Capsule

NLRP6 negatively regulates innate immunity and host defense against bacterial pathogens

Members of the intracellular nucleotide-binding and oligomerization domain (NOD)-like receptor (NLR) family contribute to immune responses through activation of nuclear factor-κB (NF-κB), type I interferon and inflammasome signaling. Mice lacking the NLR family member NLRP6 were recently shown to be susceptible to colitis and colorectal tumorigenesis, but the role of NLRP6 in microbial infections and the nature of the inflammatory signaling pathways regulated by NLRP6 remain unclear. Anand et al. show that Nlrp6-deficient mice are highly resistant to infection with the bacterial pathogens *Listeria monocytogenes*, *Salmonella typhimurium* and *Escherichia coli*. Infected Nlrp6-deficient mice had increased numbers of monocytes and neutrophils in circulation, and NLRP6 signaling in both hematopoietic and radioresistant cells contributed to increased susceptibility. Nlrp6 deficiency enhanced activation of mitogen-activated protein kinase (MAPK) and the canonical NF-κB pathway after Toll-like receptor ligation, but not cytosolic NOD1/2 ligation, in vitro. Consequently, infected Nlrp6-deficient cells produced increased levels of NF-κB- and MAPK-dependent cytokines and chemokines. These results reveal NLRP6 as a negative regulator of inflammatory signaling and demonstrate a role for this NLR in impeding clearance of both Gram-positive and negative bacterial pathogens.

Nature 2012; 488: 389

Eitan Israeli

Capsule

Endogenous antigen tunes the responsiveness of naive B cells but not T cells

In humans, up to 75% of newly generated B cells and about 30% of mature B cells show some degree of autoreactivity. Yet, how B cells establish and maintain tolerance in the face of autoantigen exposure during and after development is not certain. Studies of model B cell antigen receptor (BCR) transgenic systems have highlighted the critical role of functional unresponsiveness or 'anergy'. Unlike T cells, evidence suggests that receptor editing and anergy, rather than deletion, account for much of B cell tolerance. However, it remains unclear whether the mature diverse B cell repertoire of mice contains anergic autoreactive B cells, and if so, whether antigen was encountered during or after their development. By taking advantage of a reporter mouse in which BCR signaling rapidly and robustly induces green fluorescent protein expression under the control of the Nur77 regulatory region, antigen-dependent and antigen-independent BCR signaling events in vivo during B cell maturation were visualized. Zikherman et al. show that B cells encounter antigen during development in the spleen, and that this antigen exposure, in turn, tunes the responsiveness of BCR signaling in B cells at least partly by down-modulating expression of surface IgM but not IgD BCRs, and by modifying basal calcium levels. By contrast, no analogous process occurs in naive mature T cells. These data demonstrate not only that autoreactive B cells persist in the mature repertoire, but that functional unresponsiveness or anergy exists in the mature B cell repertoire along a continuum, a fact that has long been suspected, but never yet shown. These results have important implications for understanding how tolerance in T and B cells is differently imposed, and how these processes might go awry in disease.

Nature 2012; 489: 160

Eitan Israeli

Capsule

Passenger deletions generate therapeutic vulnerabilities in cancer

Inactivation of tumor-suppressor genes by homozygous deletion is a prototypic event in the cancer genome, yet such deletions often encompass neighboring genes. The authors propose that homozygous deletions in such passenger genes can expose cancer-specific therapeutic vulnerabilities when the collaterally deleted gene is a member of a functionally redundant family of genes carrying out an essential function. The glycolytic gene enolase 1 (ENO1) in the 1p36 locus is deleted in glioblastoma (GBM), which is tolerated by the expression of ENO2. Muller and co-scientists show that short-hairpin-RNA-mediated silencing of ENO2 selectively inhibits growth, survival and the tumorigenic potential of ENO1-deleted GBM cells, and that the enolase inhibitor phosphonoacetohydroxamate is selectively toxic to ENO1-deleted GBM cells relative to ENO1-intact GBM cells or normal astrocytes. The principle of collateral vulnerability should be applicable to other passenger-deleted genes encoding functionally redundant essential activities and provide an effective treatment strategy for cancers containing such genomic events.

