Capsule

Negative regulation of the NLRP3 inflammasome by A20 protects against arthritis

Rheumatoid arthritis is a chronic autoinflammatory disease that affects 1–2% of the world's population and is characterized by widespread joint inflammation. Interleukin-1 is an important mediator of cartilage destruction in rheumatic diseases, but our understanding of the upstream mechanisms leading to production of interleukin-1β in rheumatoid arthritis is limited by the absence of suitable mouse models of the disease in which inflammasomes contribute to pathology. Myeloid cell-specific deletion of the rheumatoid arthritis susceptibility gene *A20/Tnfaip3* in mice (A20myel-KOmice) triggers a spontaneous erosive polyarthritis that resembles rheumatoid arthritis in patients. Rheumatoid arthritis in A20myel-KO mice is not rescued by deletion of tumur necrosis factor receptor. Vande Walle and team show, however, that it crucially relies on the Nlrp3 inflammasome and interleukin-1 receptor signaling. Macrophages lacking A20 have increased basal and lipopolysaccharide-induced expression levels of the inflammasome adaptor Nlrp3 and proIL-1β. As a result, A20-deficiency in macrophages significantly enhances Nlrp3 inflammasome-mediated caspase-1 activation, pyroptosis and interleukin-1β secretion by soluble and crystalline Nlrp3 stimuli. In contrast, activation of the Nlrc4 and AIM2 inflammasomes is not altered. Importantly, increased Nlrp3 inflammasome activation contributes to the pathology of rheumatoid arthritis in vivo, because deletion of Nlrp3, caspase-1 and the interleukin-1 receptor markedly protects against rheumatoid arthritis-associated inflammation and cartilage destruction in A20myel-KO mice. These results reveal A20 as a novel negative regulator of Nlrp3 inflammasome activation, and describe A20myel-KO mice as the first experimental model for studying the role of inflammasomes in the pathology of rheumatoid arthritis.

Nature 2014; 512: 69

Eitan Israeli

Capsule

A vaccine targeting mutant IDH1 induces antitumor immunity

Monoallelic point mutations of isocitrate dehydrogenase type 1 (IDH1) are an early and defining event in the development of a subgroup of gliomas and other types of tumor. They almost uniformly occur in the critical arginine residue (Arg132) in the catalytic pocket, resulting in a neomorphic enzymatic function, production of the oncometabolite 2-hydroxyglutarate (2-HG) genomic hypermethylation, genetic instability and malignant transformation. More than 70% of diffuse grade II and grade III gliomas carry the most frequent mutation, IDH1(R132H). From an immunological perspective, IDH1(R132H) represents a potential target for immunotherapy as it is a tumor-specific potential neoantigen with high uniformity and penetrance expressed in all tumor cells. Schumacher et al. demonstrate that IDH1(R132H) contains an immunogenic epitope suitable for mutation-specific vaccination. Peptides encompassing the mutated region are presented on major histocompatibility complexes (MHC) class II and induce mutation-specific CD4+T-helper-1 (TH1) responses. CD4+ TH1 cells and antibodies spontaneously occurring in patients with IDH1(R132H)-mutated gliomas specifically recognize IDH1(R132H). Peptide vaccination of mice devoid of mouse MHC and transgenic for human MHC class I and II with IDH1(R132H) p123-142 results in an effective MHC class II-restricted mutation-specific antitumor immune response and control of pre-established syngeneic IDH1(R132H)-expressing tumors in a CD4+ T cell-dependent manner. As IDH1(R132H) is present in all tumor cells of these slow-growing gliomas, a mutation-specific anti-IDH1(R132H) vaccine may represent a viable novel therapeutic strategy for IDH1(R132H)-mutated tumors.

