Capsule

IL-17RE is the functional receptor for IL-17C and mediates mucosal immunity to infection with intestinal pathogens

Interleukin 17 receptor E (IL-17RE) is an orphan receptor of the IL-17 receptor family. Song and team show that IL-17RE is a receptor specific to IL-17C and has an essential role in host mucosal defense against infection. IL-17C activated downstream signaling through IL-17RE-IL-17RA complex for the induction of genes encoding antibacterial peptides as well as pro-inflammatory molecules. IL-17C was upregulated in colon epithelial cells during infection with *Citrobacter rodentium* and acted in synergy with IL-22 to induce the expression of antibacterial peptides in colon epithelial cells. Loss of IL-17C-mediated signaling in IL-17RE-deficient mice led to lower expression of genes encoding antibacterial molecules, greater bacterial burden and early mortality during infection. Together these data identify IL-17RE as a receptor of IL-17C that regulates early innate immunity to intestinal pathogens.

Nature Immunol 2011; 12: 1151

Eitan Israeli

Capsule

Invariant natural killer T cells recognize lipid self-antigen induced by microbial danger signals

Invariant natural killer T cells (iNKT cells) have a prominent role during infection and other inflammatory processes, and these cells can be activated through their T cell antigen receptors by microbial lipid antigens. However, increasing evidence shows that they are also activated in situations in which foreign lipid antigens would not be present, which suggests a role for lipid self-antigen. Brennan et al. found that an abundant endogenous lipid, β-D-glucopyranosylceramide (β-GlcCer), was a potent iNKT cell self antigen in mouse and human and that its activity depended on the composition of the N-acyl chain. Furthermore, β-GlcCer accumulated during infection and in response to Toll-like receptor agonists, contributing to iNKT cell activation. Thus, the authors propose that recognition of β-GlcCer by the invariant T cell antigen receptor translates innate danger signals into iNKT cell activation.

Nature Immunol 2011; 12: 1202

Eitan Israeli

Capsule

Distinct stem cells contribute to mammary gland development and maintenance

The mammary epithelium is composed of several cell lineages including luminal, alveolar and myoepithelial cells. Transplantation studies have suggested that the mammary epithelium is maintained by the presence of multipotent mammary stem cells. To define the cellular hierarchy of the mammary gland during physiological conditions, Van Keymeulen et al. performed genetic lineage-tracing experiments and clonal analysis of the mouse mammary gland during development, adulthood and pregnancy. The authors found that in postnatal unperturbed mammary gland, both luminal and myoepithelial lineages contain long-lived unipotent stem cells that display extensive renewing capacities, as demonstrated by their ability to clonally expand during morphogenesis and adult life as well as undergo massive expansion during several cycles of pregnancy. The demonstration that the mammary gland contains different types of long-lived stem cells has profound implications for our understanding of mammary gland physiology and will be instrumental in unraveling the cells at the origin of breast cancers.

Nature 20111; 479: 189

Eitan Israeli

Capsule

Suppression of bone formation by osteoclastic expression of semaphorin 4D

Most of the currently available drugs for osteoporosis inhibit osteoclastic bone resorption; only a few drugs promote osteoblastic bone formation. It is thus becoming increasingly necessary to identify the factors that regulate bone formation. Negishi-Koga and colleagues found that osteoclasts express semaphorin 4D (Sema4D), previously shown to be an axon guidance molecule, which potently inhibits bone formation. The binding of Sema4D to its receptor Plexin-B1 on osteoblasts resulted in the activation of the small GTPase RhoA, which inhibits bone formation by suppressing insulin-like growth factor-1 (IGF-1) signaling and by modulating osteoblast motility. Sema4d-/- mice, Plxnb1-/- mice and mice expressing a dominant-negative RhoA specifically in osteoblasts showed an osteosclerotic phenotype due to augmented bone formation. Notably, Sema4D-specific antibody treatment markedly prevented bone loss in a model of postmenopausal osteoporosis. Thus, Sema4D has emerged as a new therapeutic target for the discovery and development of bone-increasing drugs.

