Capsule

Cellular immune correlates of protection against symptomatic pandemic influenza

The role of T cells in mediating heterosubtypic protection against natural influenza illness in humans is uncertain. The 2009 H1N1 pandemic (pH1N1) provided a unique natural experiment to determine whether cross-reactive cellular immunity limits symptomatic illness in antibody-naive individuals. Sridhar et al. followed 342 healthy adults through the UK pandemic waves and correlated the responses of pre-existing T cells to the pH1N1 virus and conserved core protein epitopes with clinical outcomes after incident pH1N1 infection. Higher frequencies of pre-existing T cells to conserved CD8 epitopes were found in individuals who developed less severe illness, with total symptom score having the strongest inverse correlation with the frequency of interferon-gamma (IFN-γ)+interleukin-2 (IL-2)$^-$ CD8+ T cells ($r = -0.6$, $P = 0.004$). Within this functional CD8+IFN-γ+IL-2$^-$population, cells with the CD45RA+ chemokine (C-C) receptor 7 (CCR7)$^-$ phenotype inversely correlated with symptom score and had lung-homing and cytotoxic potential. In the absence of cross-reactive neutralizing antibodies, CD8+ T cells specific to conserved viral epitopes correlated with cross-protection against symptomatic influenza. This protective immune correlate could guide universal influenza vaccine development.

Nature Med 2013; 19: 1305

Eitan Israeli

Capsule

A small molecule AdipoR agonist for type 2 diabetes and short life in obesity

Adiponectin secreted from adipocytes binds to adiponectin receptors AdipoR1 and AdipoR2, and exerts anti-diabetic effects via activation of AMPK and PPAR-α pathways, respectively. Levels of adiponectin in plasma are reduced in obesity, which causes insulin resistance and type 2 diabetes. Thus, orally active small molecules that bind to and activate AdipoR1 and AdipoR2 could ameliorate obesity-related diseases such as type 2 diabetes. Iwabu et al. report the identification of orally active synthetic small molecule AdipoR agonists. One of these compounds, AdipoR agonist (AdipoRon), bound to both AdipoR1 and AdipoR2 in vitro. AdipoRon showed very similar effects to adiponectin in muscle and liver, such as activation of AMPK and PPAR-α pathways, and ameliorated insulin resistance and glucose intolerance in mice fed a high fat diet, which was completely obliterated in AdipoR1 and AdipoR2 double-knockout mice. Moreover, AdipoRon ameliorated diabetes of genetically obese rodent model *db/db* mice, and prolonged the shortened lifespan of *db/db* mice on a high fat diet. Thus, orally active AdipoR agonists such as AdipoRon are a promising therapeutic approach for the treatment of obesity-related diseases such as type 2 diabetes.

Nature 2013; 503: 493

Eitan Israeli

Capsule

The genesis and source of the H7N9 influenza viruses causing human infections in China

A novel H7N9 influenza A virus first detected in March 2013 has since caused more than 130 human infections in China, resulting in 40 deaths. Preliminary analyses suggest that the virus is a reassortant of H7, N9 and H9N2 avian influenza viruses and carries some amino acids associated with mammalian receptor binding, raising concerns of a new pandemic. However, neither the source populations of the H7N9 outbreak lineage nor the conditions for its genesis are fully known. Using a combination of active surveillance, screening of virus archives, and evolutionary analyses, Tsan-Yuk Lam et al. show that H7 viruses probably transferred from domestic duck to chicken populations in China on at least two independent occasions. The authors show that the H7 viruses subsequently reassorted with enzootic H9N2 viruses to generate the H7N9 outbreak lineage and a related previously unrecognized H7N7 lineage. The H7N9 outbreak lineage has spread over a large geographic region and is prevalent in chickens at live poultry markets, which are thought to be the immediate source of human infections. Whether the H7N9 outbreak lineage has, or will, become enzootic in China and neighboring regions requires further investigation. The discovery here of a related H7N7 influenza virus in chickens that has the ability to infect mammals experimentally suggests that H7 viruses may pose threats beyond the current outbreak. The continuing prevalence of H7 viruses in poultry could lead to the generation of highly pathogenic variants and further sporadic human infections, with a continued risk of the virus acquiring human-to-human transmissibility.