Nature 2014; 512: 324

Eitan Israeli

Capsule

Putative cis-regulatory drivers in colorectal cancer

The cis-regulatory effects responsible for cancer development have not been as extensively studied as the perturbations of the protein coding genome in tumorigenesis. To better characterize colorectal cancer (CRC) development Ongen et al. conducted an RNA-sequencing experiment of 103 matched tumor and normal colon mucosa samples from Danish CRC patients, 90 of which were germline-genotyped. By investigating allele-specific expression (ASE) the authors show that the germline genotypes remain important determinants of allelic gene expression in tumors. Using the changes in ASE in matched pairs of samples they discovered 71 genes with excess of somatic cis-regulatory effects in CRC, suggesting a cancer driver role. The authors correlated genotypes and gene expression to identify expression quantitative trait loci (eQTLs) and found 1693 and 948 eQTLs in normal samples and tumors, respectively. They estimate that 36% of the tumor eQTLs are exclusive to CRC and show that this specificity is partially driven by increased expression of specific transcription factors and changes in methylation patterns. They also show that tumor-specific eQTLs are more enriched for low CRC genome-wide association study (GWAS) *P* values than shared eQTLs, which suggests that some of the GWAS variants are tumor-specific regulatory variants. Importantly, tumor-specific eQTL genes also accumulate more somatic mutations when compared to the shared eQTL genes, raising the possibility that they constitute germline-derived cancer regulatory drivers. Collectively the integration of genome and the transcriptome reveals a substantial number of putative somatic and germline cis-regulatory cancer changes that may have a role in tumorigenesis.

Nature 2014; 512: 87

Eitan Israeli

Capsule

Altitude adaptation in Tibetans caused by introgression of Denisovan-like DNA

As modern humans migrated out of Africa, they encountered many new environmental conditions, including greater temperature extremes, different pathogens and higher altitudes. These diverse environments are likely to have acted as agents of natural selection and to have led to local adaptations. One of the most celebrated examples in humans is the adaptation of Tibetans to the hypoxic environment of the high altitude Tibetan plateau. A hypoxia pathway gene, *EPAS1*, was previously identified as having the most extreme signature of positive selection in Tibetans, and was shown to be associated with differences in hemoglobin concentration at high altitude. Re-sequencing the region around *EPAS1* in 40 Tibetan and 40 Han individuals, Huerta-Sánchez et al. found that this gene has a highly unusual haplotype structure that can only be convincingly explained by introgression of DNA from Denisovan or Denisovan-related individuals into humans. Scanning a larger set of worldwide populations, the authors find that the selected haplotype is only found in Denisovans and in Tibetans, and at very low frequency among Han Chinese. Furthermore, the length of the haplotype, and the fact that it is not found in any other populations, makes it unlikely that the haplotype sharing between Tibetans and Denisovans was caused by incomplete ancestral lineage sorting rather than introgression. These findings illustrate that admixture with other hominin species has provided genetic variation that helped humans to adapt to new environments.

Nature 2014; 512: 194

Eitan Israeli

Capsule

A potential target in a deadly brain cancer

A growth factor receptor called EGFR is often overactive in glioblastoma, a common and frequently lethal form of brain cancer. Kusne et al. found that the kinase aPKC was stimulated in glioblastoma cells not only by abnormally active EGFR but also in response to a cytokine called TNF-α released by immune cells that infiltrate the tumors. A drug that inhibited aPKC reduced tumor growth in a mouse model of glioblastoma, and glioblastoma patients with high aPKC levels had shorter survival times. Thus, two cancer-promoting pathways converge on aPKC, making it an attractive therapeutic target in glioblastoma.

Sci Signal 2014; 7: ra75

Eitan Israeli

Capsule

Clonal evolution in breast cancer revealed by single nucleus genome sequencing

Sequencing studies of breast tumor cohorts have identified many prevalent mutations, but provide limited insight into the genomic diversity within tumors. Wang et al. developed a whole-genome and exome single-cell sequencing approach called nuc-seq that uses G2/M nuclei to achieve 91% mean coverage breadth. The authors applied this method to sequence single normal and tumor nuclei from an estrogen receptor-positive (ER+) breast cancer and a triple-negative ductal carcinoma. In parallel, they performed single nuclei copy number profiling. These data show that aneuploid rearrangements occurred early in tumor evolution and remained highly stable as the tumor masses clonally expanded. In contrast, point mutations evolved gradually, generating extensive clonal diversity. Using targeted single-molecule sequencing, many of the diverse mutations were shown to occur at low frequencies (‹10%) in the tumor mass. Using mathematical modeling we found that the triple-negative tumor cells had an increased mutation rate (13.3×), whereas the ER+ tumor cells did not. These findings have important implications for the diagnosis, therapeutic treatment and evolution of chemoresistance in breast cancer.

