Capsule

Cancer cell-autonomous contribution of type I interferon signaling to the efficacy of chemotherapy

Some of the anti-neoplastic effects of anthracyclines in mice originate from the induction of innate and T cell-mediated anticancer immune responses. Sistigu et al. have demonstrated that anthracyclines stimulate the rapid production of type I interferons (IFNs) by malignant cells after activation of the endosomal pattern recognition receptor Toll-like receptor 3 (TLR3). By binding to IFNα and IFNβ receptors (IFNARs) on neoplastic cells, type I IFNs trigger autocrine and paracrine circuitries that result in the release of chemokine (C-X-C motif) ligand 10 (CXCL10). Tumors lacking Tlr3 or Ifnar failed to respond to chemotherapy unless type I IFN or Cxcl10, respectively, was artificially supplied. Moreover, a type I IFN-related signature predicted clinical responses to anthracycline-based chemotherapy in several independent cohorts of patients with breast carcinoma characterized by poor prognosis. These data suggest that anthracycline-mediated immune responses mimic those induced by viral pathogens. The authors surmise that such 'viral mimicry' constitutes a hallmark of successful chemotherapy.

Nature Med 2014; 20: 1301

Eitan Israeli

Capsule

Rapid fucosylation of intestinal epithelium sustains host-commensal symbiosis in sickness

Systemic infection induces conserved physiological responses that include both resistance and 'tolerance of infection' mechanisms. Temporary anorexia associated with an infection is often beneficial, reallocating energy from food foraging towards resistance to infection or depriving pathogens of nutrients. However, it imposes a stress on intestinal commensals, as they also experience reduced substrate availability; this affects host fitness owing to the loss of caloric intake and colonization resistance (protection from additional infections). Pickard et al. hypothesized that the host might utilize internal resources to support the gut microbiota during the acute phase of the disease. The authors show that systemic exposure to Toll-like receptor (TLR) ligands causes rapid α(1,2)-fucosylation of small intestine epithelial cells (IECs) in mice, which requires the sensing of TLR agonists, as well as the production of interleukin (IL)-23 by dendritic cells, activation of innate lymphoid cells, and expression of fucosyltransferase 2 (Fut2) by IL-22-stimulated IECs. Fucosylated proteins are shed into the lumen and fucose is liberated and metabolized by the gut microbiota, as shown by reporter bacteria and community-wide analysis of microbial gene expression. Fucose affects the expression of microbial metabolic pathways and reduces the expression of bacterial virulence genes. It also improves host tolerance of the mild pathogen *Citrobacter rodentium*. Thus, rapid IEC fucosylation appears to be a protective mechanism that utilizes the host's resources to maintain host-microbial interactions during pathogen-induced stress.

Nature 2014; 514: 638

Eitan Israeli

Capsule

How the common cold can worsen asthma

Rhinoviruses – the main cause of the common cold – can make asthma attacks worse. Now Beale and co-workers report that one reason may be because rhinoviruses cause lung epithelial cells to make the cytokine interleukin-25 (IL-25). More IL-25 is produced in people with asthma than in those who are healthy. In mice with allergic "asthma," rhinovirus infection triggered IL-25 production, and blocking the IL-25 receptor eased the increased asthma symptoms. Thus, as the cold season approaches, blocking IL-25 may be a promising therapeutic strategy in asthmatics.

Sci Transl Med 2014; 6: 256ral134

Eitan Israeli

Capsule

A new approach for treating colon cancer?

Most patients with colon cancer have a mutation that results in the Wnt/β-catenin pathway being "on" all the time. But inhibitors of this pathway interfere with the continuous renewal of the epithelial cells lining the intestinal tract. Phesse et al. discovered that the signaling pathway involving the receptor gp130, its associated Jak kinases, and the transcription factor Stat3 enhanced the growth of intestinal tumors in mice. Inhibiting this pathway stopped cell proliferation and reduced tumor growth. Drugs targeting the Jak-Stat3 pathway are currently in clinical trials for treating hematological malignancies; hopefully they will also be useful for treating colon cancer.

Sci Signal 2014; 7: ra92

Eitan Israeli

Capsule

A microRNA for retinal regeneration

Damage to the retina causes blindness in humans but not in zebrafish. Müller glia, a cell type shared by both mammals and zebrafish, helps zebrafish retinas regenerate. Rajaram et al. sought to better understand how this process works and identified miR-203, a microRNA (small RNA molecules that regulate gene expression) as a key player. Light-induced retina damage causes Müller glia cells to kick into action to generate progenitor cells, which then proliferate to help repair the retina. Under normal conditions, miR-203 blocked this, but retina damage caused miR-203 levels to decrease. miR-203 levels also decrease when mouse skin or the caudal fin in zebrafish regenerates, suggesting similarities in the molecular control of cellular replacement.

Dev Biol 2014; 392: 393

Eitan Israeli

Capsule

How to stop after copying the genome

Replication is highly regulated: failure to copy any part of the genome or copying parts of it more than once can cause genome instability with potentially disastrous consequences. Maric et al. show that the DNA replication machinery, which stably encircles DNA during the duplication process, is actively disassembled once replication is complete. The protein ring encircling the DNA is covalently modified, which allows it to be opened and the whole replication complex to be removed from DNA by a special disassembly complex.

