Capsule

Bidirectional regulation of neutrophil migration by mitogen-activated protein kinases

To kill invading bacteria, neutrophils must interpret spatial cues, migrate and reach target sites. Although the initiation of chemotactic migration has been extensively studied, little is known about its termination. Liu et al. found that two mitogen-activated protein kinases (MAPKs) had opposing roles in neutrophil trafficking. The extracellular signal-regulated kinase Erk potentiated activity of the G protein-coupled receptor kinase GRK2 and inhibited neutrophil migration, whereas the MAPK p38 acted as a non-canonical GRK that phosphorylated the formyl peptide receptor FPR1 and facilitated neutrophil migration by blocking GRK2 function. Therefore, the dynamic balance between Erk and p38 controlled neutrophil 'stop' and 'go' activity, which ensured that neutrophils reached their final destination as the first line of host defense.

Nature Immunol 2012; 13: 457

Eitan Israeli

Capsule

Replication restricted HIV

Despite its deadly nature, human immunodeficiency virus (HIV)-1 is quite limited in the types of cells that it can infect. HIV-1 primarily infects CD4+ T cells but not many myloid-derived immune cells. This is because most myeloid-derived cells express the viral restriction factor SAMHD1. Although this may seem like an advantage to the host, the virus actually gains the upper hand because it can escape detection by the innate immune system. In support of this, HIV-2 and some SIV strains that do not cause such severe pathology express Vpx, which counteracts the effects of SAMHD1. Little is known, however, about how SAMHD1 prevents HIV-1 infections from taking hold. Lahouassa et al. noted that SAMHD1 shares homology with a protein from *Enterococcus fecalis* that has nucleotide metabolism activity. Using a variety of in vitro analyses, they found that SAMHD1 exhibited phosphohydrolase activity for dNTPs and regulated the pool of dNTPs in myeloid-derived cells. SAMHD1 expression lowered the concentration of dNTPs below what is required for productive reverse transcription by HIV-1, thereby blocking infection. Thus, regulation of nucleotide pools may be a means by which cells regulate their susceptibility to viral infection, but hidden benefits for the virus may be lurking, too.

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Eitan Israeli

Capsule

NF-κB-mediated degradation of the coactivator RIP140 regulates inflammatory responses and contributes to endotoxin tolerance

Tolerance to endotoxins that is triggered by prior exposure to Toll-like receptor (TLR) ligands provides a mechanism with which to dampen inflammatory cytokines. The receptor-interacting protein RIP140 interacts with the transcription factor NF-κB to regulate the expression of genes encoding proinflammatory cytokines. Ho et al. found lipopolysaccharide stimulation of kinase Syk-mediated tyrosine phosphorylation of RIP140 and interaction of the NF-κB subunit RelA with RIP140. These events resulted in more recruitment of the E3 ligase SCF to tyrosine-phosphorylated RIP140, which degraded RIP140 to inactivate genes encoding inflammatory cytokines. Macrophages expressing non-degradable RIP140 were resistant to the establishment of endotoxin tolerance for specific 'tolerizable' genes. These results identify RelA as an adaptor with which SCF finetunes NF-κB target genes by targeting the co-activator RIP140 and show an unexpected role for RIP140 degradation in resolving inflammation and endotoxin tolerance.

Nature Immunol 2012; 13: 379

Eitan Israeli

Capsule

Distinguishing ciliopathy patients

Cilia were once thought to be evolutionary remnants, but structural defects reveal their importance in signaling pathways and human disease, such as Joubert syndrome. Either of the genes *TMEM*138 and *TMEM*216 can be found mutated in phenotypically indistinguishable ciliopathy patients. Interestingly, despite their lack of sequence homology, these genes have always been aligned in head-to-tail configuration during vertebrate evolution. The proteins expressed by these genes mark distinct tethered vesicles, which differentially carry ciliary proteins for assembly. Lee and colleagues show that the coordinated expression of these adjacent genes depends upon a co-evolved regulatory element in the non-coding intergenic region, which thus integrates the roles of both gene products. This discovery explains not only the indistinguishable pathogenesis of the patients' genotypes but also how the evolutionary clustering of genes unrelated in sequence may correlate with coordinated control of expression and function.

