Capsule

Killer cell immunoglobulin-like receptor 3DL1-mediated recognition of human leukocyte antigen B

Members of the killer cell immunoglobulin-like receptor (KIR) family, a large group of polymorphic receptors expressed on natural killer (NK) cells, recognize particular peptide-laden human leukocyte antigen (pHLA) class I molecules and have a pivotal role in innate immune responses. Allelic variation and extensive polymorphism within the three-domain KIR family (KIR3D, domains D0–D1–D2) affects pHLA binding specificity and is linked to the control of viral replication and the treatment outcome of certain hematological malignancies. Vivian et al. describe the structure of a human KIR3DL1 receptor bound to HLA-B*5701 complexed with a self-peptide. KIR3DL1 clamped around the carboxy-terminal end of the HLA-B*5701 antigen-binding cleft, resulting in two discontinuous footprints on the pHLA. First, the D0 domain, a distinguishing feature of the KIR3D family, extended towards β2-microglobulin and abutted a region of the HLA molecule with limited polymorphism, thereby acting as an 'innate HLA sensor' domain. Second, whereas the D2–HLA-B*5701 interface exhibited a high degree of complementarity, the D1–pHLA-B*5701 contacts were suboptimal and accommodated a degree of sequence variation both within the peptide and the polymorphic region of the HLA molecule. Although the two-domain KIR (KIR2D) and KIR3DL1 docked similarly onto HLA-C and HLA-B respectively, the corresponding D1-mediated interactions differed markedly, thereby providing insight into the specificity of KIR3DL1 for discrete HLA-A and HLA-B allotypes. Collectively, in association with extensive mutagenesis studies at the KIR3DL1–pHLA-B*5701 interface, the authors provide a framework for understanding the intricate interplay between peptide variability, KIR3D and HLA polymorphism in determining the specificity requirements of this essential innate interaction that is conserved across primate species.

Nature 2011; 479: 401

Eitan Israeli

Capsule

Dendritic cells control lymphocyte entry to lymph nodes through high endothelial venules

While patrolling the body in search of foreign antigens, naive lymphocytes continuously circulate from the blood, through the lymph nodes, into the lymphatic vessels and back to the blood. This process, called lymphocyte recirculation, provides the body with effective immune surveillance for foreign invaders and for alterations to the body's own cells. However, the mechanisms that regulate lymphocyte recirculation during homeostasis remain incompletely characterized. Moussion et al. show that dendritic cells (DCs), which are well known for their role in antigen presentation to T lymphocytes, control the entry of naive lymphocytes to lymph nodes by modulating the phenotype of high endothelial venules (HEVs), which are blood vessels specialized in lymphocyte recruitment. The authors found that in vivo depletion of CD11c+ DCs in adult mice over a 1 week period induces a reduction in the size and cellularity of the peripheral and mucosal lymph nodes. In the absence of DCs, the mature adult HEV phenotype reverts to an immature neonatal phenotype, and HEV-mediated lymphocyte recruitment to lymph nodes is inhibited. Co-culture experiments showed that the effect of DCs on HEV endothelial cells is direct and requires lymphotoxin-β receptor-dependent signaling. DCs express lymphotoxin, and DC-derived lymphotoxin is important for lymphocyte homing to lymph nodes in vivo. Together, these results reveal a previously unsuspected role for DCs in the regulation of lymphocyte recirculation during immune surveillance.

