-authors reveal a relationship between gut microbiota and caspase recruitment domain family member 9 (*CARD9*), a susceptibility gene for inflammatory bowel disease (IBD) that functions in the immune response against microorganisms. CARD9 promotes recovery from colitis by promoting interleukin (IL)-22 production, and *Card9*$^{-/-}$ mice are more susceptible to colitis. The microbiota is altered in *Card9*$^{-/-}$ mice, and transfer of the microbiota from *Card9*$^{-/-}$ to wild-type, germ-free recipients increases their susceptibility to colitis. The microbiota from *Card9*$^{-/-}$ mice fails to metabolize tryptophan into metabolites that act as aryl hydrocarbon receptor (AHR) ligands. Intestinal inflammation is attenuated after inoculation of mice with three *Lactobacillus* strains capable of metabolizing tryptophan or by treatment with an AHR agonist. Reduced production of AHR ligands is also observed in the microbiota from individuals with IBD, particularly in those with *CARD9* risk alleles associated with IBD. These findings reveal that host genes affect the composition and function of the gut microbiota, altering the production of microbial metabolites and intestinal inflammation.

Nature Med 2016; 22: 598

Eitan Israeli

Capsule

Cistromic and genetic evidence that the vitamin D receptor mediates susceptibility to latitude-dependent autoimmune diseases

The vitamin D receptor (VDR) is a ligand-activated transcription factor that regulates gene expression in many cell types, including immune cells. It requires binding of 1,25 dihydroxy vitamin D_3 (1,25D3) for activation. Many autoimmune diseases show latitude-dependent prevalence and/or association with vitamin D deficiency, and vitamin D supplementation is commonly used in their clinical management. 1,25D3 is regulated by genes associated with the risk of autoimmune diseases and predominantly expressed in myeloid cells. Booth et al. determined the VDR cistrome in monocytes and monocyte-derived inflammatory (DC1) and tolerogenic dendritic cells (DC2). VDR motifs were highly over-represented in ChIP-Seq peaks in stimulated monocyte (40%), DC1 (21%) and DC2 (47%), P<E-100 for all. Of the nearly 11 000 VDR-binding peaks identified across the genome in DC1s, 1317 were shared with DC2s (91% of DC2 sites) and 1579 with monocytes (83% of monocyte sites). Latitude-dependent autoimmune disease risk polymorphisms were highly over-represented within 5 kb of the peaks. Several transcription factor recognition motifs were highly over-represented in the peaks, including those for the autoimmune risk gene, *BATF*. This evidence indicates that VDR regulates hundreds of myeloid cell genes and that the molecular pathways controlled by VDR in these cells are important in maintaining tolerance.

Genes Immunity 2016; 17: 213

Eitan Israeli

"In three words I can sum up everything I've learned about life: it goes on"

Robert Frost (1874-1963), American poet, highly regarded for his realistic depictions of rural life in New England in the early twentieth century, using them to examine complex social and philosophical themes. Frost was honored frequently during his lifetime, receiving four Pulitzer Prizes for Poetry

Capsule

In situ vaccine production and delivery

We are potentially facing a post-antibiotic world of human disease management, so the need for alternative approaches is growing critical. Li and team found value in a variation of a well-known theme in disease prevention: vaccination. They developed a hybrid antigen delivery vector, directed toward pneumococcal disease, based on a combination of biological and biomaterial components. The immune response in murine models was significantly enhanced over the response to standard vaccines. Protection from 11 *Streptococcus pneumoniae* strains was provided, without toxicity.

Sci Adv 2016; 10: 1126

Eitan Israeli

Capsule

Protection against malaria at 1 year and immune correlates following PfSPZ vaccination

An attenuated *Plasmodium falciparum* (Pf) sporozoite (SPZ) vaccine, PfSPZ vaccine, is highly protective against controlled human malaria infection (CHMI) 3 weeks after immunization, but the durability of protection is unknown. Ishizuka et al. assessed how vaccine dosage, regimen, and route of administration affected durable protection in malaria-naive adults. After four intravenous immunizations with 2.7×10^5 PfSPZ, 6/11 (55%) vaccinated subjects remained without parasitemia following CHMI 21 weeks after immunization. Five non-parasitemic subjects from this dosage group underwent repeat CHMI at 59 weeks, and none developed parasitemia. Although Pf-specific serum antibody levels correlated with protection up to 21–25 weeks after immunization, antibody levels waned substantially by 59 weeks. Pf-specific T cell responses also declined in blood by 59 weeks. To determine whether T cell responses in blood reflected responses in liver, the authors vaccinated non-human primates with PfSPZ vaccine. Pf-specific interferon-γ-producing CD8 T cells were present at ~100-fold higher frequencies in liver than in blood. The findings suggest that PfSPZ vaccine conferred durable protection to malaria through long-lived tissue-resident T cells and that administration of higher doses may further enhance protection.

