Capsule

Inhaling H(2) improves survival after cardiac arrest in rats

Cardiac arrest is a precarious state between life and death that has many diverse causes. Despite increased public awareness, rapid administration of cardiopulmonary resuscitation (CPR) and improved access to automated external defibrillators (AEDs), only a fraction of individuals survive longer than one month (5–15%) after cardiac arrest, with an even smaller portion returning to normal neurological function (~2%). Lack of blood flow and oxygen (ischemia) induce global brain injury, yet rapid reperfusion can exacerbate tissue damage by driving inflammation, free radical production, and oxidative stress. Recently, inhaled hydrogen (H_2) was shown to have antioxidant properties, quenching harmful free radicals, without affecting the other reactive oxygen species critical to normal function. Leveraging these properties of H_2, Hayashida et al. demonstrated the potential of inhaled H_2 therapy in improving survival and neurological outcomes in a rat model of cardiac arrest. Six minutes after inducing arrest through ventricular fibrillation, CPR was initiated for 3 minutes followed by defibrillation. Compared with controls, 7 day survival doubled in animals receiving H_2 and/or hypothermic treatments. Neurological function, motor activity, and spatial memory also improved markedly with either H_2 or therapeutic hypothermia compared with standard treatment, with additional functional improvement in the group receiving both therapies.

Circulation 2014; 10.1161/Circulationaha.114.011848

Eitan Israeli

Capsule

A comparative encyclopedia of DNA elements in the mouse genome

The laboratory mouse shares the majority of its protein-coding genes with humans, making it the premier model organism in biomedical research, yet the two mammals differ in significant ways. To gain greater insights into both shared and species-specific transcriptional and cellular regulatory programs in the mouse, the Mouse ENCODE Consortium has mapped transcription, DNase I hypersensitivity, transcription factor binding, chromatin modifications and replication domains throughout the mouse genome in diverse cell and tissue types. By comparing with the human genome, Yue et al. not only confirm substantial conservation in the newly annotated potential functional sequences, but also find a large degree of divergence of sequences involved in transcriptional regulation, chromatin state and higher order chromatin organization. Their results illuminate the wide range of evolutionary forces acting on genes and their regulatory regions, and provide a general resource for research into mammalian biology and mechanisms of human diseases.

Nature 2014; 515: 355

Eitan Israeli

Capsule

A conserved response for tissue repair

Upon injury or infection, the body releases chemicals that trigger tissue repair and pathogen clearance. Because the medical community needs new therapeutic leads in this era of growing antibiotic resistance, identifying these molecules is a high priority. Dalli and team looked for these factors in mice infected with self-resolving *Escherichia coli*, in human breast milk, and in regenerating planaria. They identified two related molecules, conserved across these organisms, which promoted pathogen clearance, reduced inflammation, and accelerated tissue regeneration. Scientists will need to carry out further studies to determine whether these chemicals have similar properties in humans.

Proc Natl Acad Sci USA 2014;10.1073/pnas.1415006111

Eitan Israeli

Capsule

Detection of self-reactive CD8+ T cells with an anergic phenotype in healthy individuals

Immunological tolerance to self requires naturally occurring regulatory T (T_{reg}) cells. Yet how they stably control autoimmune T cells remains obscure. Maeda et al. show that Treg cells can render self-reactive human CD8+ T cells anergic (i.e., hypoproliferative and cytokine hypoproducing upon antigen restimulation) in vitro, likely by controlling the co-stimulatory function of antigen-presenting cells. Anergic T cells were naïve in phenotype, lower than activated T cells in T cell receptor affinity for cognate antigen, and expressed several co-inhibitory molecules, including cytotoxic T lymphocyte-associated antigen-4 (CTLA-4). Using these criteria, they detected in healthy individuals anergic T cells reactive with a skin antigen targeted in the autoimmune disease vitiligo. Collectively, their results suggest that T_{reg} cell-mediated induction of anergy in autoimmune T cells is important for maintaining self-tolerance.