Nature 2013; 502: 241

Eitan Israeli

Capsule

Characterization of H7N9 influenza A viruses isolated from humans

Avian influenza A viruses rarely infect humans; however, when human infection and subsequent human-to-human transmission occurs, worldwide outbreaks (pandemics) can result. The recent sporadic infections of humans in China with a previously unrecognized avian influenza A virus of the H7N9 subtype (A(H7N9)) have caused concern owing to the appreciable case-fatality rate associated with these infections (more than 25%), potential instances of human-to-human transmission, and the lack of pre-existing immunity among humans to viruses of this subtype. Watanbe and associates have characterized two early human A(H7N9) isolates, A/Anhui/1/2013 (H7N9) and A/Shanghai/1/2013 (H7N9); hereafter referred to as Anhui/1 and Shanghai/1, respectively. In mice, Anhui/1 and Shanghai/1 were more pathogenic than a control avian H7N9 virus (A/duck/Gunma/466/2011 (H7N9); Dk/GM466) and a representative pandemic 2009 H1N1 virus (A/California/4/2009 (H1N1pdm09); CA04). Anhui/1, Shanghai/1 and Dk/GM466 replicated well in the nasal turbinates of ferrets. In non-human primates, Anhui/1 and Dk/GM466 replicated efficiently in the upper and lower respiratory tracts, whereas the replicative ability of conventional human influenza viruses is typically restricted to the upper respiratory tract of infected primates. By contrast, Anhui/1 did not replicate well in miniature pigs after intranasal inoculation. Critically, Anhui/1 transmitted through respiratory droplets in one of three pairs of ferrets. Glycan arrays showed that Anhui/1, Shanghai/1 and A/Hangzhou/1/2013 (H7N9) (a third human A(H7N9) virus tested in this assay) bind to human virus-type receptors, a property that may be critical for virus transmissibility in ferrets. Anhui/1 was found to be less sensitive in mice to neuraminidase inhibitors than a pandemic H1N1 2009 virus, although both viruses were equally susceptible to an experimental antiviral polymerase inhibitor. The robust replicative ability in mice, ferrets and non-human primates and the limited transmissibility in ferrets of Anhui/1 suggest that A(H7N9) viruses have pandemic potential.

Nature 2013; 501: 551

Eitan Israeli

Capsule

Staphylococcus δ-toxin induces allergic skin disease by activating mast cells

Atopic dermatitis is a chronic inflammatory skin disease that affects 15–30% of children and approximately 5% of adults in industrialized countries. Although the pathogenesis of atopic dermatitis is not fully understood, the disease is mediated by an abnormal immunoglobulin E immune response in the setting of skin barrier dysfunction. Mast cells contribute to immunoglobulin E-mediated allergic disorders including atopic dermatitis. Upon activation, mast cells release their membrane-bound cytosolic granules leading to the release of several molecules that are important in the pathogenesis of atopic dermatitis and host defense. More than 90% of patients with atopic dermatitis are colonized with *Staphylococcus aureus* in the lesional skin whereas most healthy individuals do not harbor the pathogen. Several staphylococcal exotoxins can act as superantigens and/or antigens in models of atopic dermatitis. However, the role of these staphylococcal exotoxins in disease pathogenesis remains unclear. Nakamura and team report that culture supernatants of *S. aureus* contain potent mast cell degranulation activity. Biochemical analysis identified δ-toxin as the mast cell degranulation-inducing factor produced by *S. aureus*. Mast cell degranulation induced by δ-toxin depended on phosphoinositide 3-kinase and calcium (Ca^{2+}) influx; however, unlike that mediated by immunoglobulin E cross-linking, it did not require the spleen tyrosine kinase. In addition, immunoglobulin E enhanced δ-toxin-induced mast cell degranulation in the absence of antigen. Furthermore, *S. aureus* isolates recovered from patients with atopic dermatitis produced large amounts of δ-toxin. Skin colonization with *S. aureus*, but not a mutant deficient in δ-toxin, promoted immunoglobulin E and interleukin-4 production, as well as inflammatory skin disease. Furthermore, enhancement of immunoglobulin E production and dermatitis by δ-toxin was abrogated in $Kit^{W\text{-}sh/W\text{-}sh}$ mast cell-deficient mice and restored by mast cell reconstitution. These studies identify δ-toxin as a potent inducer of mast cell degranulation and suggest a mechanistic link between *S. aureus* colonization and allergic skin disease.