Nature 2011; 479: 542

Eitan Israeli

"The wing of a butterfly, well described, would bring me closer to divinity than a volume of metaphysics"

Denis Diderot (1713-1784), French philosopher, art critic and writer, and a prominent figure during the Enlightenment

Capsule

Development of therapies to treat lung pathologies

Although few organisms are able to fully regenerate new tissue after injury, tissue can often be repaired. The specific mechanisms that drive such repair, however, are not fully elucidated. Two studies used different models of lung injury in mice to uncover mechanisms that drive lung repair and regeneration. Kumar et al. (*Cell* 2011; 147: 525) infected mice with influenza A virus, severe cases of which can cause extensive, life-threatening lung pathology in humans. Despite early damage to lungs after infection, they had essentially returned to normal 3 months later. Repair was initiated by stem cells that proliferated in the bronchiolar epithelium and migrated to sites of damage, where they formed clusters around bronchioles and differentiated into alveolar structures destroyed by the infection. Taking a different approach, Ding et al. (*Cell* 2011; 147: 539) surgically removed the left lung of mice, which is known to drive the formation of more alveoli in the remaining lung. Pulmonary capillary endothelial cells initiated this regeneration by producing angiocrine factors, which promoted the proliferation of epithelial progenitor cells. Studies such as these may aid in the development of therapies to treat lung pathologies.

Eitan Israeli

Capsule

Crosstalk between B lymphocytes, microbiota and the intestinal epithelium governs immunity versus metabolism in the gut

Using a systems biology approach, Shulzhenko et al. discovered and dissected a three-way interaction between the immune system, the intestinal epithelium and the microbiota. The authors found that, in the absence of B cells, or of immunoglobulin A, and in the presence of the microbiota, the intestinal epithelium launches its own protective mechanisms, upregulating interferon-inducible immune response pathways and simultaneously repressing Gata4-related metabolic functions. This shift in intestinal function leads to lipid malabsorption and decreased deposition of body fat. Network analysis revealed the presence of two interconnected epithelial-cell gene networks, one governing lipid metabolism and another regulating immunity, that were inversely expressed. Gene expression patterns in gut biopsies from individuals with common variable immunodeficiency or with HIV infection and intestinal malabsorption were very similar to those of the B cell-deficient mice, providing a possible explanation for a longstanding enigmatic association between immunodeficiency and defective lipid absorption in humans.

Nature Med 2011; 17: 1585

Eitan Israeli

Capsule

Mutations causing syndromic autism define an axis of synaptic pathophysiology

Tuberous sclerosis complex and fragile X syndrome are genetic diseases characterized by intellectual disability and autism. Because both syndromes are caused by mutations in genes that regulate protein synthesis in neurons, it has been hypothesized that excessive protein synthesis is one core pathophysiological mechanism of intellectual disability and autism. Using electrophysiological and biochemical assays of neuronal protein synthesis in the hippocampus of Tsc2+/– and Fmr1–/y mice, Auerbach et al. show that synaptic dysfunction caused by these mutations actually falls at opposite ends of a physiological spectrum. Synaptic, biochemical and cognitive defects in these mutants are corrected by treatments that modulate metabotropic glutamate receptor 5 in opposite directions, and deficits in the mutants disappear when the mice are bred to carry both mutations. Thus, normal synaptic plasticity and cognition occur within an optimal range of metabotropic glutamate-receptor-mediated protein synthesis, and deviations in either direction can lead to shared behavioral impairments.

Nature 2011; 480: 63

Eitan Israeli

Capsule

Commensal microbiota and myelin autoantigen cooperate to trigger autoimmune demyelination

Active multiple sclerosis lesions show inflammatory changes suggestive of a combined attack by autoreactive T and B lymphocytes against brain white matter. These pathogenic immune cells derive from progenitors that are normal, innocuous components of the healthy immune repertoire but become autoaggressive upon pathological activation. The stimuli triggering this autoimmune conversion have been commonly attributed to environmental factors, in particular microbial infection. However, using the relapsing-remitting mouse model of spontaneously developing experimental autoimmune encephalomyelitis, Berer and team show that the commensal gut flora – in the absence of pathogenic agents – is essential in triggering immune processes, leading to a relapsing-remitting autoimmune disease driven by myelin-specific CD4+ T cells. The authors show further that recruitment and activation of autoantibody-producing B cells from the endogenous immune repertoire depends on availability of the target autoantigen, myelin oligodendrocyte glycoprotein (MOG), and commensal microbiota. These observations identify a sequence of events triggering organ-specific autoimmune disease and these processes may offer novel therapeutic targets.

