Capsule

New discovery could yield MS cure

Researchers studying diabetic mice have made leaps towards a cure for multiple sclerosis (MS). The Tel Aviv University team found that when mice with type 1 diabetes are injected with myelin protein they experience periods of relapse and remitting disability associated with brain lesions in humans who have MS. For the first time scientists have been able to monitor this brain lesion process using magnetic resonance imaging. It is believed that the discovery will lead to more effective treatments for MS and, with advances continuing to be made in MS research, that the condition will one day be controllable – like HIV/AIDS. Recent studies have identified about 20 genes associated with the development of MS and it is estimated that in the next two years there will be around 80 associated genes that will provide an accurate picture of the disease's genetic basis. Once this is achieved, development treatments for MS will be far simpler and effective.

Israel High Tech & Investment Report

What I am remains to be proved by the good I do

Mary Baker Eddy (1821-1910), founder of Christian Science, a Protestant American system of religious thought

Capsule

Generating inflammasomes

Inflammasomes are large multiprotein complexes that assemble in response to infection and are also involved in the pathogenesis of a variety of other diseases, including type 2 diabetes and atherosclerosis. The assembly of the inflammasome triggers an inflammatory cascade that results in the activation of caspase-1 and production of the cytokines interleukin-1 and -18. Very little, however, is known about the specific signals that trigger inflammasome assembly. Shenoy et al. now show that guanylate binding protein 5 (GBP5) promotes the assembly of the NLRP3-containing inflammasome in response to certain activation signals, such as pathogenic bacteria and adenosine triphosphate, but not others, like crystalline stimuli. Mice deficient in GBP5 exhibited impaired caspase-1 activation and production of cytokines. NLRP3 inflammasome-dependent responses to pathogenic bacteria and inflammatory stimuli were also impaired in mice lacking GBP5.

Science 2012; 336: 481

Eitan Israeli

Every increased possession loads us with new weariness

John Ruskin (1819-1900), leading English art critic of the Victorian era, also an art patron, draughtsman, watercolorist, a prominent social thinker and philanthropist

Capsule

Ovarian cancer origins

One to 2% of women will be diagnosed with ovarian cancer in their lifetimes. As a result, there is great interest in better understanding the molecular and cellular events that drive the development of this cancer. In fact, whether the ovary or fallopian tube gives rise to serous ovarian cancer, the subtype that causes 70% of ovarian cancer deaths, is still unknown. Kim et al. generated mice with reproductive tract-specific deletions in Dicer, the enzyme that converts pre-microRNAs to mature microRNAs, and Pten, a tumor suppressor. They found that serous ovarian carcinomas developed from the fallopian tube and then metastasized elsewhere, killing all double knockout mice by 6 to 12 months of age. Mice singly deficient in these proteins, however, did not show tumor development in the reproductive system. Histological analysis revealed that abnormal cell proliferation started in the stromal compartment of the fallopian tube rather than the epithelial layer, with the cells undergoing a stromal-to-epithelial transition. The phenotypic, histological and molecular characteristics of the cancers that developed in the double knockout mice were similar to those seen in humans. These mice may therefore provide a useful model system for studying serous ovarian cancer.

Proc Natl Acad Sci USA 2012; 109: 3921

Eitan Israeli

Capsule

Cell attachment protein VP8* of a human rotavirus specifically interacts with A-type histo-blood group antigen

As with many other viruses, the initial cell attachment of rotaviruses, which are the major causative agent of infantile gastroenteritis, is mediated by interactions with specific cellular glycans. The distally located VP8* domain of the rotavirus spike protein VP4 mediates such interactions. The existing paradigm is that 'sialidase-sensitive' animal rotavirus strains bind to glycans with terminal sialic acid (Sia), whereas 'sialidase-insensitive' human rotavirus strains bind to glycans with internal Sia such as GM1. Although the involvement of Sia in the animal strains is firmly supported by crystallographic studies, it is not yet known how VP8* of human rotaviruses interacts with Sia and whether their cell attachment necessarily involves sialoglycans. Hu et al. show that VP8* of a human rotavirus strain specifically recognizes A-type histo-blood group antigen (HBGA) using a glycan array screen comprised of 511 glycans, and that virus infectivity in HT-29 cells is abrogated by anti-A-type antibodies as well as significantly enhanced in Chinese hamster ovary cells genetically modified to express the A-type HBGA, providing a novel paradigm for initial cell attachment of human rotavirus. HBGAs are genetically determined glycoconjugates present in mucosal secretions, epithelia and on red blood cells, and are recognized as susceptibility and cell attachment factors for gastric pathogens like *Helicobacter pylori* and noroviruses. These crystallographic studies show that the A-type HBGA binds to the human rotavirus VP8* at the same location as the Sia in the VP8* of animal rotavirus, and suggest how subtle changes within the same structural framework allow for such receptor switching. These results raise the possibility that host susceptibility to specific human rotavirus strains and pathogenesis are influenced by genetically controlled expression of different HBGAs among the world's population.

