Capsule

Rare coding variants in the phospholipase D3 gene confer risk for Alzheimer's disease

Genome-wide association studies (GWAS) have identified several risk variants for late-onset Alzheimer's disease (LOAD). These common variants have replicable but small effects on LOAD risk and generally do not have obvious functional effects. Low frequency coding variants, not detected by GWAS, are predicted to include functional variants with larger effects on risk. To identify low frequency coding variants with large effects on LOAD risk, Cruchaga and fellow authors carried out whole-exome sequencing (WES) in 14 large LOAD families and follow-up analyses of the candidate variants in several large LOAD case-control data sets. A rare variant in *PLD3* (phospholipase D3; Val232Met) segregated with disease status in two independent families and doubled risk for Alzheimer's disease in seven independent case-control series with a total of more than 11,000 cases and controls of European descent. Gene-based burden analyses in 4387 cases and controls of European descent and 302 African American cases and controls, with complete sequence data for *PLD3*, reveal that several variants in this gene increase risk for Alzheimer's disease in both populations. *PLD3* is highly expressed in brain regions that are vulnerable to Alzheimer's disease pathology, including hippocampus and cortex, and is expressed at significantly lower levels in neurons from Alzheimer's disease brains compared to control brains. Overexpression of PLD3 leads to a significant decrease in intracellular amyloid-β precursor protein (APP) and extracellular Aβ42 and Aβ40 (the 42- and 40-residue isoforms of the amyloid-β peptide), and knockdown of PLD3 leads to a significant increase in extracellular Aβ42 and Aβ40. Together, our genetic and functional data indicate that carriers of *PLD3* coding variants have a twofold increased risk for LOAD and that PLD3 influences APP processing. This study provides an example of how densely affected families may help to identify rare variants with large effects on risk for disease or other complex traits.

Nature 2014; 505: 550

Eitan Israeli

Capsule

Transcranial amelioration of inflammation and cell death after brain injury

Traumatic brain injury (TBI) is increasingly appreciated to be highly prevalent and deleterious to neurological function. At present, no effective treatment options are available, and little is known about the complex cellular response to TBI during its acute phase. To gain insights into TBI pathogenesis, Roth et al. developed a novel murine closed-skull brain injury model that mirrors some pathological features associated with mild TBI in humans and used long-term intravital microscopy to study the dynamics of the injury response from its inception. The authors demonstrated that acute brain injury induces vascular damage, meningeal cell death, and the generation of reactive oxygen species (ROS) that ultimately breach the glial limitans and promote spread of the injury into the parenchyma. In response, the brain elicits a neuroprotective, purinergic receptor-dependent inflammatory response characterized by meningeal neutrophil swarming and microglial reconstitution of the damaged glial limitans. They also showed that the skull bone is permeable to small molecular-weight compounds and uses this delivery route to modulate inflammation and therapeutically ameliorate brain injury through transcranial administration of the ROS scavenger, glutathione. These results shed light on the acute cellular response to TBI and provide a means to locally deliver therapeutic compounds to the site of injury.

Nature 2014; 505: 223

Eitan Israeli

Capsule

A blood-resistant surgical glue for minimally invasive repair of vessels and heart defects

Currently, there are no clinically approved surgical glues that are non-toxic, bind strongly to tissue, and work well within wet and highly dynamic environments within the body. This is especially relevant to minimally invasive surgery that is increasingly performed to reduce postoperative complications, recovery times, and patient discomfort. Lang et al. describe the engineering of a bioinspired elastic and biocompatible hydrophobic light-activated adhesive (HLAA) that achieves a strong level of adhesion to wet tissue and is not compromised by preexposure to blood. The HLAA provided an on-demand hemostatic seal, within seconds of light application, when applied to high pressure large blood vessels and cardiac wall defects in pigs. HLAA-coated patches attached to the interventricular septum in a beating porcine heart and resisted supraphysiologic pressures by remaining attached for 24 hours, which is relevant to intracardiac interventions in humans. The HLAA could be used for many cardiovascular and surgical applications, with immediate application in repair of vascular defects and surgical hemostasis.

