Capsule

T cells stay fit during flu

Immunological memory is critical for keeping us from getting sick from many pathogens for a second time. For example, infection with chicken pox usually confers lifelong immunity. Tissue-resident memory CD8+ T cells are a key population that is responsible for this protection. By being poised at sites of pathogen entry, such as the lung, they can quickly kill virus-infected cells. But what protects these cells from virus-induced cell death so that they can carry out their duties? Wakim et al. revealed that during influenza infection in mice, the antiviral protein IFITM3 affords such protection to lung CD8+ memory T cells. IFITM3 is expressed specifically by resident CD8+ memory T cells in the lung, and cells deficient in IFITM3 did not survive well in response to secondary infection with influenza as compared to controls. Moreover, mice whose lung-resident CD8+ memory T cells were deficient in IFITM3 were more susceptible to infection with influenza. These results suggest that the selective expression of an antiviral factor in memory T cells allows the host to protect itself against subsequent viral infection.

Nat Immunol 2013; 14: 10.1038/ni.2525

Eitan Israeli

Capsule

Protecting pregnancies

Preeclampsia is a dangerous complication of up to 5% of human pregnancies. The only treatment is removal of the fetoplacental unit by surgery or delivery. To better understand this condition, Doridot et al. generated a preeclampsia mouse model by overexpressing the transcription factor STOX1, which has previously been associated with preeclampsia. When control females were mated with transgenic males, the pregnant female mice showed characteristic features of preeclampsia, such as hypertension and protein in the urine. In addition, an elevated plasma level of soluble anti-angiogenic factors was seen. When aspirin was administered early in the pregnancy via the drinking water, hypertension was prevented, as were elevated protein levels in the urine. An effect was also seen in the litter size: control mice had slightly larger litters than their transgenic counterparts; however, with administration of aspirin, litter size was normalized. These results indicate that providing low doses of aspirin to preeclamptic mice early in gestation prevents disease development and suggests a potential means of human therapeutic intervention for this life-threatening condition.

Hypertension 2013; 10.1161/HYPERTENSIONAHA.111.202994

Eitan Israeli

Capsule

Probing the microbial mix

In the past decade, it has become apparent that we are colonized by microbes that probably shape many of our most important physiological processes. Much of the work has taken a metagenomics approach – characterizing what microbes are there and what genes they express. Maurice et al. now go one step further; they are investigating how our microbial inhabitants respond to pharmacological perturbations. A combination of single-cell analysis by flow cytometry, DNA sequencing, and metatranscriptomics revealed that the bacteria within the human gut vary with respect to membrane integrity, polarization, and metabolic activity. Metabolic activity was enriched in Firmicutes, whereas Bacteroidetes were less metabolically active. Exposure to both antibiotics and host-targeted drugs resulted in alterations in the physiology, structure, and gene expression profile of the bacteria. An increase in genes associated with resistance, stress responses, and metabolism was observed after antibiotic treatment. These results represent an important step toward understanding on a broad scale how specific perturbations affect our microbial communities.

Cell 2013; 152: 39

Eitan Israeli

Capsule

Enhanced survival of lung tissue-resident memory CD8+ T cells during infection with influenza virus due to selective expression of IFITM3

Infection with influenza virus results in the deposition of anti-influenza CD8+ resident memory T cells (TRM cells) in the lung. As a consequence of their location in the lung mucosal tissue, these cells are exposed to cytopathic pathogens over the life of the organism and may themselves be susceptible to infection. Wakim et al. found that lung TRM cells selectively maintained expression of the interferon-induced transmembrane protein IFITM3, a protein that confers broad resistance to viral infection. Lung TRM cells that lacked IFITM3 expression were more susceptible to infection than were their normal counterparts and were selectively lost during a secondary bout of infection. Thus, lung TRM cells were programmed to retain IFITM3 expression, which facilitated their survival and protection from viral infection during subsequent exposures.

