Capsule

How insulin engages its primary binding site on the insulin receptor

Insulin receptor signaling has a central role in mammalian biology, regulating cellular metabolism, growth, division, differentiation and survival. Insulin resistance contributes to the pathogenesis of type 2 diabetes mellitus and the onset of Alzheimer's disease; aberrant signaling occurs in diverse cancers, exacerbated by cross-talk with the homologous type 1 insulin-like growth factor receptor (IGF1R). Despite more than three decades of investigation, the three-dimensional structure of the insulin-insulin receptor complex has proved elusive, confounded by the complexity of producing the receptor protein. Menting et al. present the first view of the interaction of insulin with its primary binding site on the insulin receptor, on the basis of four crystal structures of insulin bound to truncated insulin receptor constructs. The direct interaction of insulin with the first leucine-rich-repeat domain (L1) of insulin receptor is seen to be sparse, the hormone instead engaging the insulin receptor carboxy-terminal α-chain (αCT) segment, which is itself remodeled on the face of L1 upon insulin binding. Contact between insulin and L1 is restricted to insulin B-chain residues. The αCT segment displaces the B-chain C-terminal β-strand away from the hormone core, revealing the mechanism of a long-proposed conformational switch in insulin upon receptor engagement. This mode of hormone-receptor recognition is novel within the broader family of receptor tyrosine kinases. The authors support these findings by photo-crosslinking data that place the suggested interactions into the context of the holoreceptor and by isothermal titration calorimetry data that dissect the hormone-insulin receptor interface. Together, these findings provide an explanation for a wealth of biochemical data from the insulin receptor and IGF1R systems relevant to the design of therapeutic insulin analogues.

Nature 2013; 493: 241

Eitan Israeli

Capsule

Angiogenesis induced by CNS inflammation promotes neuronal remodeling through vessel-derived prostacyclin

Angiogenesis is a prominent feature of central nervous system (CNS) disease and has roles in both the continued promotion of inflammation and the subsequent repair processes. Muramatsu et al. report that prostacyclin (or prostaglandin I2) derived from new vessels promotes axonal remodeling of injured neuronal networks after CNS inflammation. In a localized model of experimental autoimmune encephalomyelitis (EAE), new vessels formed around the inflammatory lesion, followed by sprouting of adjacent corticospinal tract (CST) fibers. These sprouting fibers formed a compensatory motor circuit, leading to recovery of motor function. Capillary endothelial cell-derived prostacyclin bound to its receptor, the type I prostaglandin receptor (IP receptor), on CST neurons, promoting sprouting of CST fibers and contributing to the repair process. Inhibition of prostacyclin receptor signaling impaired motor recovery, whereas the IP receptor agonist iloprost promoted axonal remodeling and motor recovery after the induction of EAE. These findings reveal an important function of angiogenesis in neuronal rewiring and suggest that prostacyclin is a promising molecule for enhancing functional recovery from CNS disease.

Nature Med 2012; 18: 1658

Eitan Israeli

Capsule

Evolution of an HIV glycan-dependent broadly neutralizing antibody epitope through immune escape

Neutralizing antibodies are likely to play a crucial part in a preventive human immunodeficiency virus-1 (HIV-1) vaccine. Although efforts to elicit broadly cross-neutralizing (BCN) antibodies by vaccination have been unsuccessful, a minority of individuals naturally develop these antibodies after many years of infection. How such antibodies arise, and the role of viral evolution in shaping these responses, is unknown. Moore et al. show, in two HIV-1–infected individuals who developed BCN antibodies targeting the glycan at Asn332 on the gp120 envelope, that this glycan was absent on the initial infecting virus. However, this BCN epitope evolved within 6 months, through immune escape from earlier strain-specific antibodies that resulted in a shift of a glycan to position 332. Both viruses that lacked the glycan at amino acid 332 were resistant to the Asn332-dependent BCN monoclonal antibody PGT128, whereas escaped variants that acquired this glycan were sensitive. Analysis of large sequence and neutralization data sets showed the 332 glycan to be significantly under-represented in transmitted subtype C viruses compared to chronic viruses, with the absence of this glycan corresponding with resistance to PGT128. These findings highlight the dynamic interplay between early antibodies and viral escape in driving the evolution of conserved BCN antibody epitopes.

Nature Med 2012; 18: 1688

Eitan Israeli

Capsule

Vaccine-induced CD8+ T cells control AIDS virus replication

Developing a vaccine for human immunodeficiency virus (HIV) may be aided by a complete understanding of those rare cases in which some HIV-infected individuals control replication of the virus. Most of these elite controllers express the histocompatibility alleles HLA-B*57 or HLA-B*27. These alleles remain by far the most robust associations with low concentrations of plasma virus, yet the mechanism of control in these individuals is not entirely clear. Mudd et al. vaccinated Indian rhesus macaques that express Mamu-B*08, an animal model for HLA-B*27-mediated elite control, with three Mamu-B*08-restricted CD8+ T cell epitopes, and demonstrated that these vaccinated animals control replication of the highly pathogenic clonal simian immunodeficiency virus (SIV) mac239 virus. High frequencies of CD8+ T cells against these Vif and Nef epitopes in the blood, lymph nodes and colon were associated with viral control. Moreover, the frequency of the CD8+ T cell response against the Nef RL10 epitope (Nef amino acids 137-146) correlated significantly with reduced acute-phase viremia. Finally, two of the eight vaccinees lost control of viral replication in the chronic phase, concomitant with escape in all three targeted epitopes, further implicating these three CD8+ T cell responses in the control of viral replication. These findings indicate that narrowly targeted vaccine-induced virus-specific CD8+ T cell responses can control replication of the AIDS virus.

