Capsule

Oncogene ablation-resistant pancreatic cancer cells depend on mitochondrial function

Pancreatic ductal adenocarcinoma (PDAC) is one of the deadliest cancers in Western countries, with a median survival of 6 months and an extremely low percentage of long-term surviving patients. *KRAS* mutations are known to be a driver event of PDAC, but targeting mutant *KRAS* has proved challenging. Targeting oncogene-driven signaling pathways is a clinically validated approach for several devastating diseases. Still, despite marked tumor shrinkage, the frequency of relapse indicates that a fraction of tumor cells survives shut down of oncogenic signaling. Viale and co-workers explored the role of mutant *KRAS* in PDAC maintenance using a recently developed inducible mouse model of mutated Kras1 ($Kras^{G12D}$, herein KRas) in a p53LoxP/WT background. The authors demonstrated that a subpopulation of dormant tumor cells surviving oncogene ablation (surviving cells) and responsible for tumor relapse has features of cancer stem cells and relies on oxidative phosphorylation for survival. Transcriptomic and metabolic analyses of surviving cells revealed prominent expression of genes governing mitochondrial function, autophagy and lysosome activity, as well as a strong reliance on mitochondrial respiration and a decreased dependence on glycolysis for cellular energetics. Accordingly, surviving cells show high sensitivity to oxidative phosphorylation inhibitors, which can inhibit tumor recurrence. This integrated