Nature 2012; 485: 256

Eitan Israeli

The greatest of faults, I should say, is to be conscious of none

Thomas Carlyle (1795-1881), Scottish satirical writer, essayist, historian and teacher

Capsule

Experimental adaptation of an influenza H5 HA confers respiratory droplet transmission to a reassortant H5 HA/H1N1 virus in ferrets

Highly pathogenic avian H5N1 influenza A viruses occasionally infect humans, but currently do not transmit efficiently among humans. The viral hemagglutinin (HA) protein is a known host-range determinant as it mediates virus binding to host-specific cellular receptors. Imai et al. assessed the molecular changes in HA that would allow a virus possessing subtype H5 HA to be transmissible among mammals. The authors identified a reassortant H5 HA/H1N1 virus – comprising H5 HA (from an H5N1 virus) with four mutations and the remaining seven gene segments from a 2009 pandemic H1N1 virus – that was capable of droplet transmission in a ferret model. The transmissible H5 reassortant virus preferentially recognized human-type receptors, replicated efficiently in ferrets, caused lung lesions and weight loss, but was not highly pathogenic and did not cause mortality. These results indicate that H5 HA can convert to an HA that supports efficient viral transmission in mammals; however, the authors do not know whether the four mutations in the H5 HA identified here would render a wholly avian H5N1 virus transmissible. The genetic origin of the remaining seven viral gene segments may also critically contribute to transmissibility in mammals. Nevertheless, as H5N1 viruses continue to evolve and infect humans, receptor-binding variants of H5N1 viruses with pandemic potential, including avian-human reassortant viruses as tested here, may emerge. These findings emphasize the need to prepare for potential pandemics caused by influenza viruses possessing H5 HA, and will help individuals conducting surveillance in regions with circulating H5N1 viruses to recognize key residues that predict the pandemic potential of isolates, which will inform the development, production and distribution of effective countermeasures.

Nature 2012; doi:10.1038/nature10831

Eitan Israeli

It was in my heart to help a little because I was helped much

Kalil Gibran (1883-1931), Lebanese-American artist, poet and writer. He is chiefly known in the English-speaking world for his 1923 book *The Prophet*, an early example of inspirational fiction including a series of philosophical essays that became extremely popular in the 1960s counterculture. Gibran is the third best-selling poet of all time, behind Shakespeare and Lao-Tzu

Capsule

Clonally dominant cardiomyocytes direct heart morphogenesis

As vertebrate embryos develop to adulthood, their organs undergo marked changes in size and tissue architecture. The heart acquires muscle mass and matures structurally to fulfill increasing circulatory needs, a process that is incompletely understood. Gupta and collaborators used multicolor clonal analysis to define the contributions of individual cardiomyocytes as the zebrafish heart undergoes morphogenesis from a primitive embryonic structure into its complex adult form. The authors found that the single-cardiomyocyte-thick wall of the juvenile ventricle forms by lateral expansion of several dozen cardiomyocytes into muscle patches of variable sizes and shapes. As juvenile zebrafish mature into adults, this structure becomes fully enveloped by a new lineage of cortical muscle. Adult cortical muscle originates from a small number of cardiomyocytes – an average of approximately eight per animal – that display clonal dominance reminiscent of stem cell populations. Cortical cardiomyocytes initially emerge from internal myofibers that in rare events breach the juvenile ventricular wall, and then expand over the surface. Our results illuminate the dynamic proliferative behaviors that generate adult cardiac structure, revealing clonal dominance as a key mechanism that shapes a vertebrate organ.