Nature 2011; 479: 538

Eitan Israeli

Capsule

A SUMOylation-defective MITF germline mutation predisposes to melanoma and renal carcinoma

So far, no common environmental and/or phenotypic factor has been associated with melanoma and renal cell carcinoma (RCC). The known risk factors for melanoma include sun exposure, pigmentation and nevus phenotypes; risk factors associated with RCC include smoking, obesity and hypertension. A recent study of coexisting melanoma and RCC in the same patients supports a genetic predisposition underlying the association between these two cancers. The microphthalmia-associated transcription factor (MITF) has been proposed to act as a melanoma oncogene; it also stimulates the transcription of hypoxia inducible factor (HIF1A), whose pathway is targeted by kidney cancer susceptibility genes. Bertolotto and co-workers therefore proposed that MITF might have a role in conferring a genetic predisposition to co-occurring melanoma and RCC, and they identified a germline missense substitution in MITF (Mi-E318K) that occurred at a significantly higher frequency in genetically enriched patients affected with melanoma, RCC or both cancers, when compared with controls. Overall, Mi-E318K carriers had a higher than fivefold increased risk of developing melanoma, RCC or both cancers. Codon 318 is located in a small-ubiquitin-like modifier (SUMO) consensus site (ΨKXE) and Mi-E318K severely impaired SUMOylation of MITF. Mi-E318K enhanced MITF protein binding to the HIF1A promoter and increased its transcriptional activity compared to wild-type MITF. Further, the authors observed a global increase in Mi-E318K-occupied loci. In an RCC cell line, gene expression profiling identified a Mi-E318K signature related to cell growth, proliferation and inflammation. Lastly, the mutant protein enhanced melanocytic and renal cell clonogenicity, migration and invasion, consistent with a gain-of-function role in tumorigenesis. Our data provide insights into the link between SUMOylation, transcription and cancer.

Nature 2011; 480: 94

Eitan Israeli

"It is a truism that almost any sect, cult, or religion will legislate its creed into law if it acquires the political power to do so"

Robert A. Heinlein (1907-1988) , American science-fiction writer

Capsule

Enforced viral replication activates adaptive immunity and is essential for the control of a cytopathic virus

The innate immune system limits viral replication via type I interferon and also induces the presentation of viral antigens to cells of the adaptive immune response. Using infection of mice with vesicular stomatitis virus, Honke et al. analyzed how the innate immune system inhibits viral propagation but still allows the presentation of antigen to cells of the adaptive immune response. The researchers found that expression of the gene encoding the inhibitory protein Usp18 in metallophilic macrophages led to lower type I interferon responsiveness, thereby allowing locally restricted replication of virus. This was essential for the induction of adaptive antiviral immune responses and, therefore, for preventing the fatal outcome of infection. The authors conclude that enforced viral replication in marginal zone macrophages was an immunological mechanism that ensured the production of sufficient antigen for effective activation of the adaptive immune response.

Nature Immunol 2011; 13: 51

Eitan Israeli

Capsule

Treg cells are important regulators of immune homeostasis

Many people with autoimmune diseases experience disease flares in which disease symptoms worsen. These flares often subside for a while, only to return again. Rosenblum and collaborators sought to understand the immunological basis for this phenomenon using a mouse model of inducible T cell-driven autoimmunity in the skin that resolves spontaneously. Disease induction was accompanied by an initial expansion of effector T cells in the skin that was followed by an expansion of regulatory T cells (Tregs). Although Treg cells were present in the skin before disease induction, they proliferated in response to autoantigen expression and were more potent immune suppressors. Moreover, disease resolution was critically dependent on Treg cells. Treg cells persisted in the skin in high numbers after disease resolution and were better able to control autoimmune symptoms when autoantigens were reexpressed in the skin. These results demonstrate that Treg cells are important regulators of immune homeostasis and may be critical for containing disease flares often seen in autoimmune diseases.