Nature 2013; 503: 397

Eitan Israeli

Capsule

Cold-inducible RNA-binding protein (CIRP) triggers inflammatory responses in hemorrhagic shock and sepsis

A systemic inflammatory response is observed in patients undergoing hemorrhagic shock and sepsis. Qiang et al. report increased levels of cold-inducible RNA-binding protein (CIRP) in the blood of individuals admitted to the surgical intensive care unit with hemorrhagic shock. In animal models of hemorrhage and sepsis, CIRP is upregulated in the heart and liver and released into the circulation. In macrophages under hypoxic stress, CIRP translocates from the nucleus to the cytosol and is released. Recombinant CIRP stimulates the release of tumor necrosis factor-alpha (TNFα) and HMGB1 from macrophages and induces inflammatory responses and causes tissue injury when injected in vivo. Hemorrhage-induced TNFα and HMGB1 release and lethality were reduced in CIRP-deficient mice. Blockade of CIRP using antisera to CIRP attenuated inflammatory cytokine release and mortality after hemorrhage and sepsis. The activity of extracellular CIRP is mediated through the Toll-like receptor 4 (TLR4)-myeloid differentiation factor 2 (MD2) complex. Surface plasmon resonance analysis indicated that CIRP binds to the TLR4-MD2 complex, as well as to TLR4 and MD2 individually. In particular, human CIRP amino acid residues 106–125 bind to MD2 with high affinity. Thus, CIRP is a damage-associated molecular pattern molecule that promotes inflammatory responses in shock and sepsis.

Nature Med 2013; 19: 1489

Eitan Israeli

Capsule

Genetic identification of a neural circuit that suppresses appetite

Appetite suppression occurs after a meal and in conditions when it is unfavorable to eat, such as during illness or exposure to toxins. A brain region proposed to play a role in appetite suppression is the parabrachial nucleus, a heterogeneous population of neurons surrounding the superior cerebellar peduncle in the brainstem. The parabrachial nucleus is thought to mediate the suppression of appetite induced by the anorectic hormones amylin and cholecystokinin, as well as by lithium chloride and lipopolysaccharide, compounds that mimic the effects of toxic foods and bacterial infections, respectively. Hyperactivity of the parabrachial nucleus is also thought to cause starvation after ablation of orexigenic agouti-related peptide neurons in adult mice. However, the identities of neurons in the parabrachial nucleus that regulate feeding are unknown, as are the functionally relevant downstream projections. Carter et al. identified calcitonin gene-related peptide-expressing neurons in the outer external lateral subdivision of the parabrachial nucleus that project to the laterocapsular division of the central nucleus of the amygdala as forming a functionally important circuit for suppressing appetite. Using genetically encoded anatomic, optogenetic and pharmacogenetic tools, the authors demonstrate that activation of these neurons projecting to the central nucleus of the amygdala suppresses appetite. In contrast, inhibition of these neurons increases food intake in circumstances when mice do not normally eat and prevents starvation in adult mice whose agouti-related peptide neurons are ablated. Taken together, these data demonstrate that this neural circuit from the parabrachial nucleus to the central nucleus of the amygdala mediates appetite suppression in conditions when it is unfavorable to eat. This neural circuit may provide targets for therapeutic intervention to overcome or promote appetite.