Science 2012; 335: 966

Eitan Israeli

Capsule

Goblet cells deliver luminal antigen to CD103+ dendritic cells in the small intestine

The intestinal immune system is exposed to a mixture of foreign antigens from diet, commensal flora and potential pathogens. Understanding how pathogen-specific immunity is elicited while avoiding inappropriate responses to the background of innocuous antigens is essential for understanding and treating intestinal infections and inflammatory diseases. The ingestion of protein antigen can induce oral tolerance, which is mediated in part by a subset of intestinal dendritic cells (DCs) that promote the development of regulatory T cells. The lamina propria (LP) underlies the expansive single-cell absorptive villous epithelium and contains a large population of DCs ($CD11c^+$ $CD11b^+$ $MHCII^+$ cells) comprised of two predominant subsets: $CD103^+$ CX_3CR1^- DCs, which promote immunoglobulin A production, imprint gut homing on lymphocytes and induce the development of regulatory T cells and $CD103^-$ CX_3CR1^+ DCs (with features of macrophages), which promote tumor necrosis factor-alpha production, colitis, and the development of T_H17 T cells. However, the mechanisms by which different intestinal LP-DC subsets capture luminal antigens in vivo remains largely unexplored. Using a minimally disruptive in vivo imaging approach McDole et al. show that in the steady-state, small intestine goblet cells (GCs) function as passages delivering low molecular weight soluble antigens from the intestinal lumen to underlying $CD103^+$ LP-DCs. The preferential delivery of antigens to DCs with tolerogenic properties implies a key role for this GC function in intestinal immune homeostasis.

Nature 2012; 483: 345

Eitan Israeli

Capsule

Tissue factor and PAR1 promote microbiota-induced intestinal vascular remodelling

The gut microbiota is a complex ecosystem that has co-evolved with host physiology. Colonization of germ-free (GF) mice with a microbiota promotes increased vessel density in the small intestine, but little is known about the mechanisms involved. Tissue factor (TF) is the membrane receptor that initiates the extrinsic coagulation pathway, and it promotes developmental and tumor angiogenesis. Reinhardt et al. show that the gut microbiota promotes TF glycosylation associated with localization of TF on the cell surface, the activation of coagulation proteases, and phosphorylation of the TF cytoplasmic domain in the small intestine. Anti-TF treatment of colonized GF mice decreased microbiota-induced vascular remodelling and expression of the proangiogenic factor angiopoietin-1 (Ang-1) in the small intestine. Mice with a genetic deletion of the TF cytoplasmic domain or with hypomorphic TF (*F3*) alleles had a decreased intestinal vessel density. Coagulation proteases downstream of TF activate protease-activated receptor (PAR) signalling implicated in angiogenesis. Vessel density and phosphorylation of the cytoplasmic domain of TF were decreased in small intestine from PAR1-deficient (*F2r*$^{-/-}$) but not PAR2-deficient (*F2rl1*$^{-/-}$) mice, and inhibition of thrombin showed that thrombin–PAR1 signalling was upstream of TF phosphorylation. Thus, the microbiota-induced extravascular TF–PAR1 signaling loop is a novel pathway that may be modulated to influence vascular remodeling in the small intestine.

Nature 2012; 483: 627

Eitan Israeli

Capsule

Deleted in colorectal carcinoma suppresses metastasis in p53-deficient mammary tumors

Since its discovery in the early 1990s the deleted in colorectal cancer (*DCC*) gene, located on chromosome 18q21, has been proposed as a tumor suppressor gene as its loss is implicated in the majority of advanced colorectal and many other cancers. DCC belongs to the family of netrin 1 receptors, which function as dependence receptors as they control survival or apoptosis depending on ligand binding. However, the role of DCC as a tumor suppressor remains controversial because of the rarity of DCC-specific mutations and the presence of other tumor suppressor genes in the same chromosomal region. Krimpenfort and team show that in a mouse model of mammary carcinoma based on somatic inactivation of p53, additional loss of DCC promotes metastasis formation without affecting the primary tumor phenotype. Furthermore, we demonstrate that in cell cultures derived from p53-deficient mouse mammary tumors DCC expression controls netrin-1-dependent cell survival, providing a mechanistic basis for the enhanced metastatic capacity of tumor cells lacking DCC. Consistent with this idea, in vivo tumor cell survival is enhanced by DCC loss. Together, these data support the function of DCC as a context-dependent tumor suppressor that limits survival of disseminated tumor cells.