Nature 2011; 10.1038/*nature* 10664

Eitan Israeli

"To be capable of embarrassment is the beginning of moral consciousness. Honor grows from qualms"

John Leonard (1939-2008), American literary, television, film and cultural critic

Capsule

Alternatively activated macrophages produce catecholamines to sustain adaptive thermogenesis

All homeotherms use thermogenesis to maintain their core body temperature, ensuring that cellular functions and physiological processes can continue in cold environments. In the prevailing model of thermogenesis, when the hypothalamus senses cold temperatures it triggers sympathetic discharge, resulting in the release of noradrenaline in brown adipose tissue and white adipose tissue. Acting via the β3-adrenergic receptors, noradrenaline induces lipolysis in white adipocytes, whereas it stimulates the expression of thermogenic genes, such as PPAR-γ co-activator 1a (Ppargc1a), uncoupling protein 1 (Ucp1) and acyl-CoA synthetase long-chain family member 1 (Acsl1), in brown adipocytes. However, the precise nature of all the cell types involved in this efferent loop is not well established. Nguyen et al. report an unexpected requirement in mice for the interleukin-4 (IL-4)-stimulated program of alternative macrophage activation in adaptive thermogenesis. Exposure to cold temperature rapidly promoted alternative activation of adipose tissue macrophages, which secrete catecholamines to induce thermogenic gene expression in brown adipose tissue and lipolysis in white adipose tissue. Absence of alternatively activated macrophages impaired metabolic adaptations to cold, whereas administration of IL-4 increased thermogenic gene expression, fatty acid mobilization and energy expenditure, all in a macrophage-dependent manner. Thus, the researchers have discovered a role for alternatively activated macrophages in the orchestration of an important mammalian stress response, the response to cold.

Nature 2011; 480: 104

Eitan Israeli

Capsule

Rebuilding muscle after injury

Skeletal muscle injury can be debilitating and potentially lethal. Factors released by the damaged muscle can stimulate local skeletal muscle stem cells (satellite cells) to become motile, proliferate, and differentiate into replenishing myofibers. Stark et al. (*Development* 2011; 138: 5279) suggest that even satellite cells distant from a site of injury could be recruited to help. The authors found that satellite cell motility was controlled by cell surface proteins called ephrins that are expressed by healthy and regenerating muscle cells. Ephrins and their Eph receptors function as a guidance system in a variety of developmental processes. Ephrins elicited a repulsive signal that caused satellite cells to alter their migratory course. Mouse satellite cells grafted into either the developing hindbrain or limb bud of quail embryos respected ephrin-defined boundaries as they migrated in vivo. The authors propose that Eph-ephrin interactions may modulate satellite cell migration and patterning during muscle fiber development. In another study Page et al. (*Tissue Eng* 2011; Part A 17: 2629) used microthreads of fibrin to restore muscle function in mice with substantial leg muscle injury. When placed into the damaged area, the microthread scaffolds, seeded with adult human muscle cells that were coaxed into a stem cell-like state, restored healthy muscle fibers. Surprisingly, most of the new muscle was generated from recruited mouse satellite cells. Together, these studies point to potential therapies for treating major muscle injuries.

Eitan Israeli

Capsule

Senescence surveillance of pre-malignant hepatocytes limits liver cancer development

Upon the aberrant activation of oncogenes, normal cells can enter the cellular senescence program, a state of stable cell-cycle arrest, which represents an important barrier against tumor development in vivo. Senescent cells communicate with their environment by secreting various cytokines and growth factors, and it was reported that this 'secretory phenotype' can have pro- as well as anti-tumorigenic effects. Kang et al. show that oncogene-induced senescence occurs in otherwise normal murine hepatocytes in vivo. Pre-malignant senescent hepatocytes secrete chemo- and cytokines and are subject to immune-mediated clearance (designated as senescence surveillance), which depends on an intact CD4+ T cell-mediated adaptive immune response. Impaired immune surveillance of pre-malignant senescent hepatocytes results in the development of murine hepatocellular carcinomas (HCCs), thus showing that senescence surveillance is important for tumor suppression in vivo. In accordance with these observations, ras-specific Th1 lymphocytes could be detected in mice in which oncogene-induced senescence had been triggered by hepatic expression of NrasG12V. The authors also found that CD4+ T cells require monocytes/macrophages to execute the clearance of senescent hepatocytes. The study indicates that senescence surveillance represents an important extrinsic component of the senescence anti-tumor barrier, and illustrates how the cellular senescence program is involved in tumor immune surveillance by mounting specific immune responses against antigens expressed in pre-malignant senescent cells.