Science 2014; 346: 1536

Eitan Israeli

Capsule

Autophagy is essential for effector CD8+ T cell survival and memory formation

The importance of autophagy in the generation of memory CD8+ T cells in vivo is not well defined. Xu et al. report that autophagy was dynamically regulated in virus-specific CD8+ T cells during acute infection of mice with lymphocytic choriomeningitis virus. In contrast to the current paradigm, autophagy decreased in activated proliferating effector CD8+ T cells and was then upregulated when the cells stopped dividing just before the contraction phase. Consistent with those findings, deletion of the gene encoding either of the autophagy-related molecules Atg5 or Atg7 had little to no effect on the proliferation and function of effector cells, but these autophagy-deficient effector cells had survival defects that resulted in compromised formation of memory T cells. These studies define when autophagy is needed during effector and memory differentiation and warrant reexamination of the relationship between T cell activation and autophagy.

Nature Immunol 2014; 15: 1152

Eitan Israeli

Capsule

Identifying a rare population of dendritic cells capable of enhancing the function of cytotoxic T cells

Immune evasion is a hallmark of cancer, and tumors progress despite the accumulation of immune cells within a tumor and at the margin. By performing a systematic analysis of immune cell components in mouse tumor models and human specimens, Broz and colleagues identified a rare population of dendritic cells capable of enhancing the function of cytotoxic T cells. Although much is known on how the immune system functions to prevent disease, the mechanisms by which cytotoxic immune cells are suppressed in tumors are poorly understood. The authors used mouse models of breast cancer and melanoma, as well as human melanoma specimens, to dissect the myeloid lineage, which consists of tumor-associated macrophages (TAMs), monocytes, and dendritic cells that have the capacity to present antigens to T cells and induce cytotoxic T cell function. The authors identified a rare subset of dendritic cells (CD11b+/CD103+) that had a distinct transcription factor signature (IRF8, BATF3, and ZBTB46) as demonstrated by the reduction of this cell population in knockout mice lacking one of these transcription factors. The homing of this dendritic population was independent of colony-stimulating factor 1, which is essential for TAM infiltration, and dependent on granulocyte macrophage colony-stimulating factor (GM-CSF) and the Fms-related tyrosine kinase 3 (Flt3) ligand. These cells had elevated phagocytic capacity compared with TAMs and could stimulate cytotoxic T cells, whereas ablation of this dendritic cell population decreased the efficacy of adoptive cytotoxic T cell therapy in vivo. Bioinformatics analysis revealed that patients with a reduction in these dendritic cells had a much poorer prognosis in multiple cancers, including breast, lung, and head and neck tumors. Cancer immunotherapy is under intense investigation and offers the potential for therapeutic intervention in a variety of cancer types. The identification of stimulatory dendritic cells may provide an additional approach for immune checkpoint inhibition strategies to generate a favorable environment for the function of cytotoxic T cells.

Cancer Cell 2014: 10.1016/j.ccell.2014.09.007

Eitan Israeli

Capsule

Rational design of small molecules as vaccine adjuvants

Adjuvants increase vaccine potency largely by activating innate immunity and promoting inflammation. Limiting the side effects of this inflammation is a major hurdle for adjuvant use in vaccines for humans. It has been difficult to improve on adjuvant safety because of a poor understanding of adjuvant mechanism and the empirical nature of adjuvant discovery and development historically. Wu et al. describe new principles for the rational optimization of small-molecule immune potentiators (SMIPs) targeting Toll-like receptor 7 as adjuvants with a predicted increase in their therapeutic indices. Unlike traditional drugs, SMIP-based adjuvants need to have limited bioavailability and remain localized for optimal efficacy. These features also lead to temporally and spatially restricted inflammation that should decrease side effects. Through medicinal and formulation chemistry and extensive immunopharmacology, the authors show that in vivo potency can be increased with little to no systemic exposure, localized innate immune activation, and short in vivo residence times of SMIP-based adjuvants. This work provides a systematic and generalizable approach to engineering small molecules for use as vaccine adjuvants.