Nature 2012; 488: 337

Eitan Israeli

Capsule

Antibodies to fight Influenza

With its ability to reassort in animal hosts like pigs and birds, and to cause pandemics, influenza A viruses are often in the spotlight. However, a substantial portion of the annual flu burden is also the result of influenza B virus, which is a single influenza type that is characterized by two antigenically and genetically distinct lineages. Dreyfus and colleagues identified three monoclonal human antibodies that are able to protect against lethal infection with both lineages of influenza B virus in mice. Two antibodies, which bind to distinct regions of the viral hemagluttinin (HA) molecule, neutralize multiple strains from both lineages of influenza B virus, whereas the third antibody binds to the stem region of HA and is able to neutralize both influenza A and B strains. The structural data from these antibodies bound to HA, together with already known antibodies targeting influenza A, may provide clues for designing a universal vaccine to protect against both influenza virus types.

Science 2012; 337: 1343

Eitan Israeli

Capsule

Antiretroviral dynamics determines HIV evolution and predicts therapy outcome

Despite the high inhibition of viral replication achieved by current anti-HIV drugs, many patients fail treatment, often with emergence of drug-resistant virus. Clinical observations show that the relationship between adherence and likelihood of resistance differs dramatically among drug classes. Rosenbloom et al. developed a mathematical model that explains these observations and predicts treatment outcomes. This model incorporates drug properties, fitness differences between susceptible and resistant strains, mutations and adherence. The authors show that antiviral activity falls quickly for drugs with sharp dose-response curves and short half-lives, such as boosted protease inhibitors, limiting the time during which resistance can be selected for. They find that poor adherence to such drugs causes treatment failure via growth of susceptible virus, explaining puzzling clinical observations. Furthermore, the model predicts that certain single-pill combination therapies can prevent resistance regardless of patient adherence. This approach represents a first step for simulating clinical trials of untested anti-HIV regimens and may help in the selection of new drug regimens for investigation.

Nature Med 2012; 18: 1378

Eitan Israeli

Capsule

Cytomegalovirus and tumor stress surveillance by binding of a human γδ T cell antigen receptor to endothelial protein C receptor

T cells bearing γδ T cell antigen receptors (TCRs) function in lymphoid stress surveillance. However, the contribution of γδ TCRs to such responses is unclear. Willcox et al. found that the TCR of a human Vγ4Vδ5 clone directly bound endothelial protein C receptor (EPCR), which allowed γδ T cells to recognize both endothelial cells targeted by cytomegalovirus and epithelial tumors. EPCR is a major histocompatibility complex-like molecule that binds lipids analogously to the antigen-presenting molecule CD1d. However, the Vγ4Vδ5 TCR bound EPCR independently of lipids, in an antibody-like way. Moreover, the recognition of target cells by γδ T cells required a multimolecular stress signature composed of EPCR and costimulatory ligand(s). These results demonstrate how a γδ TCR mediates recognition of broadly stressed human cells by engaging a stress-regulated self-antigen.

Nature Immunol 2012; 13: 872
Eitan Israeli

Capsule

Crucial cerebellar glial cells

The role of glial cells and their interaction with neurons in normal behavior is unclear. To address this question, Saab and associates studied a special type of glial cell in the cerebellum. Conditional mutant mice were produced in which the two glutamate receptor subunits normally present in Bergmann glial cells were efficiently ablated in a temporally controlled manner. Glutamate signaling of the glial cells contributed to the structural and functional integrity of the cerebellar network. Bergmann glial cells also played a role in the "fine-tuning" of neuronal processing, which is crucial for the fast and precise control of complex motor behavior.

Science 2012; 337: 749
Eitan Israeli

Capsule

Bio-inspired drug delivery

Noting that platelets naturally migrate to narrowed blood vessels characterized by high fluid shear stress, Korin et al. developed a nanoparticle-based therapeutic that uses a similar targeting mechanism to deliver a drug to vessels obstructed by blood clots. Aggregates of nanoparticles coated with the clot-dissolving drug tPA (tissue plasminogen activator) were designed to fall apart and release the drug only when encountering high fluid shear stress. In preclinical models, the bio-inspired therapeutic dissolved clots and restored normal blood flow at lower doses than free tPA, suggesting that this localized delivery system may help reduce the risk of side effects such as excessive bleeding.