Nature 2011; 479: 547

Eitan Israeli

"To know is to know that you know nothing. That is the meaning of true knowledge"

Confucius (551-479 BC), Chinese thinker and philosopher who emphasized personal and governmental morality, correctness of social relationships, justice and sincerity

Capsule

Proliferation of *Legionella pneumophila* in a cell

The intravacuolar pathogen *Legionella pneumophila* injects the AnkB F-box effector into the host amoeba or human cell. Host-mediated farnesylation then anchors AnkB into the outer leaflet of the Legionella-containing vacuole (LCV) membrane, which is required for intravacuolar proliferation of *L. pneumophila* and for its virulence in vivo. Price et al. now show that AnkB promotes preferential docking of Lys48-linked polyubiquitinated host proteins to the LCV, which is followed by their proteasomal degradation. This generates an intracellular source of amino acids, which suppress an amino acid starvation response by *L. pneumophila*, and allows intravacuolar proliferation. Supplementation of amino acids completely rescued an ankB null mutant from its severe intracellular growth defect and suppressed its amino acid starvation response in amoeba and human cells.

Science 2011; 334: 1553

Eitan Israeli

Capsule

The rs4774 CIITA missense variant is associated with risk of systemic lupus erythematosus

The major histocompatibility complex (MHC) class II transactivator gene (CIITA) encodes an important transcription factor required for human leukocyte antigens (HLA) class II MHC-restricted antigen presentation. MHC genes, including the HLA class II DRB1*03:01 allele, are strongly associated with systemic lupus erythematosus (SLE). Recently the rs4774 CIITA missense variant (+1632G/C) was reported to be associated with susceptibility to multiple sclerosis. Bronson et al. (*Genes Immunity* 2011; 12: 667) investigated CIITA, DRB1*03:01 and risk of SLE using a multi-stage analysis. In stage 1, 9 CIITA variants were tested in 658 cases and 1363 controls (N=2021). In stage 2, rs4774 was tested in 684 cases and 2938 controls (N=3622). The authors also performed a meta-analysis of the pooled 1342 cases and 4301 controls (N=5643). In stage 1, rs4774*C was associated with SLE: odds ratio (OR) 1.24, 95% confidence interval (95% CI) = 1.07–1.44, $P = 4.2x10–3$. Similar results were observed in stage 2 (OR 1.16, 95% CI = 1.02–1.33, $P = 8.5x10–3$) and the meta-analysis of the combined data set (OR 1.20, 95% CI = 1.09–1.33, Pmeta = 2.5x10–4). In all three analyses, the strongest evidence for association between rs4774*C and SLE was present in individuals who carried at least one copy of DRB1*03:01 (Pmeta = 1.9x10–3). These results support a role for CIITA in SLE, which appears to be stronger in the presence of DRB1*03:01.

Eitan Israeli

Capsule

New gene functions in megakaryopoiesis and platelet formation

Platelets are the second most abundant cell type in blood and are essential for maintaining hemostasis. Their count and volume are tightly controlled within narrow physiological ranges, but there is only limited understanding of the molecular processes controlling both traits. Gieger and co-researchers carried out a high powered meta-analysis of genome-wide association studies (GWAS) in up to 66,867 individuals of European ancestry, followed by extensive biological and functional assessment. The authors identified 68 genomic loci reliably associated with platelet count and volume mapping to established and putative novel regulators of megakaryopoiesis and platelet formation. These genes show megakaryocyte-specific gene expression patterns and extensive network connectivity. Using gene silencing in *Danio rerio* and *Drosophila melanogaster*, they identified 11 of the genes as novel regulators of blood cell formation. Taken together, their findings advance understanding of novel gene functions controlling fate-determining events during megakaryopoiesis and platelet formation, providing a new example of successful translation of GWAS to function.