Sci Transl Med 2014; 6: 263ra160

Eitan Israeli

Capsule

Intravenous immunoglobulin may be an effective therapy for refractory, active diffuse cutaneous systemic sclerosis

Poelman et al. sought to retrospectively review a single-center experience using intravenous immunoglobulin (IVIG) for the treatment of refractory, active diffuse cutaneous systemic sclerosis (dcSSc). The mean modified Rodnan Skin score (mRSS) at baseline was compared to the mRSS at 6, 12, 18, and 24 months post-IVIG initiation by the paired Student *t*-test. Changes in mRSS at 6 and 12 months were also compared to data from historical controls of three large, negative, multicenter, randomized clinical trials of other medications [D-penicillamine (D-pen), recombinant human relaxin (relaxin), and oral bovine type I collagen (collagen)], and to patients treated with mycophenolate mofetil (MMF) alone using the Student *t*-test. Thirty patients were treated with adjunctive IVIG (2 g/kg/month) for refractory active dcSSc. The mean baseline mRSS of our cohort was 29.6 ± 7.2, and this significantly decreased to 24.1 ± 9.6 (n = 29, $P = 0.0011$) at 6 months, 22.5 ± 10.0 (n = 25, $P = 0.0001$) at 12 months, 20.6 ± 11.8 (n = 23, $P = 0.0001$) at 18 months, and 15.3 ± 6.4 (n = 15, $P < 0.0001$) at 24 months. The mean change in mRSS at 6 months was not significantly different in the IVIG group (-5.3 ± 7.9) compared to the relaxin trial (-4.8 ± 6.99, $P = 0.74$) or MMF group (-3.4 ± 7.4, $P = 0.26$); however, at 12 months, the mean change in mRSS was significantly better in the IVIG group (-8 ± 8.3) than in the D-pen (-2.47 ± 8.6, $P = 0.005$) and collagen (-3.4 ± 7.12, $P = 0.005$) groups, and was comparable to the group of primary MMF responders (-7.1 ± 9, $P = 0.67$). The authors suggest that IVIG may be an effective adjunctive therapy for active dcSSc in patients in whom other therapies failed.

J Rheumatol 2014;doi:10.3899/jrheum.140833

Eitan Israeli

Capsule

Metformin as adjunct antituberculosis therapy

The global burden of tuberculosis (TB) morbidity and mortality remains immense. A potential new approach to TB therapy is to augment protective host immune responses. Singhal et al. report that the antidiabetic drug metformin (MET) reduces the intracellular growth of *Mycobacterium tuberculosis* (*Mtb*) in an AMPK (adenosine monophosphate-activated protein kinase)-dependent manner. MET controls the growth of drug-resistant *Mtb* strains, increases production of mitochondrial reactive oxygen species, and facilitates phagosome-lysosome fusion. In Mtb-infected mice, use of MET ameliorated lung pathology, reduced chronic inflammation, and enhanced the specific immune response and the efficacy of conventional TB drugs. Moreover, in two separate human cohorts, MET treatment was associated with improved control of *Mtb* infection and decreased disease severity. Collectively, these data indicate that MET is a promising candidate host-adjunctive therapy for improving the effective treatment of TB.

