Capsule

Immunotherapy – the forest and the trees

The clinical success of cancer immunotherapy has been both gratifying and perplexing to immunologists. One unsolved mystery is why fewer than 20% of cancer patients respond to this treatment. Spitzer et al. hypothesized that immune cells influencing the efficacy of immunotherapy reside outside the tumor microenvironment, the focus of most previous research. They used mass cytometry to assess system-wide immune responses that contribute to antitumor immunity in mice treated with immunotherapy. They found that CD4 T cells in peripheral tissues continued to proliferate after tumor rejection and were required for protection against new tumors. These results raise the possibility that therapies exploiting the antitumor activity of CD4 T cells may benefit cancer patients who do not respond to existing immunotherapies.

Cell 2017; 168: 487

Eitan Israeli

Capsule

The search for cancer cell vulnerabilities

Efficient screening of gene essentiality in mammalian cells, enabled by clustered regularly interspaced short palindromic repeats (CRISPR)-mediated gene editing, offers the opportunity to search for genes that are particularly required for proliferation and survival of tumor cells. Wang et al. used such screens to search for genes that are essential for growth in cancer cells driven by RAS mutations commonly found in human cancers. Such screens can help reveal functionally important interactions. The authors identified Phosphatidylinositol-3,4,5-Trisphosphate Dependent Rac Exchange Factor 1 (PREX1) as a key activator of MAP kinase signaling in the studied cancer cells. PREX is a guanine nucleotide exchange factor for the small guanosine triphosphatase Rac1, best known for its roles in controlling cell motility. The strategy holds promise for the development of cancer therapies directed at specific vulnerabilities of cancer cells.

Cell 2017; 10. 1016/ j.cell. 2017. 01.013

Eitan Israeli

Capsule

Rare and low-frequency coding variants alter human adult height

Height is a highly heritable, classic polygenic trait with approximately 700 common associated variants identified through genome-wide association studies so far. Marouli et al. reported 83 height-associated coding variants with lower minor-allele frequencies, in the range of 0.1 (4.8%) with effects of up to 2 cm per allele (such as those in *IHH*, *STC2*, *AR* and *CRISPLD2*), 10 times greater than the average effect of common variants. In functional follow-up studies, rare height-increasing alleles of *STC2* (giving an increase of 1–2 cm per allele) compromised proteolytic inhibition of PAPP-A and increased cleavage of IGFBP-4 in vitro, resulting in higher bioavailability of insulin-like growth factors. These 83 height-associated variants overlap genes that are mutated in monogenic growth disorders and highlight new biological candidates (such as *ADAMTS3*, *IL11RA* and *NOX4*) and pathways (such as proteoglycan and glycosaminoglycan synthesis) involved with growth. These results demonstrate that sufficiently large sample sizes can uncover rare and low-frequency variants of moderate-to-large effect associated with polygenic human phenotypes, and that these variants implicate relevant genes and pathways.

Nature 2017; 542: 186

Eitan Israeli

Capsule

The parasite of my parasite is my friend?

Virulence factors of pathogenic bacteria can be swapped by means of bacterial viruses called phages. In turn, the pathogenic bacteria are under attack by the host immune responses. Diard et al. discovered that SopEϕ, a phage parasite of pathogenic *Salmonella* species, is encouraged to spread between bacteria by the mouse host's inflammatory responses. Conversely, mucosal vaccination against *Salmonella* reduced inflammatory responses and curbed the transfer of SopEϕ to naïve bacteria.

Science 2017; 355: 1211

Eitan Israeli

Capsule

Hair follicles: secret to preventing scars?

Although some animals easily regenerate limbs and heal broken flesh, mammals are generally not so gifted. Wounding can leave scars, which are characterized by a lack of hair follicles and cutaneous fat. Plikus and team showed that hair follicles in both mice and humans can convert myofibroblasts, the predominant dermal cell in a wound, into adipocytes. The hair follicles activated the bone morphogenetic protein (BMP) signaling pathway and adipocyte transcription factors in the myofibroblast. Thus, it may be possible to reduce scar formation after wounding by adding BMP.

Science 2017; 355: 748

Eitan Israeli

Capsule

A target for intracranial aneurysms

Surgery is the only therapeutic option currently available for intracranial aneurysms. Aoki et al. delineated a self-amplifying signaling pathway in macrophages that could be pharmacologically targeted to limit the inflammation that initiates intracranial aneurysms and causes them to enlarge. Stimulation of EP2 (prostaglandin E receptor subtype 2) in macrophages increased the levels of COX-2, the enzyme that synthesizes the ligand for EP2, and MCP-1, an attractant for macrophages. Administering an EP2 antagonist to rats prevented the formation and progression of intracranial aneurysms.