Nature 2011; 480: 201

Eitan Israeli

Capsule

Antibody based protection against HIV infection by vectored immunoprophylaxis

Despite tremendous efforts, development of an effective vaccine against human immunodeficiency virus (HIV) has proved an elusive goal. Recently, however, numerous antibodies have been identified that are capable of neutralizing most circulating HIV strains. These antibodies all exhibit an unusually high level of somatic mutation, presumably owing to extensive affinity maturation over the course of continuous exposure to an evolving antigen. Although substantial effort has focused on the design of immunogens capable of eliciting antibodies *de novo* that would target similar epitopes, it remains uncertain whether a conventional vaccine will be able to elicit analogues of the existing broadly neutralizing antibodies. As an alternative to immunization, vector-mediated gene transfer could be used to engineer secretion of the existing broadly neutralizing antibodies into the circulation. Balazs et al. describe a practical implementation of this approach, that they call vectored immunoprophylaxis (VIP), which in mice induces lifelong expression of these monoclonal antibodies at high concentrations from a single intramuscular injection. This is achieved using a specialized adeno-associated virus vector optimized for the production of full-length antibody from muscle tissue. The authors show that humanized mice receiving VIP appear to be fully protected from HIV infection, even when challenged intravenously with very high doses of replication-competent virus. These results suggest that successful translation of this approach to humans may produce effective prophylaxis against HIV.

Nature 2012; 481: 81

Eitan Israeli

"There is no exception to the rule that every rule has an exception"

James Thurber (1894-1961), American writer and cartoonist

Capsule

Interactions between cancer stem cells and their niche govern metastatic colonization

Metastatic growth in distant organs is the major cause of cancer mortality. The development of metastasis is a multistage process with several rate-limiting steps. Although dissemination of tumor cells seems to be an early and frequent event, the successful initiation of metastatic growth, a process termed 'metastatic colonization', is inefficient for many cancer types and is accomplished only by a minority of cancer cells that reach distant sites. Prevalent target sites are characteristic of many tumor entities, suggesting that inadequate support by distant tissues contributes to the inefficiency of the metastatic process. Malanchi et al. show that a small population of cancer stem cells is critical for metastatic colonization, that is, the initial expansion of cancer cells at the secondary site, and that stromal niche signals are crucial to this expansion process. The authors find that periostin (POSTN), a component of the extracellular matrix, is expressed by fibroblasts in the normal tissue and in the stroma of the primary tumor. Infiltrating tumor cells need to induce stromal POSTN expression in the secondary target organ (in this case lung) to initiate colonization. POSTN is required to allow cancer stem cell maintenance, and blocking its function prevents metastasis. POSTN recruits Wnt ligands and thereby increases Wnt signaling in cancer stem cells. They suggest that the education of stromal cells by infiltrating tumor cells is an important step in metastatic colonization and that preventing *de novo* niche formation may be a novel strategy for the treatment of metastatic disease.