Sci Transl Med 2014;6:263ra159

Eitan Israeli

Capsule

The genetics of febrile seizures

Febrile seizures – seizures caused by a high fever – occur in as many as 5% of young children. Often the fever is a result of a viral illness, but vaccine-induced fevers can also cause seizures and are considered an adverse effect of immunization. Family and twin studies confirm a strong genetic component underlying risk for febrile seizures. Genes have been identified for some epilepsy syndromes, but genetic risk factors for "simple" or self-limited febrile seizures have been elusive. Two recent studies advance our understanding of genetic susceptibility to fever-related seizures. Schubert et al. (*Nature Genet* 2014; 10.1038/ng.3130) used exome sequencing in two large families with multiple affected individuals to identify rare variants that segregate with fever-related seizures. They identified mutations in *STX1B* in both families as well as in four unrelated affected individuals. Rare variants in STX1B were associated with a broad range of seizures, ranging from simple febrile seizures to more severe epilepsy conditions, so further study is required to understand what role this gene plays in run-of-the-mill simple febrile seizures. The second study is a genome-wide association study (GWAS) by Feenstra et al. (*Nature Genet* 2014; 10.1038/ng.3129) in which they identify common genetic variants associated with risk for simple febrile seizures. They compared three groups of individuals: 929 children who had a febrile seizure after receiving the measles-mumps-rubella (MMR) vaccine, 1070 who had febrile seizures unrelated to the MMR vaccine, and 1999 controls without febrile seizures. They identified four loci associated with risk of febrile seizures overall and confirmed the associations in an independent case-control cohort. Two risk variants lie within well-known epilepsy genes that encode sodium channel subunits, *SCN1A* and *SCN2A*, so these results are not entirely surprising. Notably, variants in a different gene, *ANO3*, were associated with the highest risk of febrile seizures. Little is known about how this gene, which encodes a transmembrane protein that belongs to a family of chloride channels, might be related to seizure susceptibility. The discovery highlights new areas for research and, potentially, therapy. The fourth locus was not linked to a gene, but to a genomic region previously associated with magnesium levels – another area worthy of investigation. Perhaps most interesting, the authors identified two loci that are specific for risk of febrile seizures after the MMR vaccine, both of which are in genes that are involved in the immune response to infection: *IFI44L* and *CD46*. These results suggest that MMR vaccine-related seizures may be a subtype of simple febrile seizures.

Eitan Israeli

Capsule

Synaptic, transcriptional and chromatin genes disrupted in autism

The genetic architecture of autism spectrum disorder involves the interplay of common and rare variants and their impact on hundreds of genes. Using exome sequencing, Rubeis and collaborators show that analysis of rare coding variation in 3871 autism cases and 9937 ancestry-matched or parental controls implicates 22 autosomal genes at a false discovery rate (FDR) ‹ 0.05, plus a set of 107 autosomal genes strongly enriched for those likely to affect risk (FDR ‹ 0.30). These 107 genes, which show unusual evolutionary constraint against mutations, incur de novo loss-of-function mutations in over 5% of autistic subjects. Many of the genes implicated encode proteins for synaptic formation, transcriptional regulation and chromatin-remodeling pathways. These include voltage-gated ion channels regulating the propagation of action potentials, pacemaking and excitability-transcription coupling, as well as histone-modifying enzymes and chromatin remodelers – most prominently those that mediate post-translational lysine methylation/demethylation modifications of histones.

Nature 2014; 515: 209

Eitan Israeli

Capsule

Human genetics shape the gut microbiome

Host genetics and the gut microbiome can both influence metabolic phenotypes. However, whether host genetic variation shapes the gut microbiome and interacts with it to affect host phenotype is unclear. Goodrich et al. compared microbiotas across › 1000 fecal samples obtained from the Twins UK population, including 416 twin pairs. The authors identified many microbial taxa whose abundances were influenced by host genetics. The most heritable taxon, the family Christensenellaceae, formed a co-occurrence network with other heritable bacteria and with methanogenic Archaea. Furthermore, Christensenellaceae and its partners were enriched in individuals with low body mass index (BMI). An obese-associated microbiome was amended with *Christensenella minuta*, a cultured member of the Christensenellaceae, and transplanted to germ-free mice. *C. minuta* amendment reduced weight gain and altered the microbiome of recipient mice. These findings indicate that host genetics influence the composition of the human gut microbiome and can do so in ways that impact host metabolism.