Nature Med 2016; 22: 614

Eitan Israeli

Capsule

Prevention of tumor formation by latent gamma herpes virus infection

Recent reports suggested that chronic herpes virus infection, as a constituent of the so-called virome, may not only exert harmful effects but may also be beneficial to the host, for example mediating increased resistance to secondary infections or to tumors. To further challenge this concept, specifically regarding increased resistance to tumors, Raffegerst et al. infected chimeric HLA-DR4-H2-E (DR4) mice, a mouse strain which spontaneously develops hematological tumors, with the rodent herpes virus murine gamma herpes virus 68 (MHV-68). Using this model, the authors observed that infection with wildtype MHV-68 completely prevented tumor formation. This happened, however, at the cost of hyposplenism. In contrast to wildtype infection, infection with a latency-deficient mutant of MHV-68 neither prevented tumor formation nor induced hyposplenism. The underlying mechanisms are not known but might be related to an infection-mediated priming of the immune response, resulting in the suppression of a tumor promoting endogenous retrovirus. Thus, under certain circumstances, chronic herpes virus infection may prevent the development of tumors.

PLoS One 2015; 10 (12): e0145678

Eitan Israeli

"I am so clever that sometimes I don't understand a single word of what I am saying"

Oscar Wilde (1854-1900), Irish playwright, novelist, essayist, and poet who became one of London's most popular playwrights in the early 1890s. He is remembered for his epigrams, his novels, his plays, as well as the circumstances of his imprisonment and early death

Capsule

Location matters for immunosuppression

In the gut, food antigens and resident microbes can trigger unwanted immune responses. Immunosuppressive cell types in the gut, such as regulatory T cells (T_{regs}) and intraepithelial T lymphocytes (IELs), help to keep these responses at bay. Sujino et al. report that the specific anatomical location within the gut shapes the properties of the suppressive T cell populations that reside there. Using mice, they found that T_{regs} primarily reside in the lamina propria. T_{regs} migrate to the intestinal epithelium, where they convert to IELs in a process that depends on the microbiota and the loss of a specific transcription factor. T_{regs} and IELs also play distinct but complementary roles in suppressing intestinal inflammation.

Science 2016; 352: 158

Eitan Israeli

Capsule

Impact of pre-adapted HIV transmission

Human leukocyte antigen class I (HLA)-restricted $CD8^+$ T lymphocyte (CTL) responses are crucial to HIV-1 control. Although HIV can evade these responses, the longer-term impact of viral escape mutants remains unclear, as these variants can also reduce intrinsic viral fitness. To address this, Carlson et al. developed a metric to determine the degree of HIV adaptation to an HLA profile. The authors demonstrated that transmission of viruses that are pre-adapted to the HLA molecules expressed in the recipient is associated with impaired immunogenicity, elevated viral load and accelerated $CD4^+$ T cell decline. Furthermore, the extent of pre-adaptation among circulating viruses explains much of the variation in outcomes attributed to the expression of certain HLA alleles. Thus, viral pre-adaptation exploits 'holes' in the immune response. Accounting for these holes may be key for vaccine strategies seeking to elicit functional responses from viral variants, and to HIV cure strategies that require broad CTL responses to achieve successful eradication of HIV reservoirs.

Nature Med 2016; 22: 606

Eitan Israeli

Capsule

Evidence of innate lymphoid cell redundancy in humans

Innate lymphoid cells (ILCs) have potent immunological functions in experimental conditions in mice, but their contributions to immunity in natural conditions in humans have remained unclear. Vely et al. investigated the presence of ILCs in a cohort of patients with severe combined immunodeficiency (SCID). All ILC subsets were absent in patients with SCID who had mutation of the gene encoding the common γ-chain cytokine receptor subunit IL-2Rγ or the gene encoding the tyrosine kinase JAK3. T cell reconstitution was observed in patients with SCID after hematopoietic stem cell transplantation (HSCT), but the patients still had considerably fewer ILCs in the absence of myeloablation than did healthy control subjects, with the exception of rare cases of reconstitution of the ILC1 subset of ILCs. Notably, the ILC deficiencies observed were not associated with any particular susceptibility to disease, with follow-up extending from 7 years to 39 years after HSCT. The authors report selective ILC deficiency in humans and show that ILCs might be dispensable in natural conditions, if T cells are present and B cell function is preserved.

Nature Immunol 2016; 17: 1291

Eitan Israeli

Capsule

A hat trick for differentiation therapy?