Sci Signal 2017; 10: eaah6037

Eitan Israeli

Capsule

Being selective in fighting infection

Antibiotic-resistant bacterial strains are increasingly found in healthy people who show no symptoms. As a result, they are more vulnerable to invasive infections that can be lethal. In a perspective, Tacconelli et al. argued that existing, mostly broad-spectrum antibiotics, are not sufficient for countering this threat and that a new strategy is needed to control the spread of these strains. They call for the development of drugs that selectively target specific pathogens in the human gut while leaving other bacteria unharmed. Together with improved surveillance and reduced use of antibiotics, such selective decolonization agents could help halt the rise in antibiotic-resistant infections.

Science 2017; 355: 689

Eitan Israeli

Capsule

A radical idea for blood pressure control

Hypertension is common, especially in older adults, and it contributes to a number of other cardiovascular disorders. Although a variety of therapeutic interventions are available for this condition, none of them are specific or long-lasting, and they can all cause side effects, which decrease adherence to treatment. Hilgers et al. found that increased expression of thioredoxin, a protein that scavenges free radicals and restores proteins damaged by oxidation, reduced hypertension in mice. Injection of recombinant human thioredoxin also reduced hypertension in mouse models, and its protective effects lasted for weeks, suggesting that it may be possible to adapt this approach for long-term treatment of human patients.

Sci Transl Med 2017; 9: eaaf6094

Eitan Israeli

Capsule

Flexible control of T cell activation

Compared with effector T cells, which have previously encountered antigen, naïve T cells require a stronger stimulus to become activated, which prevents spurious activation. Thauland et al. showed that naïve cells were stiffer than effector cells and formed smaller immune synapses with antigen-presenting cells. The decreased flexibility of the naïve cells depended on the decreased activation of cofilin, which leads to the formation of a stiffer actin cytoskeleton. Thus, pharmacological modulation of T cell stiffness could change the threshold for activation.

Sci Signal 2017; 10: eaah3737

Eitan Israeli

Capsule

Blockade to pathological remodeling of infarcted heart tissue using a porcupine antagonist

The secreted Wnt signaling molecules are essential to the coordination of cell-fate decision making in multi-cellular organisms. In adult animals, the secreted Wnt proteins are critical for tissue regeneration and frequently contribute to cancer. Small molecules that disable the Wnt acyltransferase Porcupine (Porcn) are candidate anticancer agents in clinical testing. Moon et al. have systematically assessed the effects of the Porcn inhibitor (WNT-974) on the regeneration of several tissue types to identify potentially unwanted chemical effects that could limit the therapeutic utility of such agents. An unanticipated observation from these studies is pro-regenerative responses in heart muscle induced by systemic chemical suppression of Wnt signaling. Using in vitro cultures of several cell types found in the heart, the authors delineate the Wnt signaling apparatus supporting an anti-regenerative transcriptional program that includes a subunit of the nonfibrillar collagen VI. Similar to observations seen in animals exposed to WNT-974, deletion of the collagen VI subunit, *COL6A1*, has been shown to decrease aberrant remodeling and fibrosis in infarcted heart tissue. The authors demonstrated that WNT-974 can improve the recovery of heart function after left anterior descending coronary artery ligation by mitigating adverse remodeling of infarcted tissue. Injured heart tissue exposed to WNT-974 exhibits decreased scarring and reduced Col6 production. These findings support the development of Porcn inhibitors as anti-fibrotic agents that could be exploited to promote heart repair following injury.

PNAS 2017; early edition doi: 10.1073/pnas.1621346114

Eitan Israeli

Capsule

Maturation of the infant microbiome community structure and function across multiple body sites and in relation to mode of delivery