Nature 2013; 503: 111

Eitan Israeli

Capsule

Paneth cells as a site of origin for intestinal inflammation

The recognition of autophagy related 16-like 1 (*ATG16L1*) as a genetic risk factor has exposed the critical role of autophagy in Crohn's disease. Homozygosity for the highly prevalent *ATG16L1* risk allele, or murine hypomorphic (HM) activity, causes Paneth cell dysfunction. As *Atg16l1*^{HM} mice do not develop spontaneous intestinal inflammation, the mechanism(s) by which ATG16L1 contributes to disease remains obscure. Deletion of the unfolded protein response (UPR) transcription factor X-box binding protein-1 (*Xbp1*) in intestinal epithelial cells, the human orthologue of which harbors rare inflammatory bowel disease risk variants, results in endoplasmic reticulum (ER) stress, Paneth cell impairment and spontaneous enteritis. Unresolved ER stress is a common feature of inflammatory bowel disease epithelium, and several genetic risk factors of Crohn's disease affect Paneth cells. Adolph et al. show that impairment in either UPR (*Xbp1*$^{\Delta IEC}$) or autophagy function (*Atg16l1*$^{\Delta IEC}$ or *Atg7*$^{\Delta IEC}$) in intestinal epithelial cells results in each other's compensatory engagement, and severe spontaneous Crohn's-disease-like transmural ileitis if both mechanisms are compromised. *Xbp1*$^{\Delta IEC}$ mice show autophagosome formation in hypomorphic Paneth cells, which is linked to ER stress via protein kinase RNA-like endoplasmic reticulum kinase (PERK), elongation initiation factor 2α (eIF2α) and activating transcription factor 4 (ATF4). Ileitis is dependent on commensal microbiota and derives from increased intestinal epithelial cell death, inositol requiring enzyme 1α (IRE1α)-regulated NF-κB activation and tumor necrosis factor signaling, which are synergistically increased when autophagy is deficient. ATG16L1 restrains IRE1α activity, and augmentation of autophagy in intestinal epithelial cells ameliorates ER stress-induced intestinal inflammation and eases NF-κB overactivation and intestinal epithelial cell death. ER stress, autophagy induction and spontaneous ileitis emerge from Paneth cell-specific deletion of *Xbp1*. Genetically and environmentally controlled UPR function within Paneth cells may therefore set the threshold for the development of intestinal inflammation upon hypomorphic ATG16L1 function and implicate ileal Crohn's disease as a specific disorder of Paneth cells.

Nature 2013; 503: 272

Eitan Israeli

Capsule

B lymphocytes trigger monocyte mobilization and impair heart function after acute myocardial infarction

Acute myocardial infarction is a severe ischemic disease responsible for heart failure and sudden death. Zouggart et al. show that after acute myocardial infarction in mice, mature B lymphocytes selectively produce Ccl7 and induce Ly6C^{hi} monocyte mobilization and recruitment to the heart, leading to enhanced tissue injury and deterioration of myocardial function. Genetic (Baff receptor deficiency) or antibody-mediated (CD20- or Baff-specific antibody) depletion of mature B lymphocytes impeded Ccl7 production and monocyte mobilization, limited myocardial injury and improved heart function. These effects were recapitulated in mice with B cell-selective *Ccl7*deficiency. We also show that high circulating concentrations of CCL7 and BAFF in patients with acute myocardial infarction predict increased risk of death or recurrent myocardial infarction. This work identifies a crucial interaction between mature B lymphocytes and monocytes after acute myocardial ischemia and identifies new therapeutic targets for acute myocardial infarction.