Science 2012; 337: 738
Eitan Israeli

Capsule

Taming microglia for treating multiple sclerosis

Multiple sclerosis (MS) is a severely debilitating degenerative disease of the central nervous system. Resident macrophages of the brain, called microglia, are thought to be an important driver of disease. Factors that promote the conversion of pro-inflammatory, or "M1" microglia, which are thought to be the type of microglia that contribute to disease, into less dangerous, immunoregulatory "M2"-type microglia, are of therapeutic interest. Starossom et al. identified one such factor, the endogenous glycan-binding protein Galectin-1 (Gal1). In a mouse model of MS, Gal1 was expressed during the acute and chronic stages of disease by astrocytes and some populations of immune cells. Gal1 bound preferentially to M1 microglia in a glycan-dependent manner, and once bound, it inhibited the pro-inflammatory phenotype of M1 microglia by retaining the phosphatase CD45 on the cell surface. This resulted in the dephosphorylation, and therefore downmodulation, of several downstream pro-inflammatory signaling molecules. The effects of Gal1 on M1 microglia were primarily the result of astrocyte-produced Gal1. Finally, the authors showed that mice deficient in Gal1 experienced enhanced axonal damage, whereas treatment of mice with Gal1-treated microglia or with Gal1 itself had a therapeutic effect, which suggests that Gal1 may be a potential therapeutic target in MS.

Immunity 2012; 37: 10.1016/j.immuni.2012.05.023

Eitan Israeli

Capsule

A voltage-gated sodium channel is essential for the positive selection of CD4+ T cells

The sustained entry of Ca2+ into CD4+CD8+ double-positive thymocytes is required for positive selection. Lo and co-workers identified a voltage-gated Na+ channel (VGSC) that was essential for positive selection of CD4+ T cells. Pharmacological inhibition of VGSC activity inhibited the sustained Ca2+ influx induced by positively selecting ligands and the in vitro positive selection of CD4+ but not CD8+ T cells. In vivo short hairpin RNA (shRNA)-mediated knockdown of the gene encoding a regulatory β-subunit of a VGSC specifically inhibited the positive selection of CD4+ T cells. Ectopic expression of VGSC in peripheral and CD4+ T cells bestowed the ability to respond to a positively selecting ligand, which directly demonstrated that VGSC expression was responsible for the enhanced sensitivity. Thus, active VGSCs in thymocytes provide a mechanism by which a weak positive selection signal can induce the sustained Ca2+ signals required for CD4+ T cell development.

Nature Immunol 2012; 13: 880
Eitan Israeli

Capsule

Chromatin organization is a major influence on regional mutation rates in human cancer cells

Cancer genome sequencing provides the first direct information on how mutation rates vary across the human genome in somatic cells. Testing diverse genetic and epigenetic features, Schuster-Böckler et al. show that mutation rates in cancer genomes are strikingly related to chromatin organization. Indeed, at the megabase scale, a single feature – levels of the heterochromatin-associated histone modification H3K9me3 – can account for more than 40% of mutation-rate variation, and a combination of features can account for more than 55%. The strong association between mutation rates and chromatin organization is upheld in samples from different tissues and for different mutation types. This suggests that the arrangement of the genome into heterochromatin- and euchromatin-like domains is a dominant influence on regional mutation-rate variation in human somatic cells.

Nature 2012; 488: 504
Eitan Israeli

Capsule

New mutations in melanoma

Despite the increased use of sunscreens, the incidence of melanoma, the most lethal form of skin cancer, remains high. Tumor genome sequencing has led to new therapies targeting BRAF, a protein kinase that is activated by mutation in about 50% of melanomas and helps drive tumor growth. Because the development of resistance to BRAF inhibitors limits their long-term efficacy, there is considerable interest in identifying additional driver mutations that might form the basis of new or combination therapies. Toward this end, Krauthammer et al. (*Nat Genet* 2012 10.1038/ng2359) sequenced the protein-coding regions of 147 human melanoma genomes. Notably, 9% of sun-exposed melanomas harbored a point mutation in RAC1, which encodes a small GTPase (an enzyme hydrolyzing guanosine triphosphate) that regulates cytoskeletal rearrangements. Structural and functional analysis revealed that the mutation increases RAC1 binding to its downstream effectors, including PAK1 (p21-activated protein kinase), and induces melanocyte growth and migration. PAK kinases are therefore potentially druggable targets for melanoma treatment. In independent work, Hodis et al. (*Cell 2012*; 150: 251) found the same activating RAC1 mutation in 5% of their melanoma samples.