Human microbial communities are characterized by their taxonomic, metagenomic and metabolic diversity, which varies by distinct body sites and influences human physiology. However, when and how microbial communities within each body niche acquire unique taxonomical and functional signatures in early life remains underexplored. Chu and colleagues sought to determine the taxonomic composition and potential metabolic function of the neonatal and early infant microbiota across multiple body sites and assess the effect of the mode of delivery and its potential confounders or modifiers. A cohort of pregnant women in their early third trimester (n=81) were prospectively enrolled for longitudinal sampling through 6 weeks after delivery, and a second matched cross-sectional cohort (n=81) was additionally recruited for sampling once at the time of delivery. Samples across multiple body sites, including stool, oral gingiva, nares, skin and vagina were collected for each maternal–infant dyad. Whole-genome shotgun sequencing and sequencing analysis of the gene encoding the 16S rRNA were performed to interrogate the composition and function of the neonatal and maternal microbiota. The authors found that the neonatal microbiota and its associated functional pathways were relatively homogeneous across all body sites at delivery, with the notable exception of the neonatal meconium. However, by 6 weeks after delivery, the infant microbiota structure and function had substantially expanded and diversified, with the body site serving as the primary determinant of the composition of the bacterial community and its functional capacity. Although minor variations in the neonatal (immediately at birth) microbiota community structure were associated with the cesarean mode of delivery in some body sites (oral gingiva, nares and skin; $R^2 = 0.038$), this was not true for neonatal stool (meconium; Mann-Whitney $P > 0.05$), and there was no observable difference in community function regardless of delivery mode. For infants at 6 weeks of age, the microbiota structure and function had expanded and diversified with demonstrable body site specificity ($P < 0.001$, $R^2 = 0.189$) but without discernible differences in community structure or function between infants delivered vaginally or by cesarean surgery ($P = 0.057$, $R^2 = 0.007$). They conclude that within the first 6 weeks of life, the infant microbiota undergoes substantial reorganization, which is primarily driven by body site and not by mode of delivery.

Nature Med 2017; 23: 314

Eitan Israeli

Capsule

Preventing influenza by gluing up hemagglutinin

The morbidity and economic tolls of influenza virus are huge, regardless of its capacity to kill. Vaccines and therapies to control this persistent threat are limited. In structural studies, Kadam and Wilson showed how the broad-spectrum antiviral arbidol inactivates viral hemagglutinin (HA). HA is a surface glycoprotein that recognizes the host and mediates virus fusion and disgorgement of nucleic acids into the cell. Arbidol binds in hydrophobic cavities in the upper region of the HA stem, creating a network of interactions that makes the molecule rigid and prevents cell fusion. Resolving the molecular details of the arbidol-HA interactions is essential for the optimization and global deployment of this potential new influenza drug.

Proc Natl Acad Sci USA 2017; 114: 206

Eitan Israeli

Capsule

Gene therapy in a patient with sickle cell disease

Sickle cell disease results from a homozygous missense mutation in the β-globin gene that causes polymerization of hemoglobin S. Gene therapy for patients with this disorder is complicated by the complex cellular abnormalities and challenges in achieving effective, persistent inhibition of polymerization of hemoglobin S. Ribeil et al. describe the first patient treated with lentiviral vector-mediated addition of an antisickling β-globin gene into autologous hematopoietic stem cells. Adverse events were consistent with busulfan conditioning. Fifteen months after treatment, the level of therapeutic antisickling β-globin remained high (approximately 50% of β-like-globin chains) without recurrence of sickle crises and with correction of the biologic hallmarks of the disease

N Engl J Med 2017; 376:848

Eitan Israeli

Capsule

Defining B cell immunodominance to viruses

Immunodominance (ID) defines the hierarchical immune response to competing antigens in complex immunogens. Little is known regarding B cell and antibody ID despite its importance in immunity to viruses and other pathogens. Angeletti et al. showed that B cells and serum antibodies from inbred mice demonstrate a reproducible ID hierarchy to the five major antigenic sites in the influenza A virus hemagglutinin globular domain. The hierarchy changed as the immune response progressed, and it was dependent on antigen formulation and delivery. Passive antibody transfer and sequential infection experiments demonstrated 'original antigenic suppression', a phenomenon in which antibodies suppress memory responses to the priming antigenic site. This study provides a template for attaining deeper understanding of antibody ID to viruses and other complex immunogens.

Nature Immunol 2017; 18: 456

Eitan Israeli

Capsule

Faulty blood cells and heart disease

Recent studies have shown that elderly people's blood cells often harbor mutations in genes encoding certain epigenetic regulators. These mutations can lead to clonal expansion of the mutant blood cells, which increases the risk of blood cancers and cardiovascular disease. Fuster and co-authors generated a mouse model to investigate how one of these genes, *Tet2*, affects atherosclerosis development. They found that the disease progressed more rapidly in mice transplanted with *Tet2*-deficient bone marrow cells. This progression was due to increased secretion of interleukin-1β by *Tet2*-deficient macrophages in a process that depended on the action of inflammasomes.

Science 2017; 355: 842

Eitan Israeli

Capsule

Whole-genome landscape of pancreatic neuroendocrine tumors

The diagnosis of pancreatic neuroendocrine tumors (PanNETs) is increasing owing to more sensitive detection methods, and this increase is creating challenges for clinical management. Scarpa et al. performed whole-genome sequencing of 102 primary PanNETs and defined the genomic events that characterize their pathogenesis. They describe the mutational signatures they harbor, including a deficiency in G:C›T:A base excision repair due to inactivation of *MUTYH*, which encodes a DNA glycosylase. Clinically sporadic PanNETs contain a larger than expected proportion of germline mutations, including previously unreported mutations in the DNA repair genes *MUTYH*, *CHEK2* and *BRCA2*. Together with mutations in *MEN1* and *VHL*, these mutations occur in 17% of patients. Somatic mutations, including point mutations and gene fusions, were commonly found in genes involved in four main pathways: chromatin remodeling, DNA damage repair, activation of mTOR signaling (including previously undescribed *EWSR1* gene fusions), and telomere maintenance. In addition, our gene expression analyses identified a subgroup of tumors associated with hypoxia and HIF signaling.

