Capsule

A human memory T cell subset with stem cell-like properties

Immunological memory is thought to depend on a stem cell-like, self-renewing population of lymphocytes capable of differentiating into effector cells in response to antigen re-exposure. Gattinoni et al. describe a long-lived human memory T cell population that has an enhanced capacity for self-renewal and a multipotent ability to derive central memory, effector memory and effector T cells. These cells, specific to multiple viral and self-tumor antigens, were found within a CD45RO–, CCR7+, CD45RA+, CD62L+, CD27+, CD28+ and IL-7Rα+ T cell compartment characteristic of naive T cells. However, they expressed large amounts of CD95, IL-2Rβ, CXCR3, and LFA-1, and showed numerous functional attributes distinctive of memory cells. Compared with known memory populations, these lymphocytes had increased proliferative capacity and more efficiently reconstituted immunodeficient hosts, and they mediated superior antitumor responses in a humanized mouse model. The identification of a human stem cell-like memory T cell population is of direct relevance to the design of vaccines and T cell therapies.

Nature Med 2011; 17: 1290

Eitan Israeli

Capsule

Tumor suppressor BRCA1 epigenetically controls oncogenic microRNA-155

BRCA1, a well-known tumor suppressor with multiple interacting partners, is predicted to have diverse biological functions. However, so far its only well-established role is in the repair of damaged DNA and cell cycle regulation. In this regard, the etiopathological study of low-penetrant variants of BRCA1 provides an opportunity to uncover its other physiologically important functions. Using this rationale, Chang et al. studied the R1699Q variant of BRCA1, a potentially moderate-risk variant, and found that it does not impair DNA damage repair but abrogates the repression of microRNA-155 (miR-155), a bona fide oncomir. Mechanistically, we found that BRCA1 epigenetically represses miR-155 expression via its association with HDAC2, which deacetylates histones H2A and H3 on the miR-155 promoter. We show that overexpression of miR-155 accelerates but the knockdown of miR-155 attenuates the growth of tumor cell lines in vivo. Our findings demonstrate a new mode of tumor suppression by BRCA1 and suggest that miR-155 is a potential therapeutic target for BRCA1-deficient tumors.

Nature Med 2011; 171: 1275

Eitan Israeli

Capsule

Non-canonical inflammasome activation targets caspase-11

Caspase-1 activation by inflammasome scaffolds comprised of intracellular nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) and the adaptor ASC is believed to be essential for production of the pro-inflammatory cytokines interleukin (IL)-1β and IL-18 during the innate immune response. Kayagaki and team show, with C57BL/6 Casp11 gene-targeted mice, that caspase-11 (also known as caspase-4) is critical for caspase-1 activation and IL-1β production in macrophages infected with *Escherichia coli*, *Citrobacter rodentium* or *Vibrio cholerae*. Strain 129 mice, like Casp11−/− mice, exhibited defects in IL-1β production and harbored a mutation in the Casp11 locus that attenuated caspase-11 expression. This finding is important because published targeting of the Casp1 gene was done using strain 129 embryonic stem cells. Casp1 and Casp11 are too close in the genome to be segregated by recombination; consequently, the published Casp1−/− mice lack both caspase-11 and caspase-1. Interestingly, Casp11−/− macrophages secreted IL-1β normally in response to ATP and monosodium urate, indicating that caspase-11 is engaged by a non-canonical inflammasome. Casp1−/−Casp11129mt/129mt macrophages expressing caspase-11 from a C57BL/6 bacterial artificial chromosome transgene failed to secrete IL-1β regardless of stimulus, confirming an essential role for caspase-1 in IL-1β production. Caspase-11 rather than caspase-1, however, was required for non-canonical inflammasome-triggered macrophage cell death, indicating that caspase-11 orchestrates both caspase-1-dependent and independent outputs. Caspase-1 activation by non-canonical stimuli required NLRP3 and ASC, but caspase-11 processing and cell death did not, implying that there is a distinct activator of caspase-11. Lastly, loss of caspase-11 rather than caspase-1 protected mice from a lethal dose of lipopolysaccharide. These data highlight a unique pro-inflammatory role for caspase-11 in the innate immune response to clinically significant bacterial infections.