Cell 2014; 159: 789

Eitan Israeli

Capsule

A microRNA up-regulated in asthma airway T cells promotes T_H2 cytokine production

MicroRNAs (miRNAs) exert powerful effects on immunological function by tuning networks of target genes that orchestrate cell activity. Simpson et al. sought to identify miRNAs and miRNA-regulated pathways that control the type 2 helper T cell (T_H2 cell) responses that drive pathogenic inflammation in asthma. Profiling miRNA expression in human airway-infiltrating T cells revealed elevated expression of the miRNA miR-19a in asthma. Modulating miR-19 activity altered T_H2 cytokine production in both human and mouse T cells, and T_H2 cell responses were markedly impaired in cells lacking the entire miR-17~92 cluster. miR-19 promoted T_H2 cytokine production and amplified inflammatory signaling by direct targeting of the inositol phosphatase PTEN, the signaling inhibitor SOCS1 and the deubiquitinase A20. Thus, up-regulation of miR-19a in asthma may be an indicator and a cause of increased T_H2 cytokine production in the airways.

Nature Immunol 2014; 15: 1162

Eitan Israeli

Capsule

A step toward better vaccine adjuvants

The receptor TLR4 stimulates immune signaling pathways. It can do so through two adaptor proteins: MyD88, which can trigger undesirable inflammatory responses, and TRIF, which stimulates immune responses. Currently, adjuvants to boost immune responses to vaccines are developed with the idea that their structure determines the adaptor protein that TLR4 will use. However, Kolb and fellow-researchers suggest that TLR4 signaling is inherently biased toward the TRIF-dependent pathway, particularly in the context of type I interferon signaling. The findings may help in the development of more effective vaccine adjuvants that enhance immune responses without triggering potentially harmful inflammatory reactions.

Sci Signal 2014; 7: ra108

Eitan Israeli

Capsule

One clock for you and your microbes

Disrupting our circadian rhythms increases the risk of developing diabetes, obesity, cancer, and cardiovascular disease, but scientists do not fully understand why. Thaiss et al. report that conditions that cause jet lag change the composition and activities of gut microbes in mice, which can lead to metabolic disease. Gut microbe composition no longer fluctuated diurnally in mice with disrupted circadian rhythms, but normal rhythmic feeding or the transplantation of gut microbes from normal mice restored this oscillation. Normal mice that received gut microbial transplants from jet-lagged humans or mice that experienced a change in their day-night schedule gained weight and developed symptoms of metabolic disease.

Cell 2014; 159: 514

Eitan Israeli

Capsule

The gut microbiota influences blood-brain barrier permeability in mice

Pivotal to brain development and function is an intact blood-brain barrier (BBB), which acts as a gatekeeper to control the passage and exchange of molecules and nutrients between the circulatory system and the brain parenchyma. The BBB also ensures homeostasis of the central nervous system (CNS). Branistre et al. report that germ-free mice, beginning with intrauterine life, displayed increased BBB permeability compared to pathogen-free mice with a normal gut flora. The increased BBB permeability was maintained in germ-free mice after birth and during adulthood and was associated with reduced expression of the tight junction proteins occludin and claudin-5, which are known to regulate barrier function in endothelial tissues. Exposure of germ-free adult mice to a pathogen-free gut microbiota decreased BBB permeability and up-regulated the expression of tight junction proteins. These results suggest that gut microbiota-BBB communication is initiated during gestation and propagated throughout life.

Sci Transl Med 2014; 6: 263ra158

Eitan Israeli

Capsule

Limbal stem cells to treat scarring and prevent blindness

Our corneas – the transparent structures that allow us to see – are easily damaged by trauma and infection, which can cause scarring or blindness. Although corneas can be transplanted, transplants are limited by immune responses and by a shortage of cornea donors. Basu et al. devised a cell-based approach to prevent corneal scarring. They obtained stem cells from the human limbus (the region between cornea and sclera), which could be differentiated into keratocytes (corneal cells). The stem cells actively regenerated new corneal tissue when encased in a fibrin gel and applied to the wounded surface of the eye in mice. Such cells could potentially be obtained directly from a patient to treat scarring and prevent blindness.