Nature Med 2013; 19: 1273

Eitan Israeli

Capsule

Renal tubular Sirt1 attenuates diabetic albuminuria by epigenetically suppressing Claudin-1 overexpression in podocytes

Sirtuin 1 (Sirt1), a NAD$^+$-regulated deacetylase with numerous known positive effects on cellular and whole-body metabolism, is expressed in the renal cortex and medulla. It is known to have protective effects against age-related disease, including diabetes. Hasegawa et al. investigated the protective role of Sirt1 in diabetic renal damage. They found that Sirt1 in proximal tubules (PTs) was down-regulated before albuminuria occurred in streptozotocin-induced or obese (*db/db*) diabetic mice. PT-specific *SIRT1* transgenic and *Sirt*1 knockout mice showed prevention and aggravation of the glomerular changes that occur in diabetes, respectively, and non-diabetic knockout mice exhibited albuminuria, suggesting that Sirt1 in PTs affects glomerular function. Down-regulation of Sirt1 and up-regulation of the tight junction protein Claudin-1 by SIRT1-mediated epigenetic regulation in podocytes contributed to albuminuria. The authors did not observe these phenomena in 5/6 nephrectomized mice. They also demonstrated retrograde interplay from PTs to glomeruli using nicotinamide mononucleotide (NMN) from conditioned medium, measurement of the autofluorescence of photo-activatable NMN and injection of fluorescence-labeled NMN. In human subjects with diabetes, the levels of SIRT1 and Claudin-1 were correlated with proteinuria levels. These results suggest that Sirt1 in PTs protects against albuminuria in diabetes by maintaining NMN concentrations around glomeruli, thus influencing podocyte function.

Nature Med 2013; 19; 1496

Eitan Israeli

Capsule

The kinase mTOR modulates the antibody response to provide cross-protective immunity to lethal infection with influenza virus

Highly pathogenic avian influenza viruses pose a continuing global threat. Current vaccines will not protect against newly evolved pandemic viruses. The creation of 'universal' vaccines has been unsuccessful because the immunological mechanisms that promote heterosubtypic immunity are incompletely defined. Keating et al. found that rapamycin, an immunosuppressive drug that inhibits the kinase mTOR, promoted cross-strain protection against lethal infection with influenza virus of various subtypes when administered during immunization with influenza virus subtype H3N2. Rapamycin reduced the formation of germinal centers and inhibited class switching in B cells, which yielded a unique repertoire of antibodies that mediated heterosubtypic protection.These data established a requirement for the mTORC1 complex in B cell class switching and demonstrated that rapamycin skewed the antibody response away from high affinity variant epitopes and targeted more conserved elements of hemagglutinin. These findings have implications for the design of a vaccine against influenza virus.

Nature Immunol 2013; 14: 1266

Eitan Israeli

Capsule

Antigen specific B cell receptor sensitizes B cells to infection by influenza virus

Influenza A virus-specific B lymphocytes and the antibodies they produce protect against infection. However, the outcome of interactions between an influenza hemagglutinin-specific B cell via its receptor (BCR) and virus is unclear. Through somatic cell nuclear transfer Dougan and colleagues generated mice that harbor B cells with a BCR specific for the hemagglutinin of influenza A/WSN/33 virus (FluBI mice). Their B cells secrete an immunoglobulin gamma 2b that neutralizes infectious virus. Whereas B cells from FluBI and control mice bind equivalent amounts of virus through interaction of hemagglutinin with surface-disposed sialic acids, the A/WSN/33 virus infects only the hemagglutinin-specific B cells. Mere binding of virus is not sufficient for infection of B cells: this requires interactions of the BCR with hemagglutinin, causing both disruption of antibody secretion and FluBI B-cell death within 18 hours. In mice infected with A/WSN/33, lung-resident FluBI B cells are infected by the virus, thus delaying the onset of protective antibody release into the lungs, whereas FluBI cells in the draining lymph node are not infected and proliferate. The authors propose that influenza targets and kills influenza-specific B cells in the lung, thus allowing the virus to gain purchase before the initiation of an effective adaptive response.