Nature Med 2011; 17: 1473

Eitan Israeli

Capsule

Expression of A20 by dendritic cells preserves immune homeostasis and prevents colitis and spondyloarthritis

Dendritic cells (DCs), which are known to support immune activation during infection, may also regulate immune homeostasis in resting animals. Hammer et al. show that mice lacking the ubiquitin-editing molecule A20 specifically in DCs spontaneously showed DC activation and population expansion of activated T cells. Analysis of DC-specific epistasis in compound mice lacking both A20 and the signaling adaptor MyD88 specifically in DCs showed that A20 restricted both MyD88-independent signals, which drive activation of DCs and T cells, and MyD88-dependent signals, which drive population expansion of T cells. In addition, mice lacking A20 specifically in DCs spontaneously developed lymphocyte-dependent colitis, seronegative ankylosing arthritis and enthesitis, conditions stereotypical of human inflammatory bowel disease (IBD). These findings indicate that DCs need A20 to preserve immune quiescence and suggest that A20-dependent DC functions may underlie IBD and IBD-associated arthritides.

Nature Immunol 2011; 12: 118

Eitan Israeli

Capsule

DNA methylation regulates the expression of CXCL12 in rheumatoid arthritis synovial fibroblasts

In the search for specific genes regulated by DNA methylation in rheumatoid arthritis (RA), Karouzakis and associates investigated the expression of CXCL12 in synovial fibroblasts (SFs) and the methylation status of its promoter and determined its contribution to the expression of matrix metalloproteinases (MMPs). 5-azacytidine demethylation increased the expression of CXCL12 and reduced the methylation of CpG nucleotides. A lower percentage of CpG methylation was found in the CXCL12 promoter of RASFs compared with OASFs. Overall, the authors observed a significant correlation in the mRNA expression and the CXCL12 promoter DNA methylation. Stimulation of RASFs with CXCL12 increased the expression of MMPs. CXCR7 but not CXCR4 was expressed and functional in SFs. The researchers show that RASFs produce more CXCL12 than OASFs due to promoter methylation changes and that stimulation with CXCL12 activates MMPs via CXCR7 in SFs, thereby describing an endogenously activated pathway in RASFs, which promotes joint destruction.

Genes Immunity 2011; 12: 643

Eitan Israeli

Capsule

Epigenetic suppression of GAD65 expression mediates persistent pain

Chronic pain is a common neurological disease involving lasting, multifaceted maladaptations ranging from gene modulation to synaptic dysfunction and emotional disorders. Sustained pathological stimuli in many diseases alter the output activities of certain genes through epigenetic modifications, but it is unclear how epigenetic mechanisms operate in the development of chronic pain. Zhang et al. show that in the rat brainstem nucleus raphe magnus, which is important for central mechanisms of chronic pain, persistent inflammatory and neuropathic pain epigenetically suppresses Gad2 [encoding glutamic acid decarboxylase 65 (GAD65)] transcription through histone deacetylase (HDAC)-mediated histone hypoacetylation, resulting in impaired γ-aminobutyric acid (GABA) synaptic inhibition. Gad2 knockout mice showed sensitized pain behavior and impaired GABA synaptic function in their brainstem neurons. In wild-type but not Gad2 knockout mice, HDAC inhibitors strongly increased GAD65 activity, restored GABA synaptic function and relieved sensitized pain behavior. These findings suggest GAD65 and HDACs as potential therapeutic targets in an epigenetic approach to the treatment of chronic pain.