Nature 2012; 482: 538

Eitan Israeli

Capsule

Suppression of the antiviral response by an influenza histone

Viral infection is commonly associated with virus-driven hijacking of host proteins. Marazzi et al. describe a novel mechanism by which influenza virus affects host cells through the interaction of influenza non-structural protein 1 (NS1) with the infected cell epigenome. The authors show that the NS1 protein of influenza A H3N2 subtype possesses a histone-like sequence (histone mimic) that is used by the virus to target the human PAF1 transcription elongation complex (hPAF1C). They demonstrate that binding of NS1 to hPAF1C depends on the NS1 histone mimic and results in suppression of hPAF1C-mediated transcriptional elongation. Furthermore, human PAF1 has a crucial role in the antiviral response. Loss of hPAF1C binding by NS1 attenuates influenza infection, whereas hPAF1C deficiency reduces antiviral gene expression and renders cells more susceptible to viruses. The researchers propose that the histone mimic in NS1 enables the influenza virus to affect inducible gene expression selectively, thus contributing to suppression of the antiviral response.

Nature 2012; 483: 428

Eitan Israeli

Capsule

The influence of genetic variation on innate immune activation in an environment with high infectious pressure

Interleukin-10 (IL-10) production is under tight genetic control in populations living in affluent environments. However, little is known about the role of *IL*10 genetics on cytokine production in populations living in environments with high infectious pressure. Boef and co-scientists previously reported that, in a rural Ghanaian population, the most common *IL*10 haplotype associates with a pro-inflammatory response. Here, the authors aim to replicate these findings in an independent sample of the same population 2 years later. IL-10 and tumor necrosis factor-alpha (TNFα) protein concentrations were determined in whole-blood samples ex vivo stimulated with lipopolysaccharide and zymosan in 2006 (n=615) and 2008 (n=647). The association between *IL*10 single nucleotide polymorphisms and *Z*-scores of IL-10 and TNFα levels was analyzed in each population subset. The most common *IL*10 haplotype was associated with a significantly lower IL-10 production and non-significantly increased TNFα levels. The correlation between repeated cytokine assays, based on 111 individuals with measurements in both 2006 and 2008, was $r = 0.53$ ($P < 0.001$) for IL-10 and $r = 0.36$ ($P < 0.001$) for TNFα. The replication of the previously found effect of variation in the *IL*10 gene on IL-10 production and the correlation between repeated cytokine stimulation assays provide evidence that *IL*10 genetics have an important role in regulating the host response under high infectious pressure.

Genes Immun 2012; 13: 103

Eitan Israeli

Capsule

Role of major histocompatibility complex class II in the development of autoimmune type 1 diabetes and thyroiditis in rats

Although the MHC class II 'u' haplotype is strongly associated with type 1 diabetes (T1D) in rats, the role of MHC class II in the development of tissue-specific autoimmune diseases including T1D and autoimmune thyroiditis remains unclear. To clarify this, Yokoi et al. produced a congenic strain carrying MHC class II 'a' and 'u' haplotypes on the Komeda diabetes-prone (KDP) genetic background. The u/u homozygous animals developed T1D similar to the original KDP rat; a/u heterozygous animals did develop T1D but with delayed onset and low frequency. In contrast, none of the a/a homozygous animals developed T1D; about half of the animals with a/u heterozygous or a/a homozygous genotypes showed autoimmune thyroiditis. To investigate the role of genetic background in the development of thyroiditis, the authors also produced a congenic strain carrying *Cblb* mutation of the KDP rat on the PVG.R23 genetic background (MHC class II 'a' haplotype). The congenic rats with homozygous *Cblb* mutation showed autoimmune thyroiditis without T1D and slight to severe alopecia, a clinical symptom of hypothyroidism such as Hashimoto's thyroiditis. These data indicate that MHC class II is involved in the tissue-specific development of autoimmune diseases, including T1D and thyroiditis.

Genes Immun 2012; 13: 139

Eitan Israeli

Capsule

A whole genome methylation analysis of systemic lupus erythematosus

Hypomethylation of the interleukin (IL)10 and IL1R2 promoters is associated with disease activity interaction of genetic and environmental factors. Investigations have shown that environmentally driven epigenetic changes contribute to the etiology of SLE. Lin and co-authors hypothesize that aberrant DNA methylation may contribute to the activation of the immune machinery and trigger lupus disease activity. A whole-genome methylation array was applied to investigate the DNA methylation changes between 12 pairs of active systemic lupus erythematosus (SLE) patients and healthy controls. The results were further confirmed in 66 SLE patients and 102 healthy controls. The methylation statuses of the *IL*10 and *IL*1*R*2 genes were significantly reduced in the SLE patient samples relative to the healthy controls (age-adjusted odds ratios, 64.2 and 16.9, respectively, $P < 0.0001$). There was a trend toward SLE patients having hypomethylated *IL*10 and *IL*1*R*2 genes accompanied by greater disease activity. We observed that the methylation degree of *IL*10 and *IL*1*R*2 genes were reduced in the rheumatoid arthritis (RA) patients as well but the hypomethylation change was more significant in *IL*1*R*2 genes than in the *IL*10 genes in RA patients. This study demonstrated that DNA hypomethylation might be associated with SLE. Hypomethylated *IL*10 and *IL*1*R*2 genes may provide potential epigenetic markers as clinical predictors for autoimmune diseases.