Nature 2013; 503: 406

Eitan Israeli

Capsule

Integrin-modulating therapy prevents fibrosis and autoimmunity in mouse models of scleroderma

In systemic sclerosis (SSc), a common and etiologically mysterious form of scleroderma (defined as pathological fibrosis of the skin), previously healthy adults acquire fibrosis of the skin and viscera in association with autoantibodies. Familial recurrence is extremely rare and causal genes have not been identified. Although the onset of fibrosis in SSc typically correlates with the production of autoantibodies, whether they contribute to disease pathogenesis or simply serve as a marker of disease remains controversial and the mechanism for their induction is largely unknown. The study of SSc is hindered by a lack of animal models that recapitulate the etiology of this complex disease. To gain a foothold in the pathogenesis of pathological skin fibrosis, Gerber and co-scientists studied stiff skin syndrome (SSS), a rare but tractable Mendelian disorder leading to childhood onset of diffuse skin fibrosis with autosomal dominant inheritance and complete penetrance. They showed previously that SSS is caused by heterozygous missense mutations in the gene (*FBN1*) encoding fibrillin-1, the main constituent of extracellular microfibrils. SSS mutations all localize to the only domain in fibrillin-1 that harbors an Arg-Gly-Asp (RGD) motif needed to mediate cell-matrix interactions by binding to cell surface integrins. Here they show that mouse lines harboring analogous amino acid substitutions in fibrillin-1 recapitulate aggressive skin fibrosis that is prevented by integrin-modulating therapies and reversed by antagonism of the pro-fibrotic cytokine transforming growth factor-beta (TGFβ). Mutant mice show skin infiltration of pro-inflammatory immune cells including plasmacytoid dendritic cells, T helper cells and plasma cells, and also autoantibody production; these findings are normalized by integrin-modulating therapies or TGFβ antagonism. These results show that alterations in cell-matrix interactions are sufficient to initiate and sustain inflammatory and pro-fibrotic programs and highlight new therapeutic strategies.

Nature 2013; 503: 120

Eitan Israeli

Capsule

Genetic variation near IRF8 is associated with serologic and cytokine profiles in systemic lupus erythematosus and multiple sclerosis

Alleles of interferon (IFN) regulatory factor 8 (IRF8) are associated with susceptibility to both systemic lupus erythematosus (SLE) and multiple sclerosis (MS). Although high-type I IFN is thought to be causal in SLE, type I IFN is used as a therapy in MS. Chrabot and team investigated whether IRF8 alleles were associated with type I IFN levels or serologic profiles in SLE and MS. Alleles that have been previously associated with SLE or MS were genotyped in SLE and MS patients. The MS-associated rs17445836G allele was associated with anti-double-stranded DNA (dsDNA) autoantibodies in SLE patients (meta-analysis odds ratio 1.92). The same allele was associated with decreased serum IFN activity in SLE patients with anti-dsDNA antibodies, and with decreased type I IFN-induced gene expression in peripheral blood mononuclear cell from anti-dsDNA-negative SLE patients. In secondary progressive MS patients, rs17445836G was associated with decreased serum type I IFN. Rs17445836G was associated with increased IRF8 expression in SLE patient B cells. In summary, IRF8 rs17445836G is associated with human autoimmune disease characterized by low-type I IFN levels, and this may have pharmacogenetic relevance as type I IFN is modulated in SLE and MS. The association with autoantibodies and increased IRF8 expression in B cells supports a role for rs17445836G in humoral tolerance.

Genes Immun 2013; 14: 471

Eitan Israeli

Capsule

Therapeutic efficacy of potent neutralizing HIV-1-specific monoclonal antibodies in SHIV-infected rhesus monkeys