Nature Med 2011; 17: 1448

Eitan Israeli

Capsule

A novel immunodeficiency disorder characterized by genetic amplification of interleukin-25

Many primary immunodeficiency disorders of differing etiologies have been well characterized, and much understanding of immunological processes has been gained by investigating the mechanisms of disease. Green et al. have used a whole-genome approach, employing single-nucleotide polymorphism and gene expression microarrays, to provide insight into the molecular etiology of a novel immunodeficiency disorder. Using DNA copy number profiling, the researchers defined a hyperploid region on 14q11.2 in the immunodeficiency case associated with the interleukin (IL)-25 locus. This alteration was associated with significantly heightened expression of IL-25 following T cell activation. An associated dominant type 2 helper T cell bias in the immunodeficiency case provides a mechanistic explanation for recurrence of infections by pathogens met by Th1-driven responses. Furthermore, this highlights the capacity of IL-25 to alter normal human immune responses.

Genes Immunity 2011; 12: 663

Eitan Israeli

Capsule

Safety of biologic therapy in rheumatoid arthritis

Biologic therapies have revolutionized the treatment of rheumatic diseases in the past decade. As with any drug, however, a variety of important safety concerns affect the choice and use of these agents. Several issues, such as the risk of infection, malignancy, or administration reactions, apply to all of these compounds, although some conditions that affect patient selection and management within these categories seem to be specific to particular biologic treatments. Other safety concerns with biologic agents, such as congestive heart failure, demyelinating disease, and hyperlipidemia, are associated with individual agents. Despite all these concerns, the therapeutic indices for biologic agents remain fairly high in relation to non-biologic DMARDs. Available safety data for all biologic agents approved for the treatment of rheumatoid arthritis were reviewed by Woodrick and Ruderman, who conclude that with careful patient selection and appropriate vigilance on the part of treating physicians and other care providers, these compounds can be safely integrated into the therapeutic plan.

Nature Rev Rheumatol 2011; 7: 639

Eitan Israeli

Capsule

Israeli scientist develops technology to diagnose hearing loss

A researcher at Tel Aviv University has developed a fast-track gene-based technology to diagnose hearing loss. Prof. Karen Avraham, working in a unique collaboration with Prof. Moein Kannan from Bethlehem University, used "exome deep sequencing" – a method that sequences thousands of genes at a time. Exome sequencing collects relevant DNA from specific sites of the body. The process was used to identify five genetic mutations leading to deafness in a population of 11 Jewish Israelis and Palestinian Authority Arabs. None were related to each other, but all had deafness in their families. This method is faster and cheaper than current methods. Of the more than 28 million Americans who are hearing impaired, at least half of the cases can be traced to genetic causes. The condition is especially challenging for children born with hearing impairment, because spoken language, reading and cognitive development are all tied to hearing. Prof. Avraham commented: "This new technology is changing the way we practice genomic medicine, and revolutionizing genetic diagnostics."

Israel High-Tech & Investment Report

Capsule

Structural basis of RNA recognition and activation by innate immune receptor RIG-I

Retinoic-acid-inducible gene-I (RIG-I, also known as DDX58) is a cytoplasmic pathogen recognition receptor that recognizes pathogen-associated molecular pattern (PAMP) motifs to differentiate between viral and cellular RNAs. RIG-I is activated by blunt-ended double-stranded (ds)RNA with or without a 5'-triphosphate (ppp), by single-stranded RNA marked by a 5'-ppp and by polyuridine sequences. Upon binding to such PAMP motifs, RIG-I initiates a signaling cascade that induces innate immune defenses and inflammatory cytokines to establish an antiviral state. The RIG-I pathway is highly regulated and aberrant signaling leads to apoptosis, altered cell differentiation, inflammation, autoimmune diseases and cancer. The helicase and repressor domains (RD) of RIG-I recognize dsRNA and 5'-ppp RNA to activate the two amino-terminal caspase recruitment domains (CARDs) for signaling. In order to understand the synergy between the helicase and the RD for RNA binding, and the contribution of ATP hydrolysis to RIG-I activation, Jiang and fellow researchers determined the structure of human RIG-I helicase-RD in complex with dsRNA and an ATP analog. The helicase-RD organizes into a ring around dsRNA, capping one end, while contacting both strands using previously uncharacterized motifs to recognize dsRNA. Small-angle X-ray scattering, limited proteolysis and differential scanning fluorimetry indicate that RIG-I is in an extended and flexible conformation that compacts upon binding RNA. These results provide a detailed view of the role of helicase in dsRNA recognition, the synergy between the RD and the helicase for RNA binding and the organization of full-length RIG-I bound to dsRNA, and provide evidence of a conformational change upon RNA binding. The RIG-I helicase-RD structure is consistent with dsRNA translocation without unwinding and cooperative binding to RNA. The structure yields unprecedented insight into innate immunity and has a broader impact on other areas of biology, including RNA interference and DNA repair, which utilize homologous helicase domains within DICER and FANCM.