Nature 2012; 484: 479

Eitan Israeli

Too often we underestimate the power of a touch, a smile, a kind word, a listening ear, an honest compliment, or the smallest act of caring, all of which have the potential to turn a life around

Leo Buscaglia (1924-1998), American author and motivational speaker, and professor in the Department of Special Education at the University of Southern California; also known as “Dr. Love”

Capsule

Prion-like behavior and tau-dependent cytotoxicity of pyroglutamylated amyloid-β DOI:

Extracellular plaques of amyloid-β and intraneuronal neurofibrillary tangles made from tau are the histopathological signatures of Alzheimer's disease. Plaques comprise amyloid-β fibrils that assemble from monomeric and oligomeric intermediates, and are prognostic indicators of Alzheimer's disease. Despite the importance of plaques to Alzheimer's disease, oligomers are considered to be the principal toxic forms of amyloid-β. Interestingly, many adverse responses to amyloid-β, such as cytotoxicity, microtubule loss, impaired memory and learning, and neuritic degeneration, are greatly amplified by tau expression. Amino-terminally truncated, pyroglutamylated (pE) forms of amyloid-β are strongly associated with Alzheimer's disease, are more toxic than amyloid-β, residues 1–42 (Aβ1–42) and Aβ1–40, and have been proposed as initiators of Alzheimer's disease pathogenesis. Nussbaum and co-researchers report a mechanism by which pE-Aβ may trigger Alzheimer's disease. Aβ3(pE)–42 co-oligomerizes with excess Aβ1–42 to form metastable low-n oligomers (LNOs) that are structurally distinct and far more cytotoxic to cultured neurons than comparable LNOs made from Aβ1–42 alone. Tau is required for cytotoxicity, and LNOs comprising 5% Aβ3(pE)–42 plus 95% Aβ1–42 (5% pE-Aβ) seed new cytotoxic LNOs through multiple serial dilutions into Aβ1–42 monomers in the absence of additional Aβ3(pE)–42. LNOs isolated from human Alzheimer's disease brain contained Aβ3(pE)–42, and enhanced Aβ3(pE)–42 formation in mice triggered neuron loss and gliosis at 3 months, but not in a tau-null background. We conclude that Aβ3(pE)–42 confers tau-dependent neuronal death and causes template-induced misfolding of Aβ1–42 into structurally distinct LNOs that propagate by a prion-like mechanism. Our results raise the possibility that Aβ3(pE)–42 acts similarly at a primary step in Alzheimer's disease pathogenesis.

Nature 2012; doi:10.1038/nature11060

Eitan Israeli

People see God every day. They just don't recognize him

Pearl Bailey (1918-1990), African-American actress and singer

Capsule

Lowering LDL-cholesterol to levels below current recommendations may confer even more health benefits than statins alone

The use of statins to lower plasma levels of low density lipoprotein (LDL)-cholesterol can reduce the risk of cardiovascular disease by an estimated 30–40%. Yet some experts have argued that lowering LDL-cholesterol to levels below current recommendations – by co-administering drugs that act by a complementary mechanism, for example – may confer even more health benefits than statins alone. PCSK9 (proprotein convertase subtilisin/kexin type 9) is an appealing new drug target because it keeps plasma cholesterol levels high by promoting degradation of the receptor on liver cells that removes cholesterol from the blood. Interestingly, a small percentage of humans carry mutations in PCSK9 that reduce its activity and these individuals have a lower risk of heart disease, suggesting that therapeutic inhibition of PCSK9 will be safe. Stein et al. conducted small phase-1 trials of a human PCSK9 monoclonal antibody (REGN727) given to healthy volunteers and to individuals with familial and non-familial hypercholesterolemia. Injection of REGN727 induced no serious adverse effects in these short-duration trials, and in all groups the antibody significantly reduced LDL-cholesterol levels as compared with placebo.

N Engl J Med 2012; 366: 1108

Eitan Israeli

"Those who cannot forgive others break the bridge over which they themselves must pass"

Confucius (c. 551-478 BCE), Chinese philosopher and teacher

Capsule

The kinase Btk negatively regulates the production of reactive oxygen species and stimulation-induced apoptosis in human neutrophils

The function of the kinase Btk in neutrophil activation is largely unexplored. Honda et al. found that Btk-deficient neutrophils had more production of reactive oxygen species (ROS) after engagement of Toll-like receptors (TLRs) or receptors for tumor necrosis factor (TNF), which was associated with more apoptosis and was reversed by transduction of recombinant Btk. Btk-deficient neutrophils in the resting state showed hyperphosphorylation and activation of phosphatidylinositol-3-OH kinase (PI(3)K) and protein tyrosine kinases (PTKs) and were in a 'primed' state with plasma membrane-associated GTPase Rac2. In the absence of Btk, the adaptor Mal was associated with PI(3)K and PTKs at the plasma membrane, whereas in control resting neutrophils, Btk interacted with and confined Mal in the cytoplasm. These data identify Btk as a critical gatekeeper of neutrophil responses.