Human immunodeficiency virus type 1 (HIV-1)-specific monoclonal antibodies with extraordinary potency and breadth have recently been described. In humanized mice, combinations of monoclonal antibodies have been shown to suppress viremia, but the therapeutic potential of these monoclonal antibodies has not yet been evaluated in primates with an intact immune system. Barouch and colleagues show that administration of a cocktail of HIV-1-specific monoclonal antibodies, as well as the single glycan-dependent monoclonal antibody PGT121, resulted in a rapid and precipitous decline of plasma viremia to undetectable levels in rhesus monkeys chronically infected with the pathogenic simian-human immunodeficiency virus SHIV-SF162P3. A single monoclonal antibody infusion afforded up to a 3.1 log decline of plasma viral RNA in 7 days and also reduced proviral DNA in peripheral blood, gastrointestinal mucosa and lymph nodes without the development of viral resistance. Moreover, after monoclonal antibody administration, host Gag-specific T lymphocyte responses showed improved functionality. Virus rebounded in most animals after a median of 56 days when serum monoclonal antibody titers had declined to undetectable levels, although, notably, a subset of animals maintained long-term virological control in the absence of further monoclonal antibody infusions. These data demonstrate a profound therapeutic effect of potent neutralizing HIV-1-specific monoclonal antibodies in SHIV-infected rhesus monkeys as well as an impact on host immune responses. These findings strongly encourage the investigation of monoclonal antibody therapy for HIV-1 in humans.

Nature 2013; 503: 224

Eitan Israeli

Capsule

Activated ClpP kills persisters and eradicates a chronic biofilm infection

Chronic infections are difficult to treat with antibiotics but are caused primarily by drug-sensitive pathogens. Dormant persister cells that are tolerant to killing by antibiotics are responsible for this apparent paradox. Persisters are phenotypic variants of normal cells and pathways leading to dormancy are redundant, making it challenging to develop anti-persister compounds. Biofilms shield persisters from the immune system, suggesting that an antibiotic for treating a chronic infection should be able to eradicate the infection on its own. A compound capable of corrupting a target in dormant cells will probably kill persisters. The acyldepsipeptide antibiotic (ADEP4) has been shown to activate the ClpP protease, resulting in death of growing cells. Conlon et al. show that ADEP4-activated ClpP becomes a fairly non-specific protease and kills persisters by degrading over 400 proteins, forcing cells to self-digest. Null mutants of *clpP* arise with high probability, but combining ADEP4 with rifampicin produced complete eradication of *Staphylococcus aureus* biofilms in vitro and in a mouse model of a chronic infection. These findings indicate a general principle for killing dormant cells – activation and corruption of a target, rather than conventional inhibition. Eradication of a biofilm in an animal model by activating a protease suggests a realistic path towards developing therapies to treat chronic infections.

Nature 2013; 503: 365

Eitan Israeli

Capsule

Detecting and targeting tumor relapse by its resistance to innate effectors at early recurrence

Tumor recurrence represents a major clinical challenge. Kottke et al. show that emergent recurrent tumors acquire a phenotype radically different from that of their originating primary tumors. This phenotype allows them to evade a host-derived innate immune response elicited by the progression from minimal residual disease (MRD) to actively growing recurrence. Screening for this innate response predicted accurately in which mice recurrence would occur. Premature induction of recurrence resensitized MRD to the primary therapy, suggesting a possible paradigm shift for clinical treatment of dormant disease in which the current expectant approach is replaced with active attempts to uncover MRD before evolution of the escape phenotype is complete. By combining screening with second-line treatments targeting innate insensitivity, up to 100% of mice that would have otherwise relapsed were cured. These data may open new avenues for early detection and appropriately timed, highly targeted treatment of tumor recurrence irrespective of tumor type or frontline treatment.

Nature Med 2013; 19: 1625

Eitan Israeli

Capsule

Distinct fibroblast lineages determine dermal architecture in skin development and repair

