Capsule

Plant science: neuroexcitatory starfruit

The starfruit (*Averrhoa carambola*), so named for the star-like shape generated when the fruit is cut in cross-section, adds a tropical note to diverse diets. However, those with kidney failure have an unusual reaction to ingesting starfruit that includes hiccups, mental confusion, and seizures. Garcia-Cairasco et al., analyzing the response of kidney-damaged rats to starfruit extracts, have now identified the toxic element. The key compound is not the nephrotoxic oxalic acid, known to be present in the fruit, but rather a molecule somewhat like phenylalanine, which the authors have named caramboxin. When injected into rat brains, caramboxin has a neuroexcitatory effect. Experiments with brain slices showed that caramboxin has properties of a glutamatergic receptor agonist. With this potent natural product, the starfruit may be useful for more than gracing a salad.

Angew Chem Int Ed 2013; 52: 10.1002/anie.201305382

Eitan Israeli

Capsule

Two waves of distinct hematopoietic progenitor cells colonize the fetal thymus

The generation of T cells depends on the migration of hematopoietic progenitor cells to the thymus throughout life. The identity of the thymus-settling progenitor cells has been a matter of considerable debate. Ramond and colleagues found that thymopoiesis was initiated by a first wave of T cell lineage-restricted progenitor cells with limited capacity for population expansion but accelerated differentiation into mature T cells. They gave rise to αβ and γδ T cells that constituted Vγ3+ dendritic epithelial T cells. Thymopoiesis was subsequently maintained by less differentiated progenitor cells that retained the potential to develop into B cells and myeloid cells. In that second wave, which started before birth, progenitor cells had high proliferative capacity but delayed differentiation capacity and no longer gave rise to embryonic γδ T cells. This work reconciles conflicting hypotheses on the nature of thymus-settling progenitor cells.

Nature Immunol 2014; 15: 27

Eitan Israeli

Capsule

The MyD88 rs6853 and TIRAP rs8177374 polymorphic sites are associated with resistance to human pulmonary tuberculosis

Toll-like receptors recognize several components of *Mycobacterium tuberculosis*, the main causative agent of tuberculosis. The signaling pathways leading to activation of the immune response require the MyD88 and TIRAP genes. The hypothesis that polymorphic variants of these genes influenced resistance to pulmonary tuberculosis was tested by a case-control study (400 cases and 400 controls). Heterozygosity at the polymorphic sites MyD88 rs6853 (alleles: A, G) or TIRAP rs8177374 (S180L) (alleles: C, T) is associated with resistance to pulmonary tuberculosis (P: 7.8×10^{-8} and 2×10^{-6}, respectively). Double heterozygosity confers higher protection levels (P: 10^{-14} to 2×10^{-16}). The logistic regression model displayed that the double homozygous genotype GG/TT predisposes to the disease (odds ratio (OR): 5.78) and the AG/TT genotype combination neutralizes the protective activity exerted by AG (O: 3.05). The same model showed that the risk of developing the disease increases with age from 31–40 years to 71–80 years (OR 1.32–13.59).

Genes Immun 2013; 4: 504

Eitan Israeli

Capsule

Infectious disease: non-random and non-overlapping

Evolutionary pressure from pathogens appears to have generated diversity in alleles of immune response genes known as human leukocyte antigen (HLA). It remains unclear, however, how this mechanism resulted in the dominance of certain HLA allele combinations. Penman et al. investigated particular associations of HLA alleles with protection against death from specific pathogens using a mathematical model for the simple case of a two-locus two-allele system. The model reveals that a pathogen population evolves, which extirpates homozygote hosts and then enters dynamic co-evolutionary cycling of heterozygotes. The consequence is that strain structure evolves in the pathogen population as a result of this immune selection and results in non-random and non-overlapping associations among the HLA immune recognition alleles of the host.