Nature 2014; 512: 155

Eitan Israeli

Capsule

Efficacy of inactivated poliovirus vaccine in India

Inactivated poliovirus vaccine (IPV) is efficacious against paralytic disease, but its effect on mucosal immunity is debated. Jafai et al. assessed the efficacy of IPV in boosting mucosal immunity. Participants received IPV, bivalent 1 and 3 oral poliovirus vaccine (bOPV), or no vaccine. A bOPV challenge was administered 4 weeks later, and excretion was assessed 3, 7, and 14 days later. A total of 954 participants completed the study. Any fecal shedding of poliovirus type 1 was 8.8, 9.1, and 13.5% in the IPV group and 14.4, 24.1, and 52.4% in the control group by 6- to 11-month, 5-year, and 10-year groups, respectively (IPV versus control: Fisher's exact test $P < 0.001$). IPV reduced excretion for poliovirus types 1 and 3 between 38.9 and 74.2% and 52.8 and 75.7%, respectively. Thus, IPV in OPV-vaccinated individuals boosts intestinal mucosal immunity.

Science 2014; 345: 922

Eitan Israeli

Capsule

Anti-inflammatory cells for treating sepsis

Sepsis is a complication of infection that kills ~7 million people a year, with no successful molecular therapy. But cells are more versatile than molecules: They make products and respond to their environments. Fletcher et al. investigated whether cells are better equipped to battle this multifocal disease. One injection of anti-inflammatory cells derived from the lymph nodes dramatically increased survival in two mouse models of sepsis under conditions that mimic those in the clinic. These beneficial cells reduced the deadly "cytokine storm" associated with sepsis.

Sci Transl Med 2014; 6: 249ra109

Eitan Israeli

Capsule

Tumorigenicity and genetic profiling of circulating tumor cells in small-cell lung cancer

Small-cell lung cancer (SCLC), an aggressive neuroendocrine tumor with early dissemination and dismal prognosis, accounts for 15–20% of lung cancer cases and ~200,000 deaths each year. Most cases are inoperable, and biopsies to investigate SCLC biology are rarely obtainable. Circulating tumor cells (CTCs), which are prevalent in SCLC, present a readily accessible 'liquid biopsy'. Hodgkinson et al. show that CTCs from patients with either chemosensitive or chemorefractory SCLC are tumorigenic in immune-compromised mice, and the resultant CTC-derived explants (CDXs) mirror the donor patient's response to platinum and etoposide chemotherapy. Genomic analysis of isolated CTCs revealed considerable similarity to the corresponding CDX. Most marked differences were observed between CDXs from patients with different clinical outcomes. These data demonstrate that CTC molecular analysis via serial blood sampling could facilitate delivery of personalized medicine for SCLC. CDXs are readily passaged, and these unique mouse models provide tractable systems for therapy testing and understanding drug resistance mechanisms.

Nature Med 2014; 20: 897

Eitan Israeli

Capsule

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Nature 2014; 512: 69

Eitan Israeli

Capsule

Genome editing corrects a muscle disease

Patients with Duchenne muscular dystrophy find their muscles growing progressively weaker. Studies identified dystrophin as the culprit gene, which galvanized research into gene-targeted therapies. Long et al. applied genome editing to "correct" the disease-causing mutation in mice genetically destined to develop the disease. This germline editing strategy kept muscles from degenerating, even in mice harboring only a small percentage of corrected cells. Although not feasible for humans, this proof of concept sets the stage for applying genome editing to specific cell types involved in the disease.

Science 2014; 345: 1184

Eitan Israeli

Capsule

Mycobacterium make not-so-painful ulcers

Buruli ulcer disease causes extensive skin lesions and can be deadly, but the lesions themselves don't hurt, which can stop patients from seeking the appropriate care. The pathogen *Mycobacterium ulcerans* causes Buruli ulcers and also alleviates the pain. Although many scientists studying this disease thought the pathogen caused nerve damage that blocked the pain, Marion et al. show that the mycobacteria produce the mycolactone toxin, which causes analgesia by blocking the function of pain-responsive nerves. The findings could potentially help researchers develop a whole new class of painkillers.