Sci Transl Med 2014; 6: 266ra172

Eitan Israeli

Capsule

An ancient defense system eliminates unfit cells from developing tissues during cell competition

The recognition and elimination of unfit or mutant cells in cell competition is reminiscent of the detection of pathogens by the innate immune system. In Drosophila, the Toll and immune deficiency (IMD) signaling pathways govern the innate immune response to a broad range of pathogens and activate the NFκB transcription factor homologs Relish (Rel), Dorsal (dl), or Dorsal-related immunity factor (Dif). The conceptual similarities between innate immunity and cell competition led us to investigate whether the Toll and IMD pathways were required for cell competition in Drosophila wing disks. In their analysis of both *Myc*-induced and *Minute*-induced cell competition Meyer et al. revealed requirements for two related but distinct cohorts of components from the IMD and Toll pathways. Both signaling cohorts required the extracellular ligand Spätzle and non-canonical Toll-related receptors (TRRs) and led to elimination of the less-fit loser cells by inducing NFκB-dependent activation of pro-apoptotic genes. However, their analysis uncovered interesting differences between the signaling module deployed in each competitive context. In *Myc*-induced competition, elimination of wild-type loser cells required four of the nine TRRs encoded in the Drosophilagenome (*Toll-2*, *Toll*-3, *Toll-8*, and *Toll-9*) in non-redundant roles. By contrast, elimination of *RpL14*–/+ cells in Minute-induced competition required only *Toll-3* and *Toll-9*. Furthermore, the NFκB factor activated downstream of the TRRs was also context-dependent. Signal transduction within wild-type loser cells led to selective activation of Relish, whereas the death of *RpL14*–/+ loser cells in Minute-induced competition required Dorsal and Dif. These results suggest that signaling from the different TRR subsets influenced which NFκB factor was activated. Finally, although in each competitive context apoptosis of the relatively less fit cells was induced, the specific death-inducing gene expressed was determined by specifically activated NFκB factor. The authors conclude that in two genetically distinct contexts of cell competition, the ancient innate immune defense response system is activated and drives the elimination of the cells perceived as relatively less fit. In each competition paradigm, different signaling modules are employed, suggesting that the genetic identity of the competing cell populations influences the pathway that is activated. These results thus provide evidence for evolutionary adaptation of TRR-NFκB signaling modules in an organismal surveillance system that measures internal tissue fitness rather than external pathogenic stimuli.

Science 2014; 346: DOI: 10.1126/science.1258236

Eitan Israeli

Capsule

A receptor tyrosine kinase signals to YAP

The Hippo pathway limits cell proliferation by inhibiting the activity of the transcriptional coactivator YAP. In contrast, cell proliferation is stimulated by the binding of growth factors to tyrosine receptor kinases, such as the binding of neuregulin to ERBB4. Neuregulin binding also triggers the cleavage of ERBB4. Haskins et al. found that a fragment containing the intracellular domain of ERBB4 interacted with and activated YAP. Breast cancer cell migration induced by neuregulin was blocked by knocking down YAP. Thus, ERBB4 could promote tumor aggressiveness both through receptor tyrosine kinase signaling and by stimulating YAP.