Sci Transl Med 2014; 6: 218ra6

Eitan Israeli

Capsule

Perturbed neural activity disrupts cerebral angiogenesis during a postnatal critical period

During the neonatal period, activity-dependent neural-circuit remodeling coincides with growth and refinement of the cerebral microvasculature. Whether neural activity also influences the patterning of the vascular bed is not known. Whiteus et al. showed in neonatal mice that neither reduction of sensory input through whisker trimming nor moderately increased activity by environmental enrichment affects cortical microvascular development. Unexpectedly, chronic stimulation by repetitive sounds, whisker deflection or motor activity led to a near arrest of angiogenesis in barrel, auditory and motor cortices, respectively. Chemically induced seizures also caused robust reductions in microvascular density. However, altering neural activity in adult mice did not affect the vasculature. Histological analysis and time lapse in vivo two-photon microscopy revealed that hyperactivity did not lead to cell death or pruning of existing vessels but rather to reduced endothelial proliferation and vessel sprouting. This anti-angiogenic effect was prevented by administration of the nitric oxide synthase (NOS) inhibitor L-NAME and in mice with neuronal and inducible NOS deficiency, suggesting that excessive nitric oxide released from hyperactive interneurons and glia inhibited vessel growth. Vascular deficits persisted long after cessation of hyperstimulation, providing evidence for a critical period after which proper microvascular patterning cannot be reestablished. Reduced microvascular density diminished the ability of the brain to compensate for hypoxic challenges, leading to dendritic spine loss in regions distant from capillaries. Therefore, excessive sensorimotor stimulation and repetitive neural activation during early childhood may cause lifelong deficits in microvascular reserve, which could have important consequences for brain development, function and pathology.

Nature 2014; 505: 407

Eitan Israeli

Capsule

Mycobacteria manipulate macrophage recruitment through coordinated use of membrane lipids

The evolutionary survival of *Mycobacterium tuberculosis* depends on its ability to invade the host, replicate, and transmit infection. At its initial peripheral infection site in the distal lung airways, *M. tuberculosis* infects macrophages, which transport it to deeper tissues. How mycobacteria survive in these broadly microbicidal cells is an important question. Cambier et al. show in mice and zebrafish that *M. tuberculosis*, and its close pathogenic relative *Mycobacterium marinum*, preferentially recruit and infect permissive macrophages while evading microbicidal ones. This immune evasion is accomplished by using cell surface-associated phthiocerol dimycoceroserate (PDIM) lipids to mask underlying pathogen-associated molecular patterns (PAMPs). In the absence of PDIM, these PAMPs signal a Toll-like receptor (TLR)-dependent recruitment of macrophages that produce microbicidal reactive nitrogen species. Concordantly, the related phenolic glycolipids (PGLs) promote the recruitment of permissive macrophages through a host chemokine receptor 2 (CCR2)-mediated pathway. Thus, the authors identified coordinated roles for PDIM, known to be essential for mycobacterial virulence, and PGL, which (along with CCR2) is known to be associated with human tuberculosis. These findings also suggest an explanation for the longstanding observation that *M. tuberculosis* initiates infection in the relatively sterile environment of the lower respiratory tract, rather than in the upper respiratory tract, where resident microflora and inhaled environmental microbes may continually recruit microbicidal macrophages through TLR-dependent signaling.

Nature 2014; 505: 218

Eitan Israeli

Capsule

Muc5b is required for airway defense

Respiratory surfaces are exposed to billions of particulates and pathogens daily. A protective mucus barrier traps and eliminates them through mucociliary clearance (MCC). However, excessive mucus contributes to transient respiratory infections and to the pathogenesis of numerous respiratory diseases. *MUC5AC* and *MUC5B* are evolutionarily conserved genes that encode structurally related mucin glycoproteins, the principal macromolecules in airway mucus. Genetic variants are linked to diverse lung diseases, but specific roles for MUC5AC and MUC5B in MCC, and the lasting effects of their inhibition, are unknown. Roy et al. (show that mouse Muc5b (but not Muc5ac) is required for MCC, for controlling infections in the airways and middle ear, and for maintaining immune homeostasis in mouse lungs, whereas Muc5ac is dispensable. Muc5b deficiency caused materials to accumulate in upper and lower airways. This defect led to chronic infection by multiple bacterial species, including *Staphylococcus aureus*, and to inflammation that failed to resolve normally. Apoptotic macrophages accumulated, phagocytosis was impaired, and interleukin-23 (IL-23) production was reduced in *Muc5b*−/− mice. By contrast, in mice that transgenically overexpress *Muc5b*, macrophage functions improved. Existing dogma defines mucous phenotypes in asthma and chronic obstructive pulmonary disease as driven by increased MUC5AC, with MUC5B levels either unaffected or increased in expectorated sputum. However, in many patients, MUC5B production at airway surfaces decreases by as much as 90%. By distinguishing a specific role for Muc5b in MCC, and by determining its impact on bacterial infections and inflammation in mice, these results provide a refined framework for designing targeted therapies to control mucin secretion and restore MCC.