Nature 2012; 491: 129

Eitan Israeli

Capsule

The Toll-like receptor 5 ligand flagellin promotes asthma by priming allergic responses to indoor allergens

Allergic asthma is a complex disease characterized by eosinophilic pulmonary inflammation, mucus production and reversible airway obstruction. Exposure to indoor allergens is a risk factor for asthma, but this disease is also associated with high household levels of total and particularly Gram-negative bacteria. The ability of bacterial products to act as adjuvants suggests they might promote asthma by priming allergic sensitization to inhaled allergens. In support of this idea, house dust extracts (HDEs) can activate antigen-presenting dendritic cells (DCs) in vitro and promote allergic sensitization to inhaled innocuous proteins in vivo. It is unknown which microbial products provide most of the adjuvant activity in HDEs. A screen for adjuvant activity of microbial products revealed that the bacterial protein flagellin (FLA) stimulated strong allergic airway responses to an innocuous inhaled protein, ovalbumin (OVA). Moreover, Toll-like receptor 5 (TLR5), the mammalian receptor for FLA, was required for priming strong allergic responses to natural indoor allergens present in HDEs. In addition, individuals with asthma have higher serum levels of FLA-specific antibodies as compared to non-asthmatic individuals. Together, these findings suggest that household FLA promotes the development of allergic asthma by TLR5-dependent priming of allergic responses to indoor allergens.

Nature Med 2012; 18: 1705

Eitan Israeli

Capsule

Broad and potent neutralization of HIV-1 by a gp41-specific human antibody

Characterization of human monoclonal antibodies is providing considerable insight into mechanisms of broad human immunodeficiency virus-1 (HIV-1) neutralization. Huang and co-authors report an HIV-1 gp41 membrane-proximal external region (MPER)-specific antibody, named 10E8, which neutralizes ~98% of tested viruses. An analysis of sera from 78 healthy HIV-1-infected donors demonstrated that 27% contained MPER-specific antibodies and 8% contained 10E8-like specificities. In contrast to other neutralizing MPER antibodies, 10E8 did not bind phospholipids, was not autoreactive, and bound cell-surface envelope. The structure of 10E8 in complex with the complete MPER revealed a site of vulnerability comprising a narrow stretch of highly conserved gp41-hydrophobic residues and a critical arginine or lysine just before the transmembrane region. Analysis of resistant HIV-1 variants confirmed the importance of these residues for neutralization. The highly conserved MPER is a target of potent, non-self-reactive neutralizing antibodies, suggesting that HIV-1 vaccines should aim to induce antibodies to this region of HIV-1 envelope glycoprotein.

Nature 2012; 491: 406

Eitan Israeli

Capsule

Apoptotic cell clearance by bronchial epithelial cells critically influences airway inflammation

Lung epithelial cells can influence immune responses to airway allergens. Airway epithelial cells also undergo apoptosis after encountering environmental allergens; yet, relatively little is known about how these are cleared, or their effect on airway inflammation. Juncadella and co-workers show that airway epithelial cells efficiently engulf apoptotic epithelial cells and secrete anti-inflammatory cytokines, dependent upon intracellular signaling by the small GTPase Rac1. Inducible deletion of Rac1 expression specifically in airway epithelial cells in a mouse model resulted in defective engulfment by epithelial cells and aberrant anti-inflammatory cytokine production. Intranasal priming and challenge of these mice with house dust mite extract or ovalbumin as allergens led to exacerbated inflammation, augmented Th2 cytokines and airway hyper-responsiveness, with decreased interleukin (IL)-10 in bronchial lavages. Rac1-deficient epithelial cells produced much higher IL-33 upon allergen or apoptotic cell encounter, with increased numbers of nuocyte-like cells. Administration of exogenous IL-10 'rescued' the airway inflammation phenotype in Rac1-deficient mice, with decreased IL-33. Collectively, these genetic and functional studies suggest a new role for Rac1-dependent engulfment by airway epithelial cells and in establishing the anti-inflammatory environment, and that defects in cell clearance in the airways could contribute to inflammatory responses towards common allergens.