Nature 2011; 479: 423

Eitan Israeli

Capsule

Autophagy and tumor cell clearance

The process of autophagy, through which cells can digest their own components, has complicated, sometimes contradictory, effects on cancer cells. Whereas loss of autophagy can lead to genomic instability and favor generation of cancer cells, maintained or enhanced autophagy can help cancer cells survive in a stressful environment. Michaud et al. found that in mice autophagy could also have a strong influence on the response of the immune system to tumor cells dying in response to chemotherapy. Autophagy caused release of adenosine triphosphate from such cells, which helped to recruit immune cells that contributed to cancer cell clearance.

Science 2011; 334: 1573

Eitan Israeli

Capsule

A mechanism for glycoconjugate vaccine activation of the adaptive immune system and its implications for vaccine design

Glycoconjugate vaccines have provided enormous health benefits globally, but they have been less successful in some populations at high risk for developing disease. To identify new approaches to enhancing glycoconjugate effectiveness, Avci et al. investigated molecular and cellular mechanisms governing the immune response to a prototypical glycoconjugate vaccine. The authors found that in antigen-presenting cells a carbohydrate epitope is generated upon endolysosomal processing of group B streptococcal type III polysaccharide coupled to a carrier protein. In conjunction with a carrier protein-derived peptide, this carbohydrate epitope binds major histocompatibility class II (MHCII) and stimulates carbohydrate-specific CD4+ T cell clones to produce interleukins 2 and 4 – cytokines essential for providing T cell help to antibody-producing B cells. An archetypical glycoconjugate vaccine that was constructed to maximize the presentation of carbohydrate-specific T cell epitopes is 50–100 times more potent and substantially more protective in a neonatal mouse model of group B *Streptococcus* infection than a vaccine constructed by methods currently used by the vaccine industry. This discovery of how glycoconjugates are processed resulting in presentation of carbohydrate epitopes that stimulate CD4+ T cells has key implications for glycoconjugate vaccine design that could result in greatly enhanced vaccine efficacy.

Nature Med 2011; 17: 1602

Eitan Israeli

Capsule

Association of Toll-like receptor 10 and susceptibility to Crohn's disease independent of NOD2

Impaired innate inflammatory response has a key role in the Crohn's disease (CD) pathogenesis. Abad et al. investigated the possible role of the TLR10–TLR1–TLR6 gene cluster in CD susceptibility; their study population comprised 508 CD patients (284 in cohort 1 and 224 in cohort 2) and 576 controls. TLR10–TLR1–TLR6 cluster single-nucleotide polymorphisms genotyping, NOD2 mutations and TLR10 mRNA quantification were performed using TaqMan assays. One TLR10 haplotype (TLR10GGGG) was found associated with CD susceptibility in both cohorts; individuals with two copies had approximately twofold more risk of CD susceptibility than individuals having no copies (odds ratio 1.89, $P = 0.0002$). No differences in the mRNA levels were observed among the genotypes. The strongest model for predicting CD risk according to the MDR analysis was a two-locus model including NOD2 mutations and TLR10GGGG haplotype ($P < 0.0001$). The interaction gain attributed to the combination of both genes was negative (IG = –2.36%), indicating redundancy or independent effects. These results support association of the TLR10 gene with CD susceptibility. The effect of TLR10 would be independent of NOD2, suggesting different signaling pathways for both genes.

Genes Immunity 2011; 12: 635

Eitan Israeli