Nature Immunol 2012; 13: 369

Eitan Israeli

"Writing is easy. All you do is stare at a blank sheet of paper until drops of blood form on your forehead"

Gene Fowler (1890-1960), American journalist, author and dramatist

Capsule

IL-17A produced by αβ T cells drives airway hyper-responsiveness in mice and enhances mouse and human airway smooth muscle contraction

Emerging evidence suggests that the T helper 17 (T_H17) subset of αβ T cells contributes to the development of allergic asthma. Kudo et al. found that mice lacking the αvβ8 integrin on dendritic cells did not generate T_H17 cells in the lung and were protected from airway hyper-responsiveness in response to house dust mite and ovalbumin sensitization and challenge. Because loss of T_H17 cells inhibited airway narrowing without any obvious effects on airway inflammation or epithelial morphology, we examined the direct effects of T_H17 cytokines on mouse and human airway smooth muscle function. Interleukin-17A (IL-17A), but not IL-17F or IL-22, enhanced contractile force generation of airway smooth muscle through an IL-17 receptor A (IL-17RA)-IL-17RC, nuclear factor κ light chain enhancer of activated B cells (NF-κB)-ras homolog gene family, member A (RhoA)-Rho-associated coiled-coil containing protein kinase 2 (ROCK2) signaling cascade. Mice lacking integrin αvβ8 on dendritic cells showed impaired activation of this pathway after ovalbumin sensitization and challenge, and the diminished contraction of the tracheal rings in these mice was reversed by IL-17A. These data indicate that the IL-17A produced by T_H17 cells contributes to allergen-induced airway hyper-responsiveness through direct effects on airway smooth muscle.

Nature Med 2012; 18: 547

Eitan Israeli

"The most erroneous stories are those we think we know best – and therefore never scrutinize or question"

Stephen Jay Gould (1941-2002), American paleontologist, evolutionary biologist and historian of science and one of the most influential and widely read writers of popular science of his generation

Capsule

In need of nutrients for gastrointestinal infections

Gut pathogens such as *Escherichia coli* and *Salmonella* are faced with several hurdles when trying to establish an infection: the recruitment of immune cells, the secretion of antimicrobial factors, and competition in the form of the billions of commensal bacteria that normally reside in our guts. As a result, the pathogens need to have a few tricks up their sleeve. Liu et al. report on one such example, used by *Salmonella enterica* serovar *Typhimurium*, a pathogen that causes severe gastroenteritis in humans. In response to *S. typhimurium* infection, neutrophils are recruited to the gut in mice and produce the antimicrobial protein calprotectin. Calprotectin functions by sequestering essential metals, such as zinc, thus limiting an important nutrient source for the invading pathogen. *S. typhimurium* can overcome this and compete with the commensal flora, however, because it expresses a high affinity zinc transporter. Strains that lacked this transporter did not grow as well in the inflamed gut but were not at a disadvantage in the absence of inflammation. These results suggest that nutrient availability is a key factor in the establishment of gastrointestinal infections.

Cell Host Microbe 2012; 11: 227

Eitan Israeli

Capsule

Relationship between disease activity and type 1 interferon in dermatomyositis and polymyositis

Greenberg et al. report on 24 patients with dermatomyositis (DM) or polymyositis (PM) who were followed for up to 6 years (mean 1.9 years) at 2–7 follow-up visits while receiving standard clinical care. Clinical data and blood samples collected at 80 patient visits were used for the analysis of cytokine-induced gene expression for the signaling pathways of type 1 interferon (IFN), tumor necrosis factor-α, interleukin (IL)-1β, granulocyte-monocyte colony-stimulating factor, IL-10 and IL-13. A type 1 IFN signature score, but not other cytokine signature scores in the blood of patients with DM or PM, correlated highly with disease activity, decreased significantly with immunomodulatory therapies and showed concordant changes with major changes in disease activity. Type 1 IFN signature score in the blood correlates with disease activity in longitudinal follow-up of individual patients with DM or PM. The type 1 IFN-inducible gene transcripts in the blood have potential utility for monitoring disease activity in patients with DM or PM.