Most forms of acute myeloid leukemia (AML) are associated with a poor prognosis. One exception is acute promyelocytic leukemia, which is largely curable by two drugs, one originating from traditional Chinese medicine. Both drugs act by forcing leukemic precursor cells to differentiate into mature cell types that no longer divide. Given that all forms of AML are characterized by preleukemic myeloid cells whose differentiation is arrested, Sykes et al. performed an unbiased screen for compounds that induce myeloid differentiation. Unexpectedly, the most active compounds in mouse and human models were inhibitors of dihydroorotate dehydrogenase, an enzyme involved in pyrimidine biosynthesis. These inhibitors slowed AML development in mice and thus may merit further study as a therapy for the human disease.

Cell 2016; 167: 171

Eitan Israeli

Capsule

Priming for T cell memory in tissues

During infections, dendritic cells prime T cell immunity and drive a subset of T cells to become long-lived memory cells. Memory T cells come in two flavors: those that circulate and those that establish long-term residency in tissues (Trm). Iborra et al. investigated the priming requirements of each type of cell in mice. Direct antigen presentation by dendritic cells was sufficient for generating circulating memory CD8+ T cells. In contrast, CD8+ Trm cells require antigen cross-presentation by dendritic cells that express DNGR-1, a protein receptor that binds necrotic cells. Without either DNGR-1 or cross-presenting dendritic cells, mice form few Trm cells in response to viral infection.

Immunity 2016; 10.1016/j.immuni.2016.08.019

Eitan Israeli

"I can't understand why people are frightened of new ideas. I'm frightened of the old ones"

John Cage (1912-1992), American composer, music theorist, philosopher and artist. A pioneer of indeterminacy in music, electroacoustic music, and non-standard use of musical instruments, Cage was one of the leading figures of the post-war avantgarde and is considered one of the most influential American composers of the 20th century. He was also instrumental in the development of modern dance, mostly through his association with choreographer Merce Cunningham, who was also Cage's romantic partner for most of their lives. Cage is perhaps best known for his 1952 composition 4'33', which is performed in the absence of deliberate sound; musicians who present the work do nothing aside from being present for the duration specified by the title. The content of the composition is not "four minutes and 33 seconds of silence," as is often assumed, but rather the sounds of the environment heard by the audience during performance

Capsule

Engineering T cells to treat autoimmunity

Autoimmune diseases such as lupus and rheumatoid arthritis lack therapies that specifically target only the disease-causing cells. Inspired by the clinical success of using chimeric antigen receptor T cells to treat certain types of cancers, Ellebrecht et al. asked whether a similar approach might also work against antibody-driven autoimmune diseases. They engineered T cells to express chimeric receptors consisting of the disease-causing autoantigen desmoglein 3 fused to signaling domains that activate T cells. When given to diseased mice, the engineered T cells targeted and killed B cells that express antibodies targeting desmoglein 3, hinting that such a strategy may be an effective way to treat antibody-driven autoimmune diseases.

Science 2016; 353: 179

Eitan Israeli

Capsule

Nanoparticles restore tolerance

Autoimmune diseases, such as type 1 diabetes, are caused by immune cells attacking healthy cells. One way to treat type 1 diabetes is to activate T regulatory (T_{reg}) cells to suppress inflammatory T cell activity and restore tolerance, so that the inflammatory T cells stop destroying pancreatic β cells. Yeste et al. used gold nanoparticles to induce tolerance in a mouse model of type 1 diabetes. The mice had more T_{reg} cells and less severe disease symptoms when given nanoparticles coated with proteins that induced tolerance. Nanoparticle-based therapies may be useful in restoring tolerance in other autoimmune diseases as well.

Sci Signal 2016; 9: ra61

Eitan Israeli

Capsule

Long interspersed nuclear element-1 retroelements are expressed in patients with systemic autoimmune disease and induce type I interferon

Increased type I interferon (IFN-I) and a broad signature of IFN-I-induced gene transcripts are observed in patients with SLE and other systemic autoimmune diseases. To identify disease-relevant triggers of the IFN-I pathway Mavragani et al. investigated whether endogenous virus-like genomic repeat elements, normally silent, might be expressed in patients with systemic autoimmune disease, activate an innate immune response and induce IFN-I. Expression of IFN-I and long interspersed nuclear element-1 (LINE-1; L1) was studied in kidney tissue from lupus patients and minor salivary gland (MSG) tissue from patients with primary Sjogren's syndrome (SS) by polymerase chain reaction, western blot and immunohistochemistry. Induction of IFN-I by L1 was investigated by transfection of plasmacytoid dendritic cells (pDCs) or monocytes with an L1-encoding plasmid or L1 RNA. Involvement of innate immune pathways and altered L1 methylation were assessed. L1 mRNA transcripts were increased in lupus nephritis kidneys and in MSG from SS patients and correlated with IFN-I expression and L1 DNA demethylation. L1 open reading frame 1/p40 protein and IFNβ were expressed in MSG ductal epithelial cells and in lupus kidneys, and IFNα was detected in infiltrating pDCs. Transfection of pDCs or monocytes with L1-encoding DNA or RNA induced IFN-I. Inhibition of TLR7/8 reduced L1 induction of IFNα in pDCs and an inhibitor of IKKε/TBK1 abrogated induction of IFN-I by L1 RNA in monocytes. The authors conclude that L1 genomic repeat elements represent endogenous nucleic acid triggers of the IFN-I pathway in SLE and SS and may contribute to initiation or amplification of autoimmune disease.