Nature Immunol 2013; 14: 238

Eitan Israeli

Capsule

FOXO3A directs a protective autophagy program in hematopoietic stem cells

Blood production is ensured by rare, self-renewing hematopoietic stem cells (HSCs). How HSCs accommodate the diverse cellular stresses associated with their life-long activity remains elusive. Warr and co-workers identified autophagy as an essential mechanism protecting HSCs from metabolic stress. They show that mouse HSCs, in contrast to their short-lived myeloid progeny, robustly induce autophagy after ex vivo cytokine withdrawal and in vivo calorie restriction. They demonstrate that FOXO3A is critical to maintain a gene expression program that poises HSCs for rapid induction of autophagy upon starvation. Notably, they found that old HSCs retain an intact FOXO3A-driven pro-autophagy gene program, and that ongoing autophagy is needed to mitigate an energy crisis and allow their survival. These results demonstrate that autophagy is essential for the life-long maintenance of the HSC compartment and for supporting an old, failing blood system.

Nature 2012; 494: 323

Eitan Israeli

Capsule

Stabilization of cooperative virulence by the expression of an avirulent phenotype

Pathogens often infect hosts through collective actions: they secrete growth-promoting compounds or virulence factors, or evoke host reactions that fuel the colonization of the host. Such behaviors are vulnerable to the rise of mutants that benefit from the collective action without contributing to it; how these behaviors can be evolutionarily stable is not well understood. Diard and colleagues address this question using the intestinal pathogen *Salmonella enterica* serovar *Typhimurium*, which manipulates its host to induce inflammation, and thereby outcompetes the commensal microbiota. Notably, the virulence factors needed for host manipulation are expressed in a bistable fashion, leading to a slow-growing subpopulation that expresses virulence genes, and a fast-growing subpopulation that is phenotypically avirulent. The authors show that the expression of the genetically identical but phenotypically avirulent subpopulation is essential for the evolutionary stability of virulence in this pathogen. Using a combination of mathematical modeling, experimental evolution and competition experiments they found that within-host evolution leads to the emergence of mutants that are genetically avirulent and fast-growing. These mutants are defectors that exploit inflammation without contributing to it. In infection experiments initiated with wild-type *S. typhimurium*, defectors increase only slowly in frequency. In a genetically modified *S. typhimurium* strain in which the phenotypically avirulent subpopulation is reduced in size, defectors rise more rapidly, inflammation ceases prematurely, and *S. typhimurium* is quickly cleared from the gut. Their results establish that host manipulation by *S. typhimurium* is a cooperative trait that is vulnerable to the rise of avirulent defectors. The expression of a phenotypically avirulent subpopulation that grows as fast as defectors slows down this process, and thereby promotes the evolutionary stability of virulence. This points to a key role of bistable virulence gene expression in stabilizing cooperative virulence and may lead the way to new approaches for controlling pathogens.

Nature 2013; 494: 353

Eitan Israeli

Capsule

Genetic clues to meningioma

Meningiomas are the most common primary brain tumors in adults. Located within the layer of tissue covering the brain, these tumors are usually slow growing and benign but can cause serious neurological complications. About half of these tumors have mutations in the *neurofibromin* 2 gene (*NF2*). To identify other genes that contribute to meningioma pathogenesis, Clark et al. performed genome sequence analysis on 300 tumors. Meningiomas fell into two general classes: benign tumors located at the skull base – which tend to harbor mutations in the *TRAF7*, *KLF4*, *AKT1*, and *SMO* genes – and higher grade tumors located in the cerebral and cerebellar hemispheres harbor mutations in *NF2*.

Science 2013; 339: 1077

Eitan Israeli

Capsule

Randomized dose-finding clinical trial of oncolytic immunotherapeutic vaccinia JX-594 in liver cancer

Oncolytic viruses and active immunotherapeutics have complementary mechanisms of action (MOA) that are both self-amplifying in tumors, yet the impact of dose on subject outcome is unclear. JX-594 (Pexa-Vec) is an oncolytic and immunotherapeutic vaccinia virus. To determine the optimal JX-594 dose in subjects with advanced hepatocellular carcinoma (HCC), Heo et al. conducted a randomized phase 2 dose-finding trial (n=30). Radiologists infused low or high dose JX-594 into liver tumors (days 1, 15 and 29); infusions resulted in acute detectable intravascular JX-594 genomes. Objective intrahepatic Modified Response Evaluation Criteria in Solid Tumors (mRECIST) (15%) and Choi (62%) response rates and intrahepatic disease control (50%) were equivalent in injected and distant non-injected tumors at both doses. JX-594 replication and granulocyte-macrophage colony-stimulating factor (GM-CSF) expression preceded the induction of anticancer immunity. In contrast to tumor response rate and immune endpoints, subject survival duration was significantly related to dose (median survival of 14.1 months compared to 6.7 months on the high and low dose, respectively; hazard ratio 0.39; $P = 0.020$). JX-594 demonstrated oncolytic and immunotherapy MOA, tumor responses and dose-related survival in individuals with HCC.