Nature 2012; 481: 85

Eitan Israeli

"Most people think that shadows follow, precede, or surround beings or objects. The truth is that they also surround words, ideas, desires, deeds, impulses and memories"

Elie Wiesel (b. 1928), Romanian-born Jewish-American writer, political activist, Nobel Laureate, and Holocaust survivor

Capsule

miR141 and miR-200a act on ovarian tumorigenesis by controlling oxidative stress response

Although there is evidence that redox regulation has an essential role in malignancies, its impact on tumor prognosis remains unclear. Mateescu and co-authors show crosstalk between oxidative stress and the miR-200 family of microRNAs that affects tumorigenesis and chemosensitivity. miR-141 and miR-200a target p38α and modulate the oxidative stress response. Enhanced expression of these microRNAs mimics p38α deficiency and increases tumor growth in mouse models, but it also improves the response to chemotherapeutic agents. High-grade human ovarian adenocarcinomas that accumulate miR-200a have low concentrations of p38α and an associated oxidative stress signature. The miR200a-dependent stress signature correlates with improved survival of patients in response to treatment. Therefore, the role of miR-200a in stress could be a predictive marker for clinical outcome in ovarian cancer. In addition, although oxidative stress promotes tumor growth, it also sensitizes tumors to treatment, which could account for the limited success of antioxidants in clinical trials.

Nature Med 2011; 17: 1627

Eitan Israeli

Capsule

Differential estrogen receptor binding associated with clinical outcome in breast cancer

Estrogen receptor-α (ER) is the defining and driving transcription factor in the majority of breast cancers and its target genes dictate cell growth and endocrine response, yet genomic understanding of ER function has been restricted to model systems. Ross-Innes et al. have mapped genome-wide ER-binding events, by chromatin immunoprecipitation followed by high-throughput sequencing (ChIP-seq), in primary breast cancers from patients with different clinical outcomes and in distant ER-positive metastases. The authors found that drug-resistant cancers still recruit ER to the chromatin, but that ER binding is a dynamic process with the acquisition of unique ER-binding regions in tumors from patients who are likely to relapse. The acquired ER regulatory regions associated with poor clinical outcome observed in primary tumors reveal gene signatures that predict clinical outcome in ER-positive disease exclusively. They found that the differential ER-binding program observed in tumors from patients with poor outcome is not due to the selection of a rare subpopulation of cells but to the FOXA1-mediated reprogramming of ER binding on a rapid timescale. The parallel redistribution of ER and FOXA1 binding events in drug-resistant cellular contexts is supported by histological co-expression of ER and FOXA1 in metastatic samples. By establishing transcription-factor mapping in primary tumor material, they show that there is plasticity in ER-binding capacity, with distinct combinations of *cis*-regulatory elements linked with the different clinical outcomes.

Nature 2012; 481: doi:10.1038/nature10730

Eitan Israeli

"Every man is a damned fool for at least five minutes every day. Wisdom consists in not exceeding the limit"

Elbert Hubbard (1856-1915), American writer, publisher, artist and philosopher

Capsule

Fine tuning neuronal networks

The double-stranded RNA-activated protein kinase (PKR) is widely present in vertebrates, and its activation leads to the phosphorylation of several substrates, the major known cytoplasmic target being the translation initiation factor eIF2α. PKR is activated in response to a variety of cellular stresses such as viral infection and status epilepticus, and in degenerating neurons in, among others, Huntington's, Parkinson's, Alzheimer's, and Creutzfeldt-Jakob's disease. At present, little is known about its role in normal neuronal function. Using transgenic mice, electrophysiology, immunohistochemistry, and behavioral analysis, Zhu and team discovered that loss of PKR or pharmacological blockade of PKR activity in mice promoted hyperexcitability in cortical and hippocampal networks and enhanced long-lasting synaptic potentiation and long-term memory. PKR regulated these processes via selective control of GABAergic synaptic transmission mediated by interferon-gamma (IFNγ). These findings thus uncovered a new molecular signaling pathway that regulates network rhythmicity, synaptic plasticity, and memory storage in the adult brain. PKR is activated in various neuropathies and may therefore be a potential therapeutic target.

Cell 2011; 147: 1384

Eitan Israeli

"Some scientists work so hard there is no time left for serious thinking"

Francis Crick (1916-2004), English molecular biologist, biophysicist and neuroscientist, who with James Watson discovered the structure of the DNA molecule in 1953. He, Watson and Maurice Wilkins were jointly awarded the 1962 Nobel Prize for Physiology or Medicine