Arthritis Rheum 2016; doi: 10.1002/art.39795

Eitan Israeli

Capsule

Mounting the intestinal barricades

Gut microbiota are important for health and well-being, but they need to be kept under control and prevented from doing any harm. Birchenough and colleagues investigated the microbial molecules that trigger protective mucus secretion from a class of goblet cells in the colon. Once the molecules are detected, an alarm signal is transmitted from these cells via innate immune signal mediators and inflammasome components to adjacent cells, generating more mucus and repelling the invaders. Subsequently, the sentinel goblet cells are expelled from the epithelium and their remains may also add to the protective barricade.

Science 2016; 352: 1535

Eitan Israeli

Capsule

Mini-guts for testing drug therapy for cystic fibrosis

Cystic fibrosis is caused by mutations in the *CFTR* gene, which reduce the function of the CFTR protein. New drugs for treating cystic fibrosis modulate CFTR protein function, but drug efficacy is dependent on which CFTR mutation a patient carries. Dekkers et al. show that the efficacy of these drugs can be individually assessed using epithelial cells cultured as mini-guts from rectal biopsies from cystic fibrosis patients. The drug response observed in these rectal organoids can help predict which patients may be potential responders to the drug. This preclinical test may help to quickly identify responders to CFTR-modulating drug therapy, even when patients carry very rare CFTR mutations.

Sci Transl Med 2016; 8: 344ra84

Eitan Israeli

Capsule

Metabolic support for T cell functions

For immunological T cells, responding to infections is energetically demanding. T cells rewire their metabolism so that they rely more heavily on aerobic glycolysis. This helps them to support important effector functions such as secreting the cytokine interferon γ (IFNγ). Peng et al. now provide insight into how aerobic glycolysis promotes T cell effector function. Activated T cells express the aerobic glycolysis-supporting enzyme lactate dehydrogenase A (LDHA), allowing these cells to maintain high amounts of acetyl-coenzyme A, which in turn promotes histone acetylation and transcription of cytokines such as IFNγ. Engineered mice whose T cells lacked LDHA were protected from IFNγ-dependent pathologies that often characterize autoinflammatory diseases.

Science 2016; 354: 481

Eitan Israeli

Capsule

Gut microbiota and undernutrition

Poor nutrition during the early years of life can have severe consequences for subsequent skeletal, immunological, and intellectual development. Blanton et al. reviewed the evidence showing that undernutrition is not caused by food insecurity alone. Other factors range from the length of the breastfeeding period and the availability of milk oligosaccharides, enteropathogen exposure, and enteric dysfunction marked by villus atrophy and loss of gut barrier function. Unfortunately, nutritional restoration with or without antibiotic treatment may not be effective in the longer term. Differences in the succession of microbial establishment and maturity can explain much of family discordances in nutritional status. The evidence indicates that microbiota-directed therapeutics could be a promising route to nutritional restoration in these children.

Science 2016; 352: 1533

Eitan Israeli

Capsule

Clues to cancer from an identity change

The prostate and seminal vesicle have closely related developmental histories and both are regulated by the same androgenic hormones. A better understanding of the molecular mechanisms controlling the development of the two tissues could help explain why cancer arises frequently in the prostate but only rarely in seminal vesicles. Working with cell and mouse models, Dutta et al. showed that forced expression of a single gene, the homeobox gene *NKX3.1*, causes seminal vesicle epithelium to differentiate into prostate. *NKX3.1* regulates the expression of a gene program associated with prostate differentiation by interacting with the G9a histone methyltransferase. Disruption of this regulatory network probably contributes to prostate cancer development.

Science 2016; 352: 157

Eitan Israeli

"In the kingdom of the blind, the one-eyed man is king"

Desiderius Erasmus (1466-1536), Dutch Renaissance humanist, Catholic priest, social critic, teacher, and theologian

"Friendship... is born at the moment when one man says to another 'What! You too? I thought that no one but myself...' "

C.S. Lewis (1898-1963), British novelist, poet, academic, medievalist, literary critic, essayist, lay theologian, and Christian apologist. He held academic positions at both Oxford and Cambridge but is best known for his fictional work, especially *The Chronicles of Narnia*