Nature Med 2013; 19: 329

Eitan Israeli

Capsule

High frequency oscillation in early acute respiratory distress syndrome

Previous trials suggesting that high frequency oscillatory ventilation (HFOV) reduced mortality among adults with the acute respiratory distress syndrome (ARDS) were limited by the use of outdated comparator ventilation strategies and small sample sizes. In a multicenter randomized controlled trial conducted at 39 intensive care units in five countries, Ferguson et al. randomly assigned adults with new-onset, moderate-to-severe ARDS to HFOV targeting lung recruitment or to a control ventilation strategy targeting lung recruitment with the use of low tidal volumes and high positive end-expiratory pressure. The primary outcome was the rate of in-hospital death from any cause. On the recommendation of the data monitoring committee, the trial was stopped after 548 of a planned 1200 patients had undergone randomization. The two study groups were well matched at baseline. The HFOV group underwent HFOV for a median of 3 days (interquartile range 2–8); in addition, 34 of 273 patients (12%) in the control group received HFOV for refractory hypoxemia. In-hospital mortality was 47% in the HFOV group, as compared with 35% in the control group (relative risk of death with HFOV 1.33; 95% confidence interval 1.09–1.64, $P = 0.005$). This finding was independent of baseline abnormalities in oxygenation or respiratory compliance. Patients in the HFOV group received higher doses of midazolam than did patients in the control group – 199 mg/day (interquartile range 100–382) vs. 141 mg/day (interquartile range 68–240), $P < 0.001$, and more patients in the HFOV group than in the control group received neuromuscular blockers (83% vs. 68%, $P < 0.001$). In addition, more patients in the HFOV group received vasoactive drugs (91% vs. 84%, $P = 0.01$) and received them for a longer period than did patients in the control group (5 days vs. 3 days, $P = 0.01$).

N Engl J Med 2013; 368: 795

Eitan Israeli

Capsule

Genetic variation in the serotonin receptor gene affects immune responses in rheumatoid arthritis

Many genetic variants associate with the risk of developing rheumatoid arthritis (RA); however, their functional roles are largely unknown. Snir and colleagues investigated whether the RA-associated serotonin receptor 2A (*HTR2A*) haplotype affects T cell and monocyte functions. Patients with established RA (n=379) were genotyped for two single-nucleotide polymorphisms in the *HTR2A* locus, rs6314 and rs1328674, to define presence of the risk haplotype for each individual. Patients with and without the RA-associated TC haplotype were selected and T cell and monocyte function was monitored following in vitro stimulations with staphylococcal enterotoxin B and lipopolysaccharide using multiparameter flow cytometry. Within the cohort, 44 patients were heterozygous for the TC haplotype (11.6%) while none were homozygous. Upon stimulation, T cells from TC-carrier patients produced more pro-inflammatory cytokines, namely tumor necrosis factor-alpha (TNFα), interleukin-17 and interferon gamma, and monocytes produced higher levels of TNFα compared with patients carrying the non-TC haplotype ($P < 0.05$ and 0.01, respectively). Such cytokine production could be inhibited in the presence of the selective 5-HT2 receptor agonist (2,5-dimethoxy-4-iodoamphetamine, DOI); interestingly, this effect was more pronounced in TC carriers. Our data demonstrate that association of RA with a distinct serotonin receptor haplotype has functional impact by affecting the immunological phenotype of T cells and monocytes.