Sci Signal 2014; 7: ra116 and pe29

Eitan Israeli

Capsule

Chimpanzee adenovirus vector Ebola vaccine — preliminary report

The unprecedented 2014 epidemic of Ebola virus disease (EVD) has prompted an international response to accelerate the availability of a preventive vaccine. A replication-defective recombinant chimpanzee adenovirus type 3-vectored ebola virus vaccine (cAd3-EBO), encoding the glycoprotein from Zaire and Sudan species that offers protection in the non-human primate model, was rapidly advanced into phase 1 clinical evaluation. Ledgewood et al. conducted a phase 1, dose-escalation, open-label trial of cAd3-EBO. Twenty healthy adults, in sequentially enrolled groups of 10 each, received vaccination intramuscularly in doses of $2x10^{10}$ particle units or $2x10^{11}$ particle units. Primary and secondary end-points related to safety and immunogenicity were assessed throughout the first 4 weeks after vaccination. In this small study, no safety concerns were identified; however, transient fever developed within 1 day after vaccination in two participants who had received the $2x10^{11}$ particle-unit dose. Glycoprotein-specific antibodies were induced in all 20 participants; the titers were of greater magnitude in the group that received the 2x1011 particle-unit dose than in the group that received the $2x10^{10}$particle-unit dose (geometric mean titer against the Zaire antigen, 2037 vs. 331; $P = 0.001$). Glycoprotein-specific T cell responses were more frequent among those who received the $2x10^{11}$ particle-unit dose than among those who received the $2x10^{10}$ particle-unit dose, with a CD4 response in 10 of 10 participants versus 3 of 10 participants ($P = 0.004$) and a CD8 response in 7 of 10 participants versus 2 of 10 participants ($P = 0.07$). Reactogenicity and immune responses to cAd3-EBO vaccine were dose dependent. At the $2x10^{11}$ particle-unit dose, glycoprotein Zaire-specific antibody responses were in the range reported to be associated with vaccine-induced protective immunity in challenge studies involving non-human primates. Clinical trials assessing cAd3-EBO are ongoing.

N Engl J Med 2014; DOI: 10.1056/NEJMoa1410863

Eitan Israeli

Capsule

RNA viruses promote activation of the NLRP3 inflammasome through a RIP1-RIP3-DRP1 signaling pathway

The NLRP3 inflammasome functions as a crucial component of the innate immune system in recognizing viral infection, but the mechanism by which viruses activate this inflammasome remains unclear. Wang et al. found that inhibition of the serine-threonine kinases RIP1 (RIPK1) or RIP3 (RIPK3) suppressed RNA virus-induced activation of the NLRP3 inflammasome. Infection with an RNA virus initiated assembly of the RIP1-RIP3 complex, which promoted activation of the GTPase DRP1 and its translocation to mitochondria to drive mitochondrial damage and activation of the NLRP3 inflammasome. Notably, the RIP1-RIP3 complex drove the NLRP3 inflammasome independently of MLKL, an essential downstream effector of RIP1-RIP3-dependent necrosis. Together our results reveal a specific role for the RIP1-RIP3-DRP1 pathway in RNA virus-induced activation of the NLRP3 inflammasome and establish a direct link between inflammation and cell-death signaling pathways.

Nature Immunol 2014; 15: 1126

Eitan Israeli

Capsule

Variation at HLA-DRB1 is associated with resistance to enteric fever

Enteric fever affects more than 25 million people annually and results from systemic infection with *Salmonella enteric serovar typhi* or paratyphi pathovars A, B or C1. Dunstan et al. conducted a genome-wide association study of 432 individuals with blood culture-confirmed enteric fever and 2011 controls from Vietnam. We observed strong association at rs7765379, odds ratio (OR) for the minor allele = 0.18, P = 4.5 × 10–10, a marker mapping to the HLA class II region, in proximity to HLA-DQB1 and HLA-DRB1. The authors replicated this association in 595 enteric fever cases and 386 controls from Nepal and also in a second independent collection of 151 cases and 668 controls from Vietnam. Imputation-based fine-mapping across the extended MHC region showed that the classical HLADRB1*04:05 allele (OR = 0.14, P = 2.60 × 10–11) could entirely explain the association at rs7765379, thus implicating HLADRB1 as a major contributor to resistance against enteric fever, presumably through antigen presentation.

Nature Genet 2014; doi:10/1038/ng.3143

Eitan Israeli