Genes Immun 2012; 13: 214

Eitan Israeli

Capsule

The *Shigella flexneri* effector OspI deamidates UBC13 to dampen the inflammatory response

Many bacterial pathogens can enter various host cells and then survive intracellularly, transiently evade humoral immunity, and further disseminate to other cells and tissues. When bacteria enter host cells and replicate intracellularly, the host cells sense the invading bacteria as damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs) by way of various pattern recognition receptors. As a result, the host cells induce alarm signals that activate the innate immune system. Therefore, bacteria must modulate host inflammatory signaling and dampen these alarm signals. How pathogens do this after invading epithelial cells remains unclear, however. Sanada et al. show that OspI, a *Shigella flexneri* effector encoded by *ORF*169*b* on the large plasmid and delivered by the type III secretion system, dampens acute inflammatory responses during bacterial invasion by suppressing the tumor necrosis factor (TNF) receptor-associated factor 6 (TRAF6)-mediated signaling pathway. OspI is a glutamine deamidase that selectively deamidates the glutamine residue at position 100 in UBC13 to a glutamic acid residue. Consequently, the E2 ubiquitin-conjugating activity required for TRAF6 activation is inhibited, allowing *S. flexneri* OspI to modulate the diacylglycerol-CBM (CARD-BCL10-MALT1) complex-TRAF6-nuclear factor κB signaling pathway. We determined the 2.0 Å crystal structure of OspI, which contains a putative cysteine-histidine-aspartic acid catalytic triad. A mutational analysis showed this catalytic triad to be essential for the deamidation of UBC13. These results suggest that *S. flexneri* inhibits acute inflammatory responses in the initial stage of infection by targeting the UBC13-TRAF6 complex.

Nature 2012; 483: 623

Eitan Israeli

Capsule

A fine-scale chimpanzee genetic map from population sequencing

To study the evolution of recombination rates in apes, Auton et al. developed methodology to construct a fine-scale genetic map from high-throughput sequence data from 10 Western chimpanzees, *Pan troglodytes verus*. Compared to the human genetic map, broad-scale recombination rates tend to be conserved, but with exceptions, particularly in regions of chromosomal rearrangements and around the site of ancestral fusion in human chromosome 2. At fine scales, chimpanzee recombination is dominated by hotspots, which show no overlap with those of humans even though rates are similarly elevated around CpG islands and decreased within genes. The hotspot-specifying protein PRDM9 shows extensive variation among western chimpanzees, and there is little evidence that any sequence motifs are enriched in hotspots. The contrasting locations of hotspots provide a natural experiment, which demonstrates the impact of recombination on base composition.

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http://www.sciencemag.org/content/336/6078/193
Eitan Israeli

Capsule

The Cancer Cell Line Encyclopedia enables predictive modeling of anticancer drug sensitivity

The systematic translation of cancer genomic data into knowledge of tumor biology and therapeutic possibilities remains challenging. Such efforts should be greatly aided by robust preclinical model systems that reflect the genomic diversity of human cancers and for which detailed genetic and pharmacological annotation is available. Barretina et al. describe the Cancer Cell Line Encyclopedia (CCLE): a compilation of gene expression, chromosomal copy number and massively parallel sequencing data from 947 human cancer cell lines. When coupled with pharmacological profiles for 24 anticancer drugs across 479 of the cell lines, this collection allowed identification of genetic, lineage, and gene expression-based predictors of drug sensitivity. In addition to known predictors, we found that plasma cell lineage correlated with sensitivity to IGF1 receptor inhibitors; *AHR* expression was associated with MEK inhibitor efficacy in *NRAS*-mutant lines; and *SLFN*11 expression predicted sensitivity to topoisomerase inhibitors. Together, these results indicate that large, annotated cell-line collections may help to enable preclinical stratification schemata for anticancer agents. The generation of genetic predictions of drug response in the preclinical setting and their incorporation into cancer clinical trial design could speed the emergence of 'personalized' therapeutic regimens.