Proc Natl Acad Sci USA 2013; 10.1073/pnas.1304218110

Eitan Israeli

Capsule

p53 status determines the role of autophagy in pancreatic tumor development

Macroautophagy (hereafter referred to as autophagy) is a process in which organelles termed autophagosomes deliver cytoplasmic constituents to lysosomes for degradation. Autophagy has a major role in cellular homeostasis and has been implicated in various forms of human disease. The role of autophagy in cancer seems to be complex, with reports indicating both pro-tumorigenic and tumor-suppressive roles. Rosenfeldt and co-authors show, in a humanized genetically modified mouse model of pancreatic ductal adenocarcinoma (PDAC), that autophagy's role in tumor development is intrinsically connected to the status of the tumor suppressor p53. Mice with pancreases containing an activated oncogenic allele of Kras (also called Ki-Ras) – the most common mutational event in PDAC – develop a small number of precancerous lesions that stochastically develop into PDAC over time. However, mice also lacking the essential autophagy genes *Atg5* or *Atg7* accumulate low grade, premalignant pancreatic intraepithelial neoplasia lesions, but progression to high grade pancreatic intraepithelial neoplasias and PDAC is blocked. In marked contrast, in mice containing oncogenic Kras and lacking p53, loss of autophagy no longer blocks tumor progression, but in fact accelerates tumor onset, with metabolic analysis revealing enhanced glucose uptake and enrichment of anabolic pathways, which can fuel tumor growth. These findings provide considerable insight into the role of autophagy in cancer and have important implications for autophagy inhibition in cancer therapy.

Nature 2013; 504: 296

Eitan Israeli

Capsule

Vaccine for prevention of mild and moderate-to-severe influenza in children

Commonly used trivalent vaccines contain one influenza B virus lineage and may be ineffective against viruses of the other B lineage. We evaluated the efficacy of a candidate inactivated quadrivalent influenza vaccine (QIV) containing both B lineages. In this multinational, phase 3, observer-blinded study, Jaine et al. randomly assigned children 3 to 8 years of age, in a 1:1 ratio, to receive the QIV or a hepatitis A vaccine (control). The primary endpoint was influenza A or B confirmed by real-time polymerase chain reaction (rt-PCR). Secondary endpoints were rt-PCR-confirmed, moderate-to-severe influenza and rt-PCR-positive, culture-confirmed influenza. The vaccine efficacy and the effect of vaccination on daily activities and utilization of health care resources were assessed in the total vaccinated cohort (2584 children in each group) and the per-protocol cohort (2379 children in the QIV group and 2398 in the control group). In the total vaccinated cohort, 62 children in the QIV group (2.40%) and 148 in the control group (5.73%) had rt-PCR-confirmed influenza, representing a QIV efficacy of 59.3% (95% confidence interval, CI, 45.2–69.7), with efficacy against culture-confirmed influenza of 59.1% (97.5% CI 41.2–71.5). For moderate-to-severe rt-PCR-confirmed influenza, the attack rate was 0.62% (16 cases) in the QIV group and 2.36% (61 cases) in the control group, representing a QIV efficacy of 74.2% (97.5% CI 51.5–86.2). In the per-protocol cohort, the QIV efficacy was 55.4% (95% CI 39.1–67.3), and the efficacy against culture-confirmed influenza 55.9% (97.5% CI 35.4–69.9); the efficacy among children with moderate-to-severe influenza was 73.1% (97.5% CI 47.1–86.3). The QIV was associated with reduced risks of a body temperature above 39°C and lower respiratory tract illness, as compared with the control vaccine, in the per-protocol cohort (relative risk 0.29, 95% CI 0.16–0.56, and 0.20, 95% CI 0.04–0.92, respectively). The QIV was immunogenic against all four strains. Serious adverse events occurred in 36 children in the QIV group (1.4%) and in 24 children in the control group (0.9%).