Eitan Israeli

Capsule

TNF receptor 1 genetic risk mirrors outcome of anti-TNF therapy in multiple sclerosis

Although there has been much success in identifying genetic variants associated with common diseases using genome-wide association studies (GWAS), it has been difficult to demonstrate which variants are causal and what role they have in disease. Moreover, the modest contribution that these variants make to disease risk has raised questions regarding their medical relevance. Gregory et al. investigated a single nucleotide polymorphism (SNP) in the *TNFRSF1A* gene, that encodes tumor necrosis factor receptor 1 (TNFR1), which was discovered through GWAS to be associated with multiple sclerosis (MS) but not with other autoimmune conditions such as rheumatoid arthritis, psoriasis and Crohn's disease. Analysis of the MS GWAS data in conjunction with the 1000 Genomes Project data provides genetic evidence that strongly implicates this SNP, rs1800693, as the causal variant in the *TNFRSF1A* region. The authors further substantiate this through functional studies showing that the MS risk allele directs expression of a novel, soluble form of TNFR1 that can block TNF. Importantly, TNF-blocking drugs can promote onset or exacerbation of MS, but they have proven highly efficacious in the treatment of autoimmune diseases for which there is no association with rs1800693. This indicates that the clinical experience with these drugs parallels the disease association of rs1800693, and that the MS-associated TNFR1 variant mimics the effect of TNF-blocking drugs. Hence, their study demonstrates that clinical practice can be informed by comparing GWAS across common autoimmune diseases and by investigating the functional consequences of the disease-associated genetic variation.

Nature 2012; 488: 508

Eitan Israeli

Capsule

An integrated encyclopedia of DNA elements in the human genome

The human genome encodes the blueprint of life, but the function of the vast majority of its nearly three billion bases is unknown. The Encyclopedia of DNA Elements (ENCODE) project has systematically mapped regions of transcription, transcription factor association, chromatin structure and histone modification. These data enabled the authors to assign biochemical functions for 80% of the genome, in particular outside of the well-studied protein-coding regions. Many discovered candidate regulatory elements are physically associated with one another and with expressed genes, providing new insights into the mechanisms of gene regulation. The newly identified elements also show a statistical correspondence to sequence variants linked to human disease, and can thereby guide interpretation of this variation. Overall, the project provides new insights into the organization and regulation of our genes and genome and is an expansive resource of functional annotations for biomedical research.

Nature 2012; 489: 57

Eitan Israeli

Capsule

The limits in infant immunity

Natural killer (NK) cells control viral infections swiftly, releasing lytic factors that destroy infected cells shortly after infection. But infants and neonates are susceptible to viral infections in part because they lack the mature form of these powerful immune cells. Marcoe and co-researchers have discovered a factor that limits this arsenal early in life. The authors found that during mouse infancy, transforming growth factor-β (TGFβ) blocks a terminal step in NK cell maturation. TGFβ blocked the generation of mature NK cells from mouse stem cell precursors in vitro. In mice that were genetically engineered to lack a functional receptor for TGFβ in NK cells, the number of mature NK cells present at 10 days of age was equivalent to that in 56 day old normal mice. In addition to faster maturation, infant mice lacking NK cell TGFβ receptor signaling were resistant to viral infection. Analysis of mRNA points to genes that control the cell division cycle – p21 and Cdc7 – as targets of TGFβ, arresting the production of NK cells as they mature. The expression of transcription factors that push NK cells through the final stage of maturation is also limited by TGFβ. The findings raise the possibility that inactivating TGFβ signaling could prevent the deficit of NK cells during infancy.