Nature 2017; 543: 65

Eitan Israeli

Capsule

Targeting mitochondrial dysfunction can restore antiviral activity of exhausted HBV-specific CD8 T cells in chronic hepatitis B

Hepatitis B virus (HBV)-specific CD8 T cells are functionally exhausted in chronic hepatitis B infection, and this condition can be corrected only partially through the modulation of inhibitory pathways, which suggests that a more complex molecular interplay underlies T cell exhaustion. To gain broader insight into this process and identify additional targets for the restoration of T cell function, Fisicaro and associates compared the transcriptome profiles of HBV-specific CD8 T cells from patients with acute and chronic disease with those of HBV-specific CD8 T cells from patients able to resolve HBV infection spontaneously and influenza (FLU)-specific CD8 T cells from healthy participants. The results indicate that exhausted HBV-specific CD8 T cells are markedly impaired at multiple levels and show substantial downregulation of various cellular processes centered on extensive mitochondrial alterations. A notable improvement of mitochondrial and antiviral CD8 functions was elicited by mitochondrion-targeted antioxidants, which suggests a central role for reactive oxygen species (ROS) in T cell exhaustion. Thus, mitochondria represent promising targets for novel reconstitution therapies to treat chronic hepatitis B infection.

Nature Med 2017; 23: 327

Eitan Israeli

Capsule

Malaria parasites increase attractiveness of humans to mosquitoes

People infected by malaria become more attractive to the mosquito vectors of the disease, which facilitates the spread of malaria. Emami and colleagues found that red blood cells of the host respond to a parasite-derived isoprenoid called HMBPP by increasing the production of carbon dioxide and several monoterpenes and aldehydes. Mosquitoes fed HMBPP-spiked blood displayed malaria parasite-specific changes in gene transcription, which reinforced attractiveness for the mosquito. HMBPP also stimulates mosquito feeding and malaria parasite reproduction. Thus, the parasite manipulates its mammalian host to make it more attractive to the insect vectors and exploits the same molecule to amplify transmission.

Science 2017; 355: 1076

Eitan Israeli

Capsule

Natural killer (NK) cells in severe asthma: failed resolution

Anti-inflammatory corticosteroids are a first line of defense against many types of asthma, but individuals with severe asthma frequently do not respond to this therapy. Duvall and co-authors reported that this lack of response may be due in part to defects in natural killer (NK) cells, which are important mediators of inflammation resolution. NK cells from patients with severe asthma had impaired killing abilities, and corticosteroids inhibited the function of these cells further. The pro-resolving mediator LXA_4 preserved NK cell effector mechanisms. Thus, corticosteroids may be counterproductive for severe asthma, and specifically activating NK cells may provide an alternate therapeutic target.

Sci Immunol 2017; 2: eaam5446

Eitan Israeli

Capsule

A needle-free drug delivery device that works orally

No one likes to be on the receiving end of a needle, which can make routine childhood vaccinations especially problematic. Aran et al. developed a needle-free drug delivery device that works orally. The MucoJet™ device uses a simple chemical reaction to deliver a jet of vaccine, in this case ovalbumin, which penetrates the buccal mucosa when placed against the inside of a rabbit's cheek. The rabbits showed evidence of antibodies against ovalbumin in cheek tissue and ear vein blood samples 6 weeks after vaccination.

Sci Transl Med 2017; 9: eaaf6413

Eitan Israeli

Capsule

A traditional blood typing assay

Blood type matching is important for pregnancy, blood transfusion, and bone marrow transplantation. Zhang and colleagues developed a blood typing assay based on color changes assisted by a common pH indicator dye. Red blood cells (RBCs) and plasma were separated from small blood samples by using antibodies immobilized on paper test strips. The assays allowed forward grouping (detecting anti-A and/or anti-B antigens on RBCs) and reverse grouping (monitoring agglutination between RBCs and anti-A and/or anti-B antibodies in plasma) within 2 minutes. The test could also perform Rh and rare blood typing. This economical and robust assay will be useful in time- and resource-limited environments.

Sci Transl Med 2017; 9: eaaf9209

Eitan Israeli