N Engl J Med 2013; 369: 2481

Eitan Israeli

Capsule

Isolation and characterization of a bat SARS-like coronavirus that uses the ACE2 receptor

The 2002–2003 pandemic caused by severe acute respiratory syndrome coronavirus (SARS-CoV) was one of the most significant public health events in recent history. An ongoing outbreak of Middle East respiratory syndrome coronavirus suggests that this group of viruses remains a key threat and that their distribution is wider than previously recognized. Although bats have been suggested to be the natural reservoirs of both viruses, attempts to isolate the progenitor virus of SARS-CoV from bats have been unsuccessful. Diverse SARS-like coronaviruses (SL-CoVs) have now been reported from bats in China, Europe and Africa, but none is considered a direct progenitor of SARS-CoV because of their phylogenetic disparity from this virus and the inability of their spike proteins to use the SARS-CoV cellular receptor molecule, the human angiotensin-converting enzyme II (ACE2). Ge et al. reported whole-genome sequences of two novel bat coronaviruses from Chinese horseshoe bats (family: Rhinolophidae) in Yunnan, China: RsSHC014 and Rs3367. These viruses are far more closely related to SARS-CoV than any previously identified bat coronaviruses, particularly in the receptor binding domain of the spike protein. Most importantly, they report the first recorded isolation of a live SL-CoV (bat SL-CoV-WIV1) from bat fecal samples in Vero E6 cells, which has typical coronavirus morphology, 99.9% sequence identity to Rs3367 and uses ACE2 from humans, civets and Chinese horseshoe bats for cell entry. Preliminary in vitro testing indicates that WIV1 also has a broad species tropism. These results provide the strongest evidence to date that Chinese horseshoe bats are natural reservoirs of SARS-CoV, and that intermediate hosts may not be necessary for direct human infection by some bat SL-CoVs. They also highlight the importance of pathogen-discovery programs targeting high risk wildlife groups in emerging disease hotspots as a strategy for pandemic preparedness.

Nature 2013; 503: 535

Eitan Israeli

Capsule

Dysfunctional nitric oxide signaling increases risk of myocardial infarction

The importance of genetic predisposition to coronary artery disease and myocardial infarction is best documented by the predictive value of a positive family history. Next-generation sequencing in families with several affected individuals has revolutionized mutation identification. Erdmann and collaborators report the segregation of two private, heterozygous mutations in two functionally related genes, *GUCY1A3*(p.Leu163Phefs*24) and *CCT7* (p.Ser525Leu), in an extended myocardial infarction family. *GUCY1A3* encodes the α1 subunit of soluble guanylyl cyclase (α1-sGC), and *CCT7* encodes CCTη, a member of the tailless complex polypeptide 1 ring complex, which, among other functions, stabilizes soluble guanylyl cyclase. After stimulation with nitric oxide, soluble guanylyl cyclase generates cGMP, which induces vasodilation and inhibits platelet activation. The authors demonstrate in vitro that mutations in both *GUCY1A3* and *CCT7* severely reduce α1-sGC as well as β1-sGC protein content, and impair soluble guanylyl cyclase activity. Moreover, platelets from digenic mutation carriers contained less soluble guanylyl cyclase protein and consequently displayed reduced nitric oxide-induced cGMP formation. Mice deficient in α1-sGC protein displayed accelerated thrombus formation in the microcirculation after local trauma. Starting with a severely affected family, they have identified a link between impaired soluble guanylyl cyclase-dependent nitric oxide signaling and myocardial infarction risk, possibly through accelerated thrombus formation. Reversing this defect may provide a new therapeutic target for reducing the risk of myocardial infarction.