Science 2014; 346: 477

Eitan Israeli

Capsule

Excess signaling is bad for the aging brain

Preventing antiviral-like responses may protect function in the aging brain. Baruch and colleagues monitored messenger RNA production in the choroid plexus, the interface between the blood and cerebrospinal fluid, in young and old mice. They detected an inflammatory response in older mice not present in the brain of young mice that was also seen in old aged human samples postmortem. Preventing signaling by the cytokine interferon-I, which normally helps in the antiviral response of the immune system, helped prevent the decrease in cognitive function seen in aged mice.

Science 2014; 346: 89

Eitan Israeli

Capsule

Resident memory T cells sound the alarm

Immunological memory protects against reinfection. Resident memory T cells (TRM) are long-lived and remain in the tissues where they first encountered a pathogen. Schenkel et al. and Ariotti et al. (*Science* 2014; 346: 98, 101) found that CD8+ TRM cells act like first responders in the female reproductive tissue or the skin of mice upon antigen reencounter. By secreting inflammatory proteins, TRM cells rapidly activated local immune cells to respond, so much so that they protected against infection with an unrelated pathogen. Iijima and Iwasaki (*Science* 2014; 346: 93) found that CD4+ TRM cells protected mice against reinfection with intravaginal herpes simplex virus 2.

Eitan Israeli

Capsule

Overcoming Staph infections is hardwired

Several evolutionarily conserved components of anti-staphylococcal immunity have been identified, using Drosophila as a model organism. However, no vertebrate ortholog has been identified for the Toll ligand Spaetzle, which plays a key role in controlling gram-positive infection in flies. Hepburn and group have now identified NGF-β as a functional equivalent to Spaetzle in vertebrates. NGF-β acts as a paracrine "alarmin" orchestrating macrophage and neutrophil responses to *S. aureus* infection. People with deleterious mutations in genes encoding NGF-β or its high-affinity receptor TRKA are predisposed to recurrent and severe Staph infections. *S. aureus* proteins selectively trigger macrophage production of NGF-β, which enhances uptake and superoxide-dependent killing of *S. aureus*, stimulates pro-inflammatory cytokine production, and promotes neutrophil recruitment. Moreover, TrkA silencing in vivo increases susceptibility to *S. aureus*. Thus, the NGF-β-TRKA pathway is a critical, evolutionarily conserved component of vertebrate immunity to *S. aureus* infection.

Science 2014; 346: 641

Eitan Israeli

Capsule

Pulmonary macrophage transplantation therapy

Bone marrow transplantation is an effective cell therapy but requires myeloablation, which increases infection risk and mortality. Recent lineage-tracing studies documenting that resident macrophage populations self-maintain independently of hematological progenitors prompted us to consider organ-targeted, cell-specific therapy. Suzuki et al., using granulocyte-macrophage colony-stimulating factor (GM-CSF) receptor-β-deficient (*Csf2rb*$^{-/-}$) mice that develop a myeloid cell disorder identical to hereditary pulmonary alveolar proteinosis (hPAP) in children with *CSF2RA* or *CSF2RB* mutations, show that pulmonary macrophage transplantation (PMT) of either wild-type or *Csf2rb*-gene-corrected macrophages without myeloablation was safe and well-tolerated. They showed that one administration corrected the lung disease, secondary systemic manifestations and normalized disease-related biomarkers, and prevented disease-specific mortality. PMT-derived alveolar macrophages persisted for at least one year, as did therapeutic effects. These findings identify mechanisms regulating alveolar macrophage population size in health and disease, indicate that GM-CSF is required for phenotypic determination of alveolar macrophages, and support translation of PMT as the first specific therapy for children with hPAP.

Nature 2014; 514: 450

Eitan Israeli

Capsule

A dendritic cell target for immunotherapy

Cancer immunotherapies work by activating T cells to kill tumors. Antigen-presenting cells (APCs), such as dendritic cells and macrophages, activate T cells by engaging protein receptors on the T cell surface. This then tells the T cells to attack the tumors. But T cells typically cannot attack tumors because the immunosuppressive microenvironment of tumors keeps APCs from turning these signals on. Broz and fellow researchers report, however, that low numbers of dendritic cells capable of activating T cells exist in tumors in mice. T cell-mediated clearance of tumors depended on these cells. In humans, an increased genetic signature of these cells correlated with better outcomes in a variety of tumor types.

Can Cell 2014; 10.1016/j.ccell.2014.09.007

Eitan Israeli

Capsule

Cancer's deadly mutational tug of war

As cancers grow, they mutate, which allows their continued growth and metastasis. Mutations are either driver mutations (required for tumors to progress) or passenger mutations (additional random mutations that result from such rapid adaptation). How do passenger mutations affect tumors? McFarland and team found that passenger mutations are 100 times more common than driver mutations and have smaller effects on tumors, but the effects are often deleterious. Thus driver and passenger mutations are in a "tug of war" that determines whether a tumor will progress. A better understanding of how passenger mutations accumulate could explain the success of current treatments or provide additional avenues to explore for therapeutic benefit.

Proc Natl Acad Sci USA 2014; 10.1073/pnas.1404341111

Eitan Israeli