Nature 2013; 493: 547

Eitan Israeli

Capsule

Lymph node T cell responses predict the efficacy of live attenuated SIV vaccines

Live attenuated simian immunodeficiency virus (SIV) vaccines (LAVs) remain the most efficacious of all vaccines in non-human primate models of human immunodeficiency virus and AIDS, yet the basis of their robust protection remains poorly understood. Fukazawa et al. show that the degree of LAV-mediated protection against intravenous wild-type SIVmac239 challenge strongly correlates with the magnitude and function of SIV-specific, effector-differentiated T cells in the lymph node but not with the responses of such T cells in the blood or with other cellular, humoral and innate immune parameters. The authors found that maintenance of protective T cell responses is associated with persistent LAV replication in the lymph node, which occurs almost exclusively in follicular helper T cells. Thus, effective LAVs maintain lymphoid tissue-based, effector-differentiated, SIV-specific T cells that intercept and suppress early wild-type SIV amplification and, if present in sufficient frequencies, can completely control and perhaps clear infection, an observation that provides a rationale for the development of safe, persistent vectors that can elicit and maintain such responses.

Nature Med 2012; 18: 1637

Eitan Israeli

Capsule

Mosaic PPM1D mutations are associated with predisposition to breast and ovarian cancer

Improved sequencing technologies offer unprecedented opportunities for investigating the role of rare genetic variation in common disease. However, there are considerable challenges with respect to study design, data analysis and replication. Using pooled next-generation sequencing of 507 genes implicated in the repair of DNA in 1150 samples, an analytical strategy focused on protein-truncating variants (PTVs) and a large-scale sequencing case-control replication experiment in 13,642 individuals. Ruark et al. show that rare PTVs in the p53-inducible protein phosphatase PPM1D are associated with predisposition to breast cancer and ovarian cancer. PPM1D PTV mutations were present in 25 of 7781 cases versus 1 of 5861 controls ($P = 1.12 \times 10–5$), including 18 mutations in 6912 individuals with breast cancer ($P = 2.42 \times 10–4$) and 12 mutations in 1121 individuals with ovarian cancer ($P = 3.10 \times 10–9$). Notably, all of the identified PPM1D PTVs were mosaic in lymphocyte DNA and clustered within a 370 basepair region in the final exon of the gene, carboxy-terminal to the phosphatase catalytic domain. Functional studies demonstrate that the mutations result in enhanced suppression of p53 in response to ionizing radiation exposure, suggesting that the mutant alleles encode hyperactive PPM1D isoforms. Thus, although the mutations cause premature protein truncation, they do not result in the simple loss-of-function effect typically associated with this class of variant, but instead probably have a gain-of-function effect. These results have implications for the detection and management of breast and ovarian cancer risk. More generally, these data provide new insights into the role of rare and of mosaic genetic variants in common conditions, and the use of sequencing in their identification.

Nature 2013; 493: 406

Eitan Israeli

Capsule

A shift in cancer's inflammatory balance

One of the many factors that contribute to the initiation and progression of cancer is inflammation. Inflammation can support tumor development, both directly and indirectly, and tumors can promote a chronic inflammatory environment that results in immunosuppression, which benefits the tumor. In their review of the components of the immune system that contribute to the chronic inflammation seen in tumors, Coussens et al. found that potential therapies might shift this inflammatory environment toward one more characteristic of an acute, resolving inflammation, similar to what is observed during a pathogenic infection. Such a shift would relieve immunosuppression and drive antitumor immunity that, when combined with other therapies, may ultimately result in tumor cell clearance.

Science 2013; 339: 286

Eitan Israeli

Capsule

β-arrestin 2 regulates Aβ generation and γ-secretase activity in Alzheimer's disease

β-arrestins are associated with numerous aspects of G protein-coupled receptor (GPCR) signaling and regulation and accordingly influence diverse physiological and pathophysiological processes. Thathiah and co-authors report that β-arrestin 2 expression is elevated in two independent cohorts of individuals with Alzheimer's disease. Overexpression of β-arrestin 2 leads to an increase in amyloid-β (Aβ) peptide generation, whereas genetic silencing of Arrb2 (encoding β-arrestin 2) reduces generation of Aβ in cell cultures and in Arrb2−/− mice. Moreover, in a transgenic mouse model of Alzheimer's disease, genetic deletion of Arrb2 leads to a reduction in the production of Aβ40 and Aβ42. Two GPCRs implicated previously in Alzheimer's disease (GPR3 and the β2-adrenergic receptor) mediate their effects on Aβ generation through interaction with β-arrestin 2. β-arrestin 2 physically associates with the Aph-1a subunit of the γ-secretase complex and redistributes the complex toward detergent-resistant membranes, increasing the catalytic activity of the complex. Collectively, these studies identify β-arrestin 2 as a new therapeutic target for reducing amyloid pathology and GPCR dysfunction in Alzheimer's disease

Nature Med 2013; 19: 43

Eitan Israeli

Capsule

Wasting disease and the bacterium Desulfovibrio

Malnutrition is well known in Malawi, including a severe form – kwashiorkor – in which children do not simply waste away, they also suffer edema, liver damage, skin ulceration, and anorexia. Smith et al. investigated the microbiota of pairs of twins in Malawian villages and found notable differences in the composition of the gut microbiota in children with kwashiorkor. In these children, a bacterial species related to Desulfovibrio, which has been associated with bowel disease and inflammation, was noticeable. When the fecal flora from either the healthy or the sick twin was transplanted into groups of germ-free mice, the mice that received the kwashiorkor sample started to lose weight, like their human counterpart.

Science 2013; 339: 548

Eitan Israeli