Cell 2014;157: 1565

Eitan Israeli

Capsule

Bringing in the agent of your own destruction

Cells need mechanisms to detect and disable pathogens that infect them. Tam et al. now show that complement C3, a protein that binds to pathogens in the blood, can enter target cells together with the pathogen. Once inside the cell, the presence of C3 triggers both immune signaling and degradation of the internalized pathogen. The discovery of this pathway reveals that cells possess an early warning system of invasion that works against a diverse array of pathogens and does not require recognition of any specific pathogen molecules.

Science 2014; 345: 10.1126/science.1256070

Eitan Israeli

Capsule

Two signals for maximal T cell activation

T cell activation requires increased intracellular calcium and the activity of various enzymes, such as the kinase Itk. Wang et al. report that two signals, calcium and lipids, converged on Itk for maximal activation of T cells. The same region of the Itk protein bound to the signaling lipid PI(3,4,5)P3 and to the calcium-binding protein calmodulin. PI(3,4,5)P3 and calmodulin enhanced the binding of each other to Itk. The binding of both PI(3,4,5)P3 and calmodulin was necessary so that T cells produced maximal levels of an inflammatory cytokine, interleukin-17A.

Sci Signal 2014; 7: ra74

Eitan Israeli

Capsule

Hearing sounds can improve your vision

Sounds can draw our attention to a specific location and make us aware of something that we may otherwise overlook. But do auditory cues improve the function of other senses, such as sight? To find out, Feng et al. recorded the electrical activity in people's brains when they were seeing and hearing stimuli. The researchers played a sound from one side and then quickly flashed a visual stimulus either on the same side as the sound or on the opposite side. When the sound and the visual stimulus came on the same side, electrical activity in the brain increased and people correctly identified the visual stimulus more often. This suggests that sound helps the brain process co-localized visual input.

J Neurosci 2014; 34: 9817

Eitan Israeli

Capsule

The long and short of hair growth

The length of your eyelashes probably differs from the length of the hair on your head – and unlike your hair, your eyelashes can never reach your shoulders. What controls how long hair can get? To find out, Higgins et al. studied people with a rare disorder called familial trichomegaly, who have very long eyelashes and longer hair on the arms. They found that these people had a mutation in the gene that encodes fibroblast growth factor 5 (FGF5). When human hair follicles produce FGF5, they stop growing hair. Targeting FGF5 could potentially control the growth and rest phases of hair follicles, preventing unwanted hair from sprouting or growing longer lashes and locks.

Proc Natl Acad Sci USA. 2014;10.1073/pnas.1402862111

Eitan Israeli

Capsule

Connecting DNA damage to fibrosis

In the autoimmune disease systemic sclerosis (SSc), high collagen production by fibroblasts causes "scarring" of the skin and internal organs. During this process, called fibrosis, the Wnt signaling pathway is frequently activated. Svegliati and coworkers found that antibodies in the serum from SSc patients stimulated a pathway that suppressed the expression of WIF-1, which encodes a Wnt inhibitor, and triggered collagen production in fibroblasts from normal individuals. Effects were similar when cells were treated with DNA-damaging agents. In fibroblasts from SSc patients, inhibiting this pathway caused the cells to express WIF-1 and produce less collagen. In a mouse model of fibrosis, inhibiting this pathway prevented fibrotic skin thickening.

Sci Signal 2014; 7: ra84

Eitan Israeli

Capsule

How immune cells fight TB and show it

Mycobacterium tuberculosis causes an infection that can sometimes kill, but it proceeds to disease in only about 10% of individuals. Now, Montoya and team provide a clue to how most people keep this bacterium in check. They show that when people fight tuberculosis, their immune cells secrete the cytokine interleukin-32, which may work through an antimicrobial pathway that uses vitamin D. The researchers analyzed five different clinical data sets and found that interleukin-32 may indicate latent tuberculosis. Interleukin-32 therefore may both contribute directly to the host response to tuberculosis and reflect protection against the disease.

Sci Transl Med 2014; 6: 250ra114

Eitan Israeli