Nature 2014; 505: 412

Eitan Israeli

Capsule

Cancer cell profiling by barcoding allows multiplexed protein analysis in fine-needle aspirates

Immunohistochemistry-based clinical diagnoses require invasive core biopsies and use a limited number of protein stains to identify and classify cancers. Ullal et al. introduced a technology that allows analysis of hundreds of proteins from minimally invasive fine-needle aspirates (FNAs), which contain much smaller numbers of cells than core biopsies. The method capitalizes on DNA-barcoded antibody sensing, where barcodes can be photocleaved and digitally detected without any amplification steps. After extensive benchmarking in cell lines, this method showed high reproducibility and achieved single-cell sensitivity. The authors used this approach to profile ~90 proteins in cells from FNAs and subsequently map patient heterogeneity at the protein level. Additionally, they demonstrated how the method could be used as a clinical tool to identify pathway responses to molecularly targeted drugs and to predict drug response in patient samples. This technique combines specificity with ease of use to offer a new tool for understanding human cancers and designing future clinical trials.

Sci Transl Med 2014; 6: 219ra9

Eitan Israeli

Capsule

Immunological and virological mechanisms of vaccine-mediated protection against SIV and HIV

A major challenge for the development of a highly effective AIDS vaccine is the identification of mechanisms of protective immunity. To address this question, Roederer and co-authors used a non-human primate challenge model with simian immunodeficiency virus (SIV). The authors show that antibodies to the SIV envelope are necessary and sufficient to prevent infection. Moreover, sequencing of viruses from breakthrough infections revealed selective pressure against neutralization-sensitive viruses; they identified a two amino acid signature that alters antigenicity and confers neutralization resistance. A similar signature confers resistance of human immunodeficiency virus (HIV)-1 to neutralization by monoclonal antibodies against variable regions 1 and 2 (V1V2), suggesting that SIV and HIV share a fundamental mechanism of immune escape from vaccine-elicited or naturally elicited antibodies. These analyses provide insight into the limited efficacy seen in HIV vaccine trials.

Nature 2014; 505: 502

Eitan Israeli

Capsule

Sugar sabotage in diabetes

In patients with diabetes, too much of a good thing – glucose – in the bloodstream causes the debilitating loss of biological functions and can eventually lead to death. Scientists continue to home in on the precise mechanisms by which this occurs, in hope of mitigating the damage. Warren and team have found a mechanism by which excess glucose can alter the functions of vascular endothelial cells, one of the main sites of complications in diabetes. In mouse endothelial cells, too much glucose leads to the overproduction of reactive oxygen species in the mitochondria. This excess of ROS causes the phosphorylation of the receptor for vascular endothelial growth factor (VEGF) within the Golgi, rendering the receptor vulnerable to proteolysis. This reduces the levels of VEGF receptor at the cell surface, where it would be able to detect circulating VEGF. Thus, cells chronically exposed to excess glucose become less responsive to VEGF, which is necessary for the proper growth, function, and survival of endothelial cells.