Fibroblasts are the major mesenchymal cell type in connective tissue and deposit the collagen and elastic fibers of the extracellular matrix (ECM). Even within a single tissue, fibroblasts exhibit considerable functional diversity, but it is not known whether this reflects the existence of a differentiation hierarchy or is a response to different environmental factors. Using transplantation assays and lineage tracing in mice, Driskell and co-researchers show that the fibroblasts of skin connective tissue arise from two distinct lineages. One forms the upper dermis, including the dermal papilla that regulates hair growth and the arrector pili muscle, which controls piloerection. The other forms the lower dermis, including the reticular fibroblasts that synthesize the bulk of the fibrillar ECM, and the pre-adipocytes and adipocytes of the hypodermis. The upper lineage is required for hair follicle formation. In wounded adult skin, the initial wave of dermal repair is mediated by the lower lineage and upper dermal fibroblasts are recruited only during re-epithelialization. Epidermal β-catenin activation stimulates the expansion of the upper dermal lineage, rendering wounds permissive for hair follicle formation. These findings explain why wounding is linked to formation of ECM-rich scar tissue that lacks hair follicles. They also form a platform for discovering fibroblast lineages in other tissues and for examining fibroblast changes in aging and disease.

Nature 2013; 504: 277

Eitan Israeli

Capsule

CD28 and ITK signals regulate autoreactive T cell trafficking

Activation of self-reactive T cells and their trafficking to target tissues leads to autoimmune organ destruction. Mice lacking the co-inhibitory receptor cytotoxic T lymphocyte antigen 4 (CTLA-4) develop fatal autoimmunity characterized by lymphocytic infiltration into non-lymphoid tissues. Jain et al. demonstrate that the CD28 co-stimulatory pathway regulates the trafficking of self-reactive *Ctla*4$^{-/-}$ T cells to tissues. Concurrent ablation of the CD28-activated Tec family kinase ITK does not block spontaneous T cell activation but instead causes self-reactive *Ctla*4$^{-/-}$ T cells to accumulate in secondary lymphoid organs. Despite excessive spontaneous T cell activation and proliferation in lymphoid organs, *Itk*$^{-/-}$; *Ctla*4$^{-/-}$ mice are otherwise healthy, mount antiviral immune responses, and exhibit a long lifespan. The authors propose that ITK specifically licenses autoreactive T cells to enter tissues to mount destructive immune responses. Notably, ITK inhibitors mimic the null mutant phenotype and also prevent pancreatic islet infiltration by diabetogenic T cells in mouse models of type 1 diabetes, highlighting their potential utility for the treatment of human autoimmune disorders.

Nature Med 2013; 19: 1632

Eitan Israeli

Capsule

HIV1 evades innate immune recognition through specific cofactor recruitment

Human immunodeficiency virus (HIV)-1 is able to replicate in primary human macrophages without stimulating innate immunity despite reverse transcription of genomic RNA into double-stranded DNA, an activity that might be expected to trigger innate pattern recognition receptors. Rasaiyaah et al. reasoned that if correctly orchestrated HIV-1 uncoating and nuclear entry is important for evasion of innate sensors, then manipulation of specific interactions between HIV-1 capsid and host factors that putatively regulate these processes should trigger pattern recognition receptors and stimulate type 1 interferon (IFN) secretion. The authors show that HIV-1 capsid mutants N74D and P90A, which are impaired for interaction with cofactors cleavage and polyadenylation specificity factor subunit 6 (CPSF6) and cyclophilins (Nup358 and CypA), respectively, cannot replicate in primary human monocyte-derived macrophages because they trigger innate sensors leading to nuclear translocation of NF-κB and IRF3, the production of soluble type 1 IFN and induction of an antiviral state. Depletion of CPSF6 with short hairpin RNA expression allows wild-type virus to trigger innate sensors and IFN production. In each case, suppressed replication is rescued by IFN-receptor blockade, demonstrating a role for IFN in restriction. IFN production is dependent on viral reverse transcription but not integration, indicating that a viral reverse transcription product comprises the HIV-1 pathogen-associated molecular pattern. Finally, they show that they can pharmacologically induce wild-type HIV-1 infection to stimulate IFN secretion and an antiviral state using a non-immunosuppressive cyclosporine analogue. The authors conclude that HIV-1 has evolved to use CPSF6 and cyclophilins to cloak its replication, allowing evasion of innate immune sensors and induction of a cell-autonomous innate immune response in primary human macrophages.

Nature 2013; 503: 402

Eitan Israeli