Genes Immunity 2013; 14: 83

Eitan Israeli

Capsule

T helper-1 cell cytokines drive cancer into senescence

Cancer control by adaptive immunity involves a number of defined death and clearance mechanisms. However, efficient inhibition of exponential cancer growth by T cells and interferon-γ (IFNγ) requires additional undefined mechanisms that arrest cancer cell proliferation. Braumüller et al. show that the combined action of the T helper-1 cell cytokines IFNγ and tumor necrosis factor (TNF) directly induces permanent growth arrest in cancers. To safely separate senescence induced by tumor immunity from oncogene-induced senescence, the authors used a mouse model in which the Simian virus 40 large T antigen (Tag) expressed under the control of the rat insulin promoter creates tumors by attenuating p53- and Rb-mediated cell cycle control. When combined, IFNγ and TNF drive Tag-expressing cancers into senescence by inducing permanent growth arrest in G1/G0, activation of p16INK4a (also known as CDKN2A), and downstream Rb hypophosphorylation at serine 795. This cytokine-induced senescence strictly requires STAT1 and TNFR1 (also known as TNFRSF1A) signaling in addition to p16INK4a. In vivo, Tag-specific T helper-1 cells permanently arrest Tag-expressing cancers by inducing IFNγ and TNFR1-dependent senescence. Conversely, Tnfr1−/− Tag-expressing cancers resist cytokine-induced senescence and grow aggressively, even in TNFR1-expressing hosts. Finally, as IFNγ and TNF induce senescence in numerous murine and human cancers, this may be a general mechanism for arresting cancer progression.

Nature 2012; 494: 361

Eitan Israeli

Capsule

The 'obligate diploid' *Candida albicans* forms mating-competent haploids

Candida albicans, the most prevalent human fungal pathogen, is considered to be an obligate diploid that carries recessive lethal mutations throughout the genome. Hickman et al. demonstrate that *C. albicans* has a viable haploid state that can be derived from diploid cells under in vitro and in vivo conditions, and that seems to arise through a concerted chromosome loss mechanism. Haploids undergo morphogenetic changes like those of diploids, including the yeast-hyphal transition, chlamydospore formation and a white-opaque switch that facilitates mating. Haploid opaque cells of opposite mating type mate efficiently to regenerate the diploid form, restoring heterozygosity and fitness. Homozygous diploids arise spontaneously by auto-diploidization, and both haploids and auto-diploids show a similar reduction in fitness, in vitro and in vivo, relative to heterozygous diploids, indicating that homozygous cell types are transient in mixed populations. Finally, the authors constructed stable haploid strains with multiple auxotrophies that will facilitate molecular and genetic analyses of this important pathogen.

Nature 2013; 494: 55

Eitan Israeli

Capsule

Towards germline gene therapy of inherited mitochondrial diseases

Mutations in mitochondrial DNA (mtDNA) are associated with severe human diseases and are maternally inherited through the egg's cytoplasm. Tachibana et al. investigated the feasibility of mtDNA replacement in human oocytes by spindle transfer (ST, also called spindle-chromosomal complex transfer). Of 106 human oocytes donated for research, 65 were subjected to reciprocal ST and 33 served as controls. Fertilization rate in ST oocytes (73%) was similar to controls (75%); however, a significant portion of ST zygotes (52%) showed abnormal fertilization as determined by an irregular number of pronuclei. Among normally fertilized ST zygotes, blastocyst development (62%) and embryonic stem cell isolation (38%) rates were comparable to controls. All embryonic stem cell lines derived from ST zygotes had normal euploid karyotypes and contained exclusively donor mtDNA. The mtDNA can be efficiently replaced in human oocytes. Although some ST oocytes displayed abnormal fertilization, remaining embryos were capable of developing to blastocysts and producing embryonic stem cells similar to controls.

Nature 2012; 493: 627

Eitan Israeli

Capsule

Nocturnal glucose control with an artificial pancreas at a diabetes camp

Recent studies have shown that an artificial pancreas system can improve glucose control and reduce nocturnal hypoglycemia. However, it is not known whether such results can be replicated in settings outside the hospital. In this multicenter multinational randomized crossover trial, Phillip et al. assessed the short-term safety and efficacy of an artificial pancreas system for control of nocturnal glucose levels in patients (age 10 to 18 years) with type 1 diabetes at a diabetes camp. In two consecutive overnight sessions, the authors randomly assigned 56 patients to receive treatment with an artificial pancreas on the first night and a sensor-augmented insulin pump (control) on the second night, or to the reverse order of therapies on the first and second nights. Thus, all the patients received each treatment in a randomly assigned order. The primary end-points were the number of hypoglycemic events (defined as a sensor glucose value of ‹ 63 mg/dl for at least 10 consecutive minutes), the time spent with glucose levels below 60 mg/dl, and the mean overnight glucose level for individual patients. When comparing nights when the artificial pancreas was used with nights when the sensor-augmented insulin pump was used, there were significantly fewer episodes of night-time glucose levels below 63 mg/dl (7 vs. 22) and significantly shorter periods when glucose levels were below 60 mg/dl ($P = 0.003$ and $P = 0.02$, respectively, after adjustment for multiplicity). Median values for the individual mean overnight glucose levels were 126.4 mg/dl (interquartile range 115.7–139.1) with the artificial pancreas and 140.4 mg/dl (interquartile range 105.7–167.4) with the sensor-augmented pump. No serious adverse events were reported.