Nature 2013; 504: 432

Eitan Israeli

Capsule

Attention to eyes is present but in decline in 2–6 month old infants later diagnosed with autism

Deficits in eye contact have been a hallmark of autism since the condition's initial description. They are cited widely as a diagnostic feature and figure prominently in clinical instruments; however, the early onset of these deficits is not known. Jones et al. show in a prospective longitudinal study that infants later diagnosed with autism spectrum disorders (ASDs) exhibit mean decline in eye fixation from 2 to 6 months of age, a pattern not observed in infants who do not develop ASD. These observations mark the earliest known indicators of social disability in infancy, but also falsify a prior hypothesis: in the first months of life, this basic mechanism of social adaptive action – eye looking – is not immediately diminished in infants later diagnosed with ASD; instead, eye looking appears to begin at normative levels prior to decline. The timing of decline highlights a narrow developmental window and reveals the early derailment of processes that would otherwise have a key role in canalizing typical social development. Finally, the observation of this decline in eye fixation – rather than outright absence – offers a promising opportunity for early intervention that could build on the apparent preservation of mechanisms subserving reflexive initial orientation towards the eyes.

Nature 2013; 504: 427

Eitan Israeli

Capsule

Cancer immunosurveillance gone bad?

A subset of patients who develop scleroderma, a debilitating autoimmune disease, have an elevated risk of developing cancer. These patients harbor autoantibodies to RPC1, an RNA polymerase subunit encoded by the *POLR3A* gene. Joseph and fellow researchers explored whether the RPC1 autoantibodies target a "foreign" antigen derived from a mutated *POLR3A* gene. Sequence analysis revealed that *POLR3A* mutations were present in tumors from six of eight patients with RPC1 autoantibodies but in no tumors from eight control patients who lacked RPC1 autoantibodies. Cell culture data suggested that the *POLR3A* mutations triggered cellular and humoral immune responses in the patients. These results provide support for the "immunosurveillance" hypothesis, which posits the continual eradication of nascent tumor cells via immune responses.

Science 2104; 343: 152

Eitan Israeli

Capsule

Gliomas are back with new mutations

After surgery, gliomas (a type of brain tumor) recur in nearly all patients and often in a more aggressive form. Johnson et al. used exome sequencing to explore whether recurrent tumors harbor different mutations than the primary tumors and whether the mutational profile in the recurrences is influenced by postsurgical treatment of patients with temozolomide (TMZ), a chemotherapeutic drug known to damage DNA. In more than 40% of cases, at least half of the mutations in the initial glioma were undetected at recurrence. The recurrent tumors in many of the TMZ-treated patients bore the signature of TMZ-induced mutagenesis and appeared to follow an evolutionary path to high grade glioma distinct from that in untreated patients.

Science 2014; 343: 189

Eitan Israeli

Capsule

Antibacterial membrane attack by a pore-forming intestinal C-type lectin

Human body surface epithelia coexist in close association with complex bacterial communities and are protected by a variety of antibacterial proteins. C-type lectins of the RegIII family are bactericidal proteins that limit direct contact between bacteria and the intestinal epithelium and thus promote tolerance to the intestinal microbiota. RegIII lectins recognize their bacterial targets by binding peptidoglycan carbohydrate, but the mechanism by which they kill bacteria is unknown. Mukherjee et al. elucidated the mechanistic basis for RegIII bactericidal activity. They show that human RegIIIα (also known as HIP/PAP) binds membrane phospholipids and kills bacteria by forming a hexameric membrane-permeabilizing oligomeric pore. The authors derived a three-dimensional model of the RegIIIα pore by docking the RegIIIα crystal structure into a cryo-electron microscopic map of the pore complex, and showed that the model accords with experimentally determined properties of the pore. Lipopolysaccharide inhibited RegIIIα pore-forming activity, explaining why RegIIIα is bactericidal for Gram-positive but not Gram-negative bacteria. These findings identified C-type lectins as mediators of membrane attack in the mucosal immune system, and provide detailed insight into an antibacterial mechanism that promotes mutualism with the resident microbiota.