Nat Immunol 2012; 11: 10.1038/ni.2388

Eitan Israeli

Capsule

HVEM signaling at mucosal barriers provides host defense against pathogenic bacteria

The herpes virus entry mediator (HVEM), a member of the tumor-necrosis factor receptor family, has diverse functions, augmenting or inhibiting the immune response. HVEM was recently reported as a colitis risk locus in patients, and in a mouse model of colitis the authors demonstrated an anti-inflammatory role for HVEM, but its mechanism of action in the mucosal immune system was unknown. Shui et al. report an important role for epithelial HVEM in innate mucosal defense against pathogenic bacteria. HVEM enhances immune responses by NF-κB-inducing kinase-dependent Stat3 activation, which promotes the epithelial expression of genes important for immunity. During intestinal *Citrobacter rodentium* infection, a mouse model for enteropathogenic *Escherichia coli* infection, Hvem−/− mice showed decreased Stat3 activation, impaired responses in the colon, higher bacterial burdens and increased mortality. We identified the immunoglobulin superfamily molecule CD160, expressed predominantly by innate-like intraepithelial lymphocytes, as the ligand engaging epithelial HVEM for host protection. Likewise, in pulmonary *Streptococcus pneumoniae* infection HVEM is also required for host defense. These results pinpoint HVEM as an important orchestrator of mucosal immunity, integrating signals from innate lymphocytes to induce optimal epithelial Stat3 activation, which indicates that targeting HVEM with agonists could improve host defense.

Nature 2012; 488: 222

Eitan Israeli

Capsule

Transcranial electrical stimulation highly effective and reduced seizure duration

Deep brain electrical stimulation can be a successful therapy in Parkinson's disease, in depression, and in several other psychiatric diseases, especially in drug-resistant cases. Unfortunately, chronic, continuous stimulation is associated with multiple side effects. This could be alleviated by delivering the electrical perturbation only when it is necessary, using closed-loop stimulation. Such an approach is essential for epilepsy, where seizures occur very rarely but with serious consequences. In a rat model for epilepsy, Berényi et al. prevented seizures by transcranial electrical stimulation using a closed-loop system. Transcranial electrical stimulation was highly effective and reduced seizure duration, on average, by 60%.

Science 2012; 337: 735

Eitan Israeli

Capsule

Landscape of somatic retrotransposition in human cancers

Transposable elements (TEs) are abundant in the human genome, and some are capable of generating new insertions through RNA intermediates. In cancer, the disruption of cellular mechanisms that normally suppress TE activity may facilitate mutagenic retrotranspositions. Lee et al. performed single-nucleotide resolution analysis of TE insertions in 43 high-coverage whole-genome sequencing data sets from five cancer types. We identified 194 high-confidence somatic TE insertions, as well as thousands of polymorphic TE insertions in matched normal genomes. Somatic insertions were present in epithelial tumors but not in blood or brain cancers. Somatic L1 insertions tend to occur in genes that are commonly mutated in cancer, disrupt the expression of the target genes, and are biased toward regions of cancer-specific DNA hypomethylation, highlighting their potential impact in tumorigenesis.

Science 2012; 337: 967

Eitan Israeli

Capsule

An anatomically comprehensive atlas of the adult human brain transcriptome

Neuroanatomically precise, genome-wide maps of transcript distributions are critical resources to complement genomic sequence data and to correlate functional and genetic brain architecture. Hawrylycz et al. describe the generation and analysis of a transcriptional atlas of the adult human brain, comprising extensive histological analysis and comprehensive microarray profiling of ~900 neuroanatomically precise subdivisions in two individuals. Transcriptional regulation varies enormously by anatomical location, with different regions and their constituent cell types displaying robust molecular signatures that are highly conserved between individuals. Analysis of differential gene expression and gene co-expression relationships demonstrates that brain-wide variation strongly reflects the distributions of major cell classes such as neurons, oligodendrocytes, astrocytes and microglia. Local neighborhood relationships between fine anatomical subdivisions are associated with discrete neuronal subtypes and genes involved with synaptic transmission. The neocortex displays a relatively homogeneous transcriptional pattern, but with distinct features associated selectively with primary sensorimotor cortices and with enriched frontal lobe expression. Notably, the spatial topography of the neocortex is strongly reflected in its molecular topography – the closer two cortical regions, the more similar their transcriptomes. This freely accessible online data resource forms a high-resolution transcriptional baseline for neurogenetic studies of normal and abnormal human brain function.

Nature 2012; 489: 391

Eitan Israeli