Sci Signal 2014; 7: ra1

Eitan Israeli

Capsule

CNVs conferring risk of autism or schizophrenia affect cognition in controls

In a small fraction of patients with schizophrenia or autism, alleles of copy-number variants (CNVs) in their genomes are probably the strongest factors contributing to the pathogenesis of the disease. These CNVs may provide an entry point for investigations into the mechanisms of brain function and dysfunction alike. They are not fully penetrant and offer an opportunity to study their effects separate from that of manifest disease. Stefansson et al. show in an Icelandic sample that a few of the CNVs clearly alter fecundity (measured as the number of children by age 45). Furthermore, they use various tests of cognitive function to demonstrate that control subjects carrying the CNVs perform at a level that is between that of schizophrenia patients and population controls. The CNVs do not all affect the same cognitive domains, hence the cognitive deficits that drive or accompany the pathogenesis vary from one CNV to another. Controls carrying the chromosome 15q11.2 deletion between breakpoints 1 and 2 (15q11.2(BP1-BP2) deletion) have a history of dyslexia and dyscalculia, even after adjusting for IQ in the analysis, and the CNV only confers modest effects on other cognitive traits. The 15q11.2(BP1-BP2) deletion affects brain structure in a pattern consistent with both that observed during first-episode psychosis in schizophrenia and that of structural correlates in dyslexia.

Nature 2014; 505: 361

Eitan Israeli

Capsule

Human-pathogen co-evolution

Helicobacter pylori is the principal cause of gastric cancer, the second leading cause of cancer mortality worldwide. However, *H. pylori* prevalence generally does not predict cancer incidence. To determine whether co-evolution between host and pathogen influences disease risk, Kodaman et al. examined the association between the severity of gastric lesions and patterns of genomic variation in matched human and *H. pylori* samples. Patients were recruited from two geographically distinct Colombian populations with significantly different incidences of gastric cancer, but virtually identical prevalence of *H. pylori* infection. All *H. pylori* isolates contained the genetic signatures of multiple ancestries, with an ancestral African cluster predominating in a low risk coastal population and a European cluster in a high risk mountain population. The human ancestry of the biopsied individuals also varied with geography: mostly African ancestry in the coastal region (58%) and mostly Amerindian ancestry in the mountain region (67%). The interaction between the host and pathogen ancestries completely accounted for the difference in the severity of gastric lesions in the two regions of Colombia. In particular, African *H. pylori* ancestry was relatively benign in humans of African ancestry but was deleterious in individuals with substantial Amerindian ancestry. Thus, co-evolution likely modulated disease risk, and the disruption of co-evolved human and *H. pylori* genomes can explain the high incidence of gastric disease in the mountain population.

PNAS 2014; doi: 10.1073/pnas.1318093111

Eitan Israeli

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

Capsule

Pan-viral specificity of IFN-induced genes reveals new roles for cGAS in innate immunity

The type I interferon (IFN) response protects cells from viral infection by inducing hundreds of interferon-stimulated genes (ISGs), some of which encode direct antiviral effectors. Recent screening studies have begun to catalogue ISGs with antiviral activity against several RNA and DNA viruses. However, antiviral ISG specificity across multiple distinct classes of viruses remains largely unexplored. Schoggins et al. used an ectopic expression assay to screen a library of more than 350 human ISGs for effects on 14 viruses representing 7 families and 11 genera. The authors show that 47 genes inhibited one or more viruses, and 25 genes enhanced virus infectivity. Comparative analysis revealed that the screened ISGs targeted positive-sense single-stranded RNA viruses more effectively than negative-sense single-stranded RNA viruses. Gene clustering highlights the cytosolic DNA sensor cyclic GMP-AMP synthase (*cGAS*, also known as *MB21D1*) as a gene whose expression also broadly inhibits several RNA viruses. In vitro, lentiviral delivery of enzymatically active cGAS triggers a STING-dependent, IRF3-mediated antiviral program that functions independently of canonical IFN/STAT1 signaling. In vivo, genetic ablation of murine cGAS revealed its requirement in the antiviral response to two DNA viruses, and an unappreciated contribution to the innate control of an RNA virus. These studies uncover new paradigms for the preferential specificity of IFN-mediated antiviral pathways spanning several virus families.

Nature 201; 505: 691

Eitan Israel

Capsule

Sun exposure can lower blood pressure

Liu and collaborators investigated the effects of UVA exposure – equivalent to 30 minutes of sun exposure at noon on a clear day in Southern Europe – on 24 healthy volunteers, controlling for both temperature and dietary nitrate. The researchers found plasma nitrate and nitrite changes as well as reductions in blood pressure, that were consistent with the release of NO from skin storage. These observations support a mechanism for the modulation of systemic NO bioactivity and a possible role of the skin in cardiovascular homeostasis. Clinically speaking, tests to evaluate blood pressure response to repeated UVA exposure with respect to age, gender, and disease states (such as hypertension) are needed. But if the blood pressure-reducing effects of UVA light hold up in larger trials, the authors suggested that a reevaluation of the risks and benefits associated with sun exposure might be in order. Still, this work is in the early stage. For now, people should not take these findings as any mitigation against the well-founded recommendation by dermatologists to avoid excessive sun exposure.