Nature 2011; 479: 117

Eitan Israeli

Capsule

Desperately seeking XMRV – probably no connection to chronic fatigue syndrome

A report that patients with chronic fatigue syndrome (CFS) are infected with a retrovirus called XMRV attracted considerable attention, but follow-up work by other investigators failed to confirm the finding. In a study by Simmons and collaborators, nine laboratories – including the authors of the original report – independently analyzed blind-coded blood samples from 15 individuals previously found to be positive for the virus (14 with CFS) and 15 healthy controls previously found to be negative. Only the two laboratories associated with the original report detected XMRV. However, in these laboratories, the virus was found in healthy controls as often as in CFS patients and replicate samples yielded inconsistent results. In addition to showing that current assays for detecting XMRV are unreliable, these data support previous studies that questioned the association between XMRV and CFS.

Science 2011; 334: 814

Eitan Israeli

Capsule

Awareness and attention

There has been a long-standing controversy on whether activity in the primary visual cortex is necessary for perceptual awareness. In human brain-imaging experiments, Watanabe et al. were able to dissociate perceptual awareness from simple attention. Awareness was manipulated in a binocular flash suppression paradigm, and attention was manipulated by using standard attentional instructions. Activity in the primary visual cortex varied little, whether a target was visible or not. However, activity in the human primary visual cortex varied when subjects attended to the target or ignored it. Thus, humans do not need primary visual cortical activity in order to be aware of seeing something.

Science 2011; 334: 829

Eitan Israeli

Capsule

Clearance of p16Ink4a-positive senescent cells delays aging-associated disorders

Advanced age is the main risk factor for most chronic diseases and functional deficits in humans, but the fundamental mechanisms that drive aging remain largely unknown, impeding the development of interventions that might delay or prevent age-related disorders and maximize healthy lifespan. Cellular senescence, which halts the proliferation of damaged or dysfunctional cells, is an important mechanism to constrain the malignant progression of tumor cells. Senescent cells accumulate in various tissues and organs with aging and have been hypothesized to disrupt tissue structure and function because of the components they secrete. However, whether senescent cells are causally implicated in age-related dysfunction and whether their removal is beneficial has remained unknown. To address these fundamental questions, Baker and co-authors made use of a biomarker for senescence, p16Ink4a, to design a novel transgene, INK-ATTAC, for inducible elimination of p16Ink4a-positive senescent cells upon administration of a drug. They show that in the BubR1 progeroid mouse background, INK-ATTAC removes p16Ink4a-positive senescent cells upon drug treatment. In tissues – such as adipose tissue, skeletal muscle and eye – in which p16Ink4a contributes to the acquisition of age-related pathologies, life-long removal of p16Ink4a-expressing cells delayed onset of these phenotypes. Furthermore, late-life clearance attenuated progression of already established age-related disorders. These data indicate that cellular senescence is causally implicated in generating age-related phenotypes and that removal of senescent cells can prevent or delay tissue dysfunction and extend health span.

Nature 2011; 479: 232

Eitan Israeli

Capsule

A *Burkholderia pseudomallei* toxin inhibits helicase activity of translation factor eIF4A

The gram-negative bacterium *Burkholderia pseudomallei*, the causative agent of melioidosis, is endemic in Southeast Asia and northern Australia and is often associated with stagnant water and rice paddy fields. Clinical manifestations of melioidosis include subclinical infections, acute septicemia, and subacute and chronic disease. There is no licensed vaccine against *B. pseudomallei*, which can infect almost any tissues of its hosts and is resistant to a number of antibiotics. Cruz-Migoni et al. report the identification and molecular characterization of a *B. pseudomallei* protein that can act as a potent toxin in mice and human cells and can inhibit protein translation. Expression levels of bpsl1549 correlate with conditions expected to promote or suppress pathogenicity. BPSL1549 promotes deamidation of glutamine-339 of the translation initiation factor eIF4A, abolishing its helicase activity and inhibiting translation. The authors propose to name BPSL1549 Burkholderia lethal factor 1.