N Engl J Med 2013; 368: 824

Eitan Israeli

Capsule

CCR5 is a receptor for *Staphylococcus aureus* leukotoxin ED

Pore-forming toxins are critical virulence factors for many bacterial pathogens and are central to *Staphylococcus aureus*-mediated killing of host cells. *S. aureus* encodes pore-forming bi-component leukotoxins that are toxic towards neutrophils, but also specifically target other immune cells. Despite decades since the first description of staphylococcal leukocidal activity, the host factors responsible for the selectivity of leukotoxins towards different immune cells remain unknown. Alonzo et al. identify the human immunodeficiency virus (HIV) co-receptor CCR5 as a cellular determinant required for cytotoxic targeting of subsets of myeloid cells and T lymphocytes by the *S. aureus* leukotoxin ED (LukED). The authors further demonstrate that LukED-dependent cell killing is blocked by CCR5 receptor antagonists, including the HIV drug maraviroc. Remarkably, CCR5-deficient mice are largely resistant to lethal *S. aureus* infection, highlighting the importance of CCR5 targeting in *S. aureus* pathogenesis. Thus, depletion of CCR5+ leukocytes by LukED suggests a new immune evasion mechanism of *S. aureus* that can be therapeutically targeted.

Nature 2013; 493: 51

Eitan Israeli

Capsule

Common and specific signatures of gene expression and protein–protein interactions in autoimmune diseases

In an attempt to understand intracellular regulatory mechanisms in peripheral blood mononuclear cells (PBMCs), which are either common to many autoimmune diseases or specific to some of them, Tuller et al. incorporated large-scale data such as protein–protein interactions, gene expression and demographic information of hundreds of patients and healthy subjects, related to six autoimmune diseases with available large-scale gene expression measurements: multiple sclerosis, systemic lupus erythematosus, juvenile rheumatoid arthritis, Crohn's disease, ulcerative colitis and type 1 diabetes. These data were analyzed concurrently by statistical and systems biology approaches tailored for this purpose. The authors found that chemokines such as CXCL1-3, 5, 6 and the interleukin-8 tend to be differentially expressed in PBMCs of patients with the analyzed autoimmune diseases. In addition, the anti-apoptotic gene *BCL3*, interferon-gamma, and the vitamin D receptor (*VDR*) gene physically interact with significantly many genes that tend to be differentially expressed in PBMCs of patients with the analyzed autoimmune diseases. In general, similar cellular processes tend to be differentially expressed in PBMC in the analyzed autoimmune diseases. Specifically, the cellular processes related to cell proliferation (for example, epidermal growth factor, platelet-derived growth factor, nuclear factor-κB, Wnt/β-catenin signaling, stress-activated protein kinase c-Jun NH2-terminal kinase), inflammatory response (for example, interleukins 2 and 6, the cytokine granulocyte-macrophage colony-stimulating factor and the B cell receptor), general signaling cascades (for example, mitogen-activated protein kinase, extracellular signal-regulated kinase, p38 and TRK) and apoptosis are activated in most of the analyzed autoimmune diseases. However, these results suggest that in each of the analyzed diseases, apoptosis and chemotaxis are activated via different subsignaling pathways. Analyses of the expression levels of dozens of genes and the protein–protein interactions among them demonstrated that Crohn's disease and ulcerative colitis have relatively similar gene expression signatures, whereas the gene expression signatures of type 1 diabetes and juvenile rheumatoid arthritis relatively differ from the signatures of the other autoimmune diseases. These diseases are the only ones activated via the Fcε pathway. The relevant genes and pathways reported in this study may be helpful in the diagnoses and understanding of autoimmunity and/or specific autoimmune diseases.

Genes Immunity 2013; 14: 67

Eitan Israeli