J Invest Dermatol 2014; doi: 10.1038/jid.2014.27

Eitan Israeli

Capsule

Transmissible dog cancer genome reveals the origin and history of an ancient cell lineage

Canine transmissible venereal tumor (CTVT) is the oldest known somatic cell lineage. It is a transmissible cancer that propagates naturally in dogs. CTVT is an unusual form of cancer because the infectious agent is not a virus or bacterium but the tumor cells themselves, which are passed from one dog to another during coitus. Murchison et al. sequenced the genomes of two CTVT tumors and found that CTVT has acquired 1.9 million somatic substitution mutations and bears evidence of exposure to ultraviolet light. CTVT is remarkably stable and lacks subclonal heterogeneity despite thousands of rearrangements, copy-number changes, and retrotransposon insertions. More than 10,000 genes carry non-synonymous variants, and 646 genes have been lost. CTVT first arose in a dog with low genomic heterozygosity that may have lived about 11,000 years ago. The cancer spawned by this individual dispersed across continents about 500 years ago. These results provide a genetic identikit of an ancient dog and demonstrate the robustness of mammalian somatic cells to survive for millennia despite a massive mutation burden.

Science 2014; 343: 437

Eitan Israeli

Capsule

Vascular endothelium and tissue regeneration

The vascular endothelium is increasingly being recognized to play a role during organogenesis and tissue regeneration. Hu et al. found that rapid down-regulation of endothelial-derived angiopoietin-2 following partial hepatectomy releases an endogenous transforming growth factor β1-driven paracrine proliferative brake on hepatocytes. Later, recovery of endothelial angiopoetin-2 expression facilitates angiogenesis in the regenerating liver in a vascular endothelial growth factor receptor 2-dependent manner. Thus, the vascular endothelium may help to orchestrate tissue regeneration through the control of inhibitory and stimulatory pathways in parenchymal and non-parenchymal cells.

Science 2014; 343: 416

Eitan Israeli

Capsule

New substance that attacks antibiotic-resistant bacteria

A group of Israeli-U.S. researchers has isolated a protein that kills bacteria – a first step toward developing a substitute for antibiotics. This substance prevents bacteria from dividing, thus destroying them and combating infection. In recent decades the increased resistance of bacteria to antibiotics has left modern medicine sometimes powerless to fight infection and bacterial diseases. The World Health Organization has defined this problem as one of the three greatest threats to public health. Dr. Rotem Sorek of Weizmann Institute of Sciences' molecular genetics department considers this the first major breakthrough in the war between bacteriophages and bacteria. The Russians developed the use of bacteriophages to fight infection during the Cold War. Sorek notes: "Every Russian was issued ampoules containing phages. The ampoules were to be used against intestinal and other kinds of infections." The use of bacteriophages spread to the west in the 1990s, partly thanks to scientists who immigrated to western countries from the former Soviet Union.

Israel High-Tech & Investment Report December 2013

Capsule

The complete genome sequence of a Neanderthal from the Altai Mountains

Prufer el al. presented a high quality genome sequence of a Neanderthal woman from Siberia. They show that her parents were related at the level of half-siblings and that mating among close relatives was common among her recent ancestors. The authors also sequenced the genome of a Neanderthal from the Caucasus to low coverage. An analysis of the relationships and population history of available archaic genomes and 25 present-day human genomes shows that several gene flow events occurred among Neanderthals, Denisovans and early modern humans, possibly including gene flow into Denisovans from an unknown archaic group. Thus, interbreeding, albeit of low magnitude, occurred among many hominin groups in the Late Pleistocene. In addition, the high quality Neanderthal genome allows us to establish a definitive list of substitutions that became fixed in modern humans after their separation from the ancestors of Neanderthals and Denisovans.

Nature 2014; 505: 43

Eitan Israeli