Nature 2014;5 05: 103

Eitan Israeli

Capsule

Host cell sensors for Plasmodium activate innate immunity against liver-stage infection

Before they infect red blood cells and cause alaria, Plasmodium parasites undergo an obligate and clinically silent expansion phase in the liver that is supposedly undetected by the host. Liehl et al. demonstrated the engagement of a type I interferon (IFN) response during Plasmodium replication in the liver. The authors identified Plasmodium RNA as a previously unrecognized pathogen-associated molecular pattern (PAMP) capable of activating a type I IFN response via the cytosolic pattern recognition receptor Mda5. This response, initiated by liver-resident cells through the adaptor molecule for cytosolic RNA sensors, Mavs, and the transcription factors Irf3 and Irf7, is propagated by hepatocytes in an IFN-α/β receptor-dependent manner. This signaling pathway is critical for immune cell-mediated host resistance to liver stage Plasmodium infection, which we found can be primed with other PAMPs, including hepatitis C virus RNA. Together, our results show that the liver has sensor mechanisms for Plasmodium that mediate a functional antiparasite response driven by type I IFN.

Nature Med 2014; 20: 47

Capsule

Perivascular macrophages mediate neutrophil recruitment during bacterial skin infection

Transendothelial migration of neutrophils in postcapillary venules is a key event in the inflammatory response against pathogens and tissue damage. The precise regulation of this process is incompletely understood. Abtin and team report that perivascular macrophages are critical for neutrophil migration into skin infected with the pathogen *Staphylococcus aureus*. Using multiphoton intravital microscopy we showed that neutrophils extravasate from inflamed dermal venules in close proximity to perivascular macrophages, which are a major source of neutrophil chemoattractants. The virulence factor α-hemolysin produced by *S. aureus* lyses perivascular macrophages, which leads to decreased neutrophil transmigration. These data illustrate a previously unrecognized role for perivascular macrophages in neutrophil recruitment to inflamed skin and indicate that *S. aureus* uses hemolysin-dependent killing of these cells as an immune evasion strategy.

Nature Immunol 2014; 15: 45

Eitan Israeli

Capsule

Persistent bacteria and survival in phagocytes

The role of persister cells – dormant cells that survive multi-drug – treatment in the context of bacterial pathogenesis has not been explored in depth. Using a single-cell fluorescent dilution technique, Helaine and collaborators examined *Salmonella typhimurium* persister-cell formation in vitro and in infections in mice. Within 30 minutes after phagocytosis by macrophages, Salmonella cells follow one of two fates: either to replication and generation of virulence effectors or to remaining viable but become non-replicating persisters. Salmonella living within a macrophage vacuole are exposed to potentially stressful conditions that induce the expression of 14 Type II toxin-antidote loci in a ppGpp/lon protease-dependent manner, and this system appears to play a role in both virulence factor induction and persister-cell formation. The non-replicating bacteria represent at least four distinct subpopulations, as defined by their ability to resume growth and their metabolic activity, but different phenotypes are observed in different pathogens and *Escherichia coli* persisters are distinct from Salmonella persisters.

Science 2014; 343: 204

Capsule

‘Watch’ stops unnecessary heart attack deaths

It looks like a watch but it’s a sophisticated blood-oxygen heart rate monitor. About half the people at risk of death from cardiac or pulmonary arrest could gain the chance to live, once Israeli entrepreneur Leon Eisen’s new Oxitone device goes to market some time this year. Using two optical sensors and another special high-tech tool, Eisen developed the world’s first “watch” that can just about tell when your time may be up. With all the technology out there – personal monitoring devices, crocodile clips for your finger, even those panic buttons – nothing helps if the user is not able to mobilize these devices in time. And many patients may not be able to read the signs that cardiac arrest is imminent. That’s why Eisen developed a wearable watch-like mobile device – synched with Bluetooth, Android or iPhone devices – that takes minute-by-minute readings of heart rate and oxygen levels in the blood. Oxitone was recently chosen from 400 applicants by GE Healthcare’s Start-Up Health Academy Entrepreneurship Program.

Israel High-Tech & Investment Report