Genes Immun 2012; 13: 207

Eitan Israeli

Capsule

Commensal bacteria-derived signals regulate basophil hematopoiesis and allergic inflammation

Commensal bacteria that colonize mammalian barrier surfaces are reported to influence T helper type 2 (T_H2) cytokine-dependent inflammation and susceptibility to allergic disease, although the mechanisms that underlie these observations are poorly understood. Hill and colleagues found that deliberate alteration of commensal bacterial populations via oral antibiotic treatment resulted in elevated serum immunoglobulin (Ig) E concentrations, increased steady-state circulating basophil populations and exaggerated basophil-mediated T_H2 cell responses and allergic inflammation. Elevated serum IgE levels correlated with increased circulating basophil populations in mice and subjects with hyperimmunoglobulinemia E syndrome. Furthermore, B cell-intrinsic expression of myeloid differentiation factor 88 (MyD88) was required to limit serum IgE concentrations and circulating basophil populations in mice. Commensal-derived signals were found to influence basophil development by limiting proliferation of bone marrow-resident precursor populations. Collectively, these results identified a previously unrecognized pathway through which commensal-derived signals influence basophil hematopoiesis and susceptibility to T_H2 cytokine-dependent inflammation and allergic disease.

Nature Med 2012; 18: 538

Eitan Israeli

"The only gift is giving to the poor
All else is exchange"

Thiruvalluvar (c. 30 BCE), Tamil poet and philosopher

Capsule

NLRP4 negatively regulates type I interferon signaling by targeting the kinase TBK1 for degradation via the ubiquitin ligase DTX4

Stringent control of the type I interferon signaling pathway is important for maintaining host immune responses and homeostasis, yet the molecular mechanisms responsible for its tight regulation are still poorly understood. Cui and group report that the pattern-recognition receptor NLRP4 regulated the activation of type I interferon mediated by double-stranded RNA or DNA by targeting the kinase TBK1 for degradation. NLRP4 recruited the E3 ubiquitin ligase DTX4 to TBK1 for Lys48 (K48)-linked polyubiquitination at Lys670, which led to degradation of TBK1. Knockdown of either DTX4 or NLRP4 abrogated K48-linked ubiquitination and degradation of TBK1 and enhanced the phosphorylation of TBK1 and the transcription factor IRF3. These results identify a previously unrecognized role for NLRP4 in the regulation of type I interferon signaling and provide molecular insight into the mechanisms by which NLRP4-DTX4 targets TBK1 for degradation.

Nature Immunol 2012; 13: 387

Eitan Israeli

Flatter me, and I may not believe you. Criticize me, and I may not like you. Ignore me, and I may not forgive you. Encourage me, and I will not forget you

William Arthur Ward (1921-1994), American college administrator and writer and one of the most quoted writers of inspirational maxims

Capsule

The leukocyte integrin antagonist Del-1 inhibits IL-17-mediated inflammatory bone loss

Aging is linked to greater susceptibility to chronic inflammatory diseases, several of which, including periodontitis, involve neutrophil-mediated tissue injury. Eskan and fellow researchers found that aging-associated periodontitis was accompanied by lower expression of Del-1, an endogenous inhibitor of neutrophil adhesion dependent on the integrin LFA-1, and by reciprocal higher expression of interleukin 17 (IL-17). Consistent with that, IL-17 inhibited gingival endothelial cell expression of Del-1, thereby promoting LFA-1-dependent recruitment of neutrophils. Young Del-1-deficient mice developed spontaneous periodontitis that featured excessive neutrophil infiltration and IL-17 expression; disease was prevented in mice doubly deficient in Del-1 and LFA-1 or in Del-1 and the IL-17 receptor. Locally administered Del-1 inhibited IL-17 production, neutrophil accumulation and bone loss. Therefore, Del-1 suppressed LFA-1-dependent recruitment of neutrophils and IL-17-triggered inflammatory pathology and may thus be a promising therapeutic agent for inflammatory diseases.

Nature Immunol 2012; 13: 465

Eitan Israeli

Capsule

Yeast prion protein responds to an environmental stressor

It is not clear if prion induction in yeast is truly linked to physiological roles. Suzuki et al. show that the yeast prion protein Mod5 (a transfer RNA isopentenyltransferase) responds to an environmental stressor by converting to an aggregated amyloid form, which leads to phenotypic changes in cell metabolism and drug resistance. Introduction of Mod5 amyloid into yeast resulted in the formation of a dominantly heritable prion state (*MOD*$^{+}$), in which Mod5 is aggregated. (*MOD*$^{+}$) yeast showed high ergosterol levels and acquired resistance to several antifungal agents. Selective pressure by antifungal drugs on non-prion (*mod*$^{-}$) yeast induced the (*MOD*$^{+}$) prion state, formation of amyloid, and increased cell survival.

Science 2012; 336: 355

Eitan Israeli

"Life is what happens when we are making other plans

Allen Saunders (1899-1986), American writer, journalist and cartoonist"