Science 2011; 334: 821

Eitan Israeli

Capsule

Clinical features, pathogenesis and treatment of juvenile and adult dermatomyositis

Juvenile and adult dermatomyositis have multiple commonalities, yet display differing prevalence of features, outcomes and comorbidities. In general, compared with the disease in adults, children with dermatomyositis have more vasculopathy and a greater likelihood of calcinosis, periungual and gingival telangiectasias, and ulceration, but have a better long-term prognosis with improved survival. Adults with dermatomyositis are more likely to have myositis-specific antibodies, develop interstitial lung disease, have amyopathic disease, as well as a marked association with malignancy and other comorbidities. Both diseases have similar features on muscle biopsy and interferon gene signature, although subtle differences can exist in pathogenesis and pathology, such as more capillary loss and a greater degree of C5b-9 complement deposition in affected muscle of juvenile patients. Initiatives are underway to improve classification, markers of disease activity and ability to predict outcome of juvenile and adult dermatomyositis.

Nature Rev Rheumatol 2011; 7: 664

Eitan Israeli

Capsule

New targets for intervention in the treatment of postmenopausal osteoporosis

Postmenopausal osteoporosis is a disease of high bone remodeling, with an imbalance of bone resorption over bone formation, resulting in decreased bone mineral density and disruption of bone microarchitecture. With our improved understanding of the molecular and cellular regulators and mediators of bone remodeling, new targets for therapeutic intervention have been identified. Lewiecki reviewed the new approaches. Receptor activator of nuclear factor κB ligand (RANKL) is the principal regulator of osteoclast differentiation, activity and survival; denosumab, a fully human monoclonal antibody to RANKL, inhibits bone resorption and is approved for the treatment of women with postmenopausal osteoporosis at high risk of fractures. Cathepsin K is a protease produced by activated osteoclasts that degrades the protein matrix of bone. An inhibitor of cathepsin K, odanacatib, is in phase III clinical trials for the treatment of postmenopausal osteoporosis; it decreases bone resorption while seeming to suppress bone formation less than other antiresorptive agents. Sclerostin is a cytokine produced by osteocytes that inhibits osteoblastic bone formation; investigational monoclonal antibodies to sclerostin, such as AMG 785, have osteoanabolic properties with the potential to improve clinical outcomes in patients with osteoporosis. These and other novel interventions that target newly recognized regulators of bone remodeling are promising agents for the treatment of osteoporosis.

Nature Rev Rheumatol 2011; 7: 631

Eitan Israeli

Capsule

Interleukin-6 enhances insulin secretion by increasing glucagon-like peptide-1 secretion from L cells and alpha cells

Exercise, obesity and type 2 diabetes are associated with elevated plasma concentrations of interleukin-6 (IL-6). Glucagon-like peptide-1 (GLP-1) is a hormone that induces insulin secretion. Ellingsgaard and co-workers show that administration of IL-6 or elevated IL-6 concentrations in response to exercise stimulates GLP-1 secretion from intestinal L cells and pancreatic alpha cells, improving insulin secretion and glycemia. IL-6 increased GLP-1 production from alpha cells through increased proglucagon (which is encoded by GCG) and prohormone convertase 1/3 expression. In models of type 2 diabetes, the beneficial effects of IL-6 were maintained, and IL-6 neutralization resulted in further elevation of glycemia and reduced pancreatic GLP-1. Hence, IL-6 mediates crosstalk between insulin-sensitive tissues, intestinal L cells and pancreatic islets to adapt to changes in insulin demand. This previously unidentified endocrine loop implicates IL-6 in the regulation of insulin secretion and suggests that drugs modulating this loop may be useful in type 2 diabetes.

Nature Med 2011; 17: 1481

Eitan Israeli

Capsule

Epidermal growth factor receptor promotes glomerular injury and renal failure in rapidly progressive crescentic glomerulonephritis

Rapidly progressive glomerulonephritis (RPGN) is a life-threatening clinical syndrome and a morphological manifestation of severe glomerular injury that is marked by a proliferative histological pattern ('crescents') with accumulation of T cells and macrophages and proliferation of intrinsic glomerular cells. Bollée and co-researchers show de novo induction of heparin-binding epidermal growth factor-like growth factor (HB-EGF) in intrinsic glomerular epithelial cells (podocytes) from both mice and humans with RPGN. HB-EGF induction increases phosphorylation of the epidermal growth factor receptor (EGFR, also known as ErbB1) in mice with RPGN. In HB-EGF-deficient mice, EGFR activation in glomeruli is absent and the course of RPGN is improved. Autocrine HB-EGF induces a phenotypic switch in podocytes in vitro. Conditional deletion of the Egfr gene from podocytes of mice alleviates the severity of RPGN. Likewise, pharmacological blockade of EGFR also improves the course of RPGN, even when started 4 days after the induction of experimental RPGN. This suggests that targeting the HB-EGF-EGFR pathway could also be beneficial in treatment of human RPGN.