Nature 2012; 483: 603

Eitan Israeli

Capsule

Atg7 modulates p53 activity to regulate cell cycle and survival during metabolic stress

Withdrawal of nutrients triggers an exit from the cell division cycle, the induction of autophagy, and eventually the activation of cell death pathways. The relation, if any, among these events is not well characterized. Lee et al. found that starved mouse embryonic fibroblasts lacking the essential autophagy gene product Atg7 failed to undergo cell cycle arrest. Independent of its E1-like enzymatic activity, Atg7 could bind to the tumor suppressor p53 to regulate the transcription of the gene encoding the cell cycle inhibitor $p21^{CDKN1A}$. With prolonged metabolic stress, the absence of Atg7 resulted in augmented DNA damage with increased p53-dependent apoptosis. Inhibition of the DNA damage response by deletion of the protein kinase Chk2 partially rescued postnatal lethality in $Atg7^{-/-}$ mice. Thus, when nutrients are limited, Atg7 regulates p53-dependent cell cycle and cell death pathways.

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Eitan Israeli

Capsule

Amino acid position 11 of HLA-DRβ1 is a major determinant of chromosome 6p association with ulcerative colitis

The major histocompatibility complex (MHC) on chromosome 6p is an established risk locus for ulcerative colitis (UC) and Crohn's disease (CD). Achkar and team aimed to better define MHC association signals in UC and CD by combining data from dense single-nucleotide polymorphism (SNP) genotyping and from imputation of classical human leukocyte antigen (HLA) types, their constituent SNPs and corresponding amino acids in 562 UC, 611 CD and 1428 control subjects. Univariate and multivariate association analyses were performed, controlling for ancestry. In univariate analyses, absence of the rs9269955 C allele was strongly associated with risk for UC ($P = 2.67 \times 10^{-13}$). rs9269955 is an SNP in the codon for amino acid position 11 of HLA-DRβ1, located in the P6 pocket of the HLA-DR antigen binding cleft. This amino acid position was also the most significantly UC-associated amino acid in omnibus tests ($P = 2.68 \times 10^{-13}$). Multivariate modeling identified rs9269955-C and 13 other variants in best predicting UC vs. control status. In contrast, there was only suggestive association evidence between the MHC and CD. Taken together, these data demonstrate that variation at HLA-DRβ1, amino acid 11 in the P6 pocket of the HLA-DR complex antigen binding cleft is a major determinant of chromosome 6p association with UC.

Genes Immun 2012; 13: 245

Eitan Israeli

Capsule

NLRC4 driven production of IL-1β discriminates between pathogenic and commensal bacteria and promotes host intestinal defense

Intestinal phagocytes transport oral antigens and promote immune tolerance, but their role in innate immune responses remains unclear. Franchi and collaborators found that intestinal phagocytes were anergic to ligands for Toll-like receptors (TLRs) or commensals but constitutively expressed the precursor to interleukin 1β (pro-IL-1β). After infection with pathogenic Salmonella or Pseudomonas, intestinal phagocytes produced mature IL-1β through the NLRC4 inflammasome but did not produce tumor necrosis factor (TNF) or IL-6. BALB/c mice deficient in NLRC4 or the IL-1 receptor were highly susceptible to orogastric but not intraperitoneal infection with Salmonella. That enhanced lethality was preceded by impaired expression of endothelial adhesion molecules, lower neutrophil recruitment and poor intestinal pathogen clearance. Thus, NLRC4-dependent production of IL-1β by intestinal phagocytes represents a specific response that discriminates pathogenic bacteria from commensal bacteria and contributes to host defense in the intestine.

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Eitan Israeli

Capsule

Joint decisions in a group of people

In many instances, decisions made by relatively homogeneous groups (two or more people) coalesce around the choice that people are most confident in, and this in turn stems from the sampling of representations that individuals perform when making their choices. Koriat found that if most of the group members are able to form accurate judgments, then confidence and accuracy coincide and the consensus choice is the correct one. By contrast, if few people know the right answer, then heterogeneity in people's representations appeared to offer a surer path to accuracy.

Science 2012; 336: 360

Eitan Israeli

Capsule

The mechanisms of protein aggregation

Amyloid fibrils are insoluble protein aggregates that play a role in various degenerative diseases. Recent experiments have provided insight into fibrillar structures; however, the mechanisms of aggregation remain unclear. Neudecker et al. describe the structure of a transient folding intermediate in a protein SH3 domain known to undergo aggregation. The intermediate is stabilized by non-native interactions and exposes an aggregation-prone β strand. Thus, for this protein, folding from the intermediate state will compete with aggregation.

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Eitan Israeli