Nature Med 2011; 17: 1242

Eitan Israeli

Capsule

Polymeric IgA1 controls erythroblast proliferation and accelerates erythropoiesis recovery in anemia

Anemia due to insufficient production of and/or response to erythropoietin (Epo) is a major complication of chronic kidney disease and cancer. The mechanisms modulating the sensitivity of erythroblasts to Epo remain poorly understood. Coulon et al. show that, when cultured with Epo at suboptimal concentrations, the growth and clonogenic potential of erythroblasts was rescued by transferrin receptor 1 (TfR1)-bound polymeric IgA1 (pIgA1). Under homeostatic conditions, erythroblast numbers were increased in mice expressing human IgA1 compared to control mice. Hypoxic stress of these mice led to increased amounts of pIgA1 and erythroblast expansion. Expression of human IgA1 or treatment of wild-type mice with the TfR1 ligands pIgA1 or iron-loaded transferrin (Fe-Tf) accelerated recovery from acute anemia. TfR1 engagement by either pIgA1 or Fe-Tf increased cell sensitivity to Epo by inducing activation of mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K) signaling pathways. These cellular responses were mediated through the TfR1-internalization motif, YXXΦ. These results show that pIgA1 and TfR1 are positive regulators of erythropoiesis in both physiological and pathological situations. Targeting this pathway may provide alternate approaches to the treatment of ineffective erythropoiesis and anemia.

Nature Med 2011; 17: 1456

Eitan Israeli

Capsule

Tissue factor-protease-activated receptor 2 signaling promotes diet-induced obesity and adipose inflammation

Tissue factor, the initiator of the coagulation cascade, mediates coagulation factor VIIa-dependent activation of protease-activated receptor 2 (PAR2). Badeanlou et al. delineate a role for this signaling pathway in obesity and its complications. Mice lacking PAR2 (F2rl1) or the cytoplasmic domain of tissue factor were protected from weight gain and insulin resistance induced by a high-fat diet. In hematopoietic cells, genetic ablation of tissue factor-PAR2 signaling reduced adipose tissue macrophage inflammation, and specific pharmacological inhibition of macrophage tissue factor signaling rapidly ameliorated insulin resistance. In contrast, non-hematopoietic cell tissue factor-VIIa-PAR2 signaling specifically promoted obesity. Mechanistically, adipocyte tissue factor cytoplasmic domain-dependent VIIa signaling suppressed Akt phosphorylation with concordant adverse transcriptional changes of key regulators of obesity and metabolism. Pharmacological blockade of adipocyte tissue factor in vivo reversed these effects of tissue factor-VIIa signaling and rapidly increased energy expenditure. Thus, inhibition of tissue factor signaling is a potential therapeutic avenue for improving impaired metabolism and insulin resistance in obesity.

Nature Med 2011; 17: 1490

Eitan Israeli

Capsule

Melanopsin signaling in mammalian iris and retina

Non-mammalian vertebrates have an intrinsically photosensitive iris and thus a local pupillary light reflex (PLR). In contrast, it is thought that the PLR in mammals generally requires neuronal circuitry connecting the eye and the brain. Xue et al. report that an intrinsic component of the PLR is in fact widespread in nocturnal and crepuscular mammals. In mouse, this intrinsic PLR requires the visual pigment melanopsin; it also requires PLCβ4, a vertebrate homologue of the Drosophila NorpA phospholipase C which mediates rhabdomeric phototransduction. The Plcb4−/− genotype, in addition to removing the intrinsic PLR, also essentially eliminates the intrinsic light response of the M1 subtype of melanopsin-expressing, intrinsically photosensitive retinal ganglion cells (M1-ipRGCs), which are by far the most photosensitive ipRGC subtype and also have the largest response to light. Ablating in mouse the expression of both TRPC6 and TRPC7, members of the TRP channel superfamily, also essentially eliminated the M1-ipRGC light response but the intrinsic PLR was not affected. Thus, melanopsin signaling exists in both iris and retina, involving a PLCβ4-mediated pathway that nonetheless diverges in the two locations.

Nature 2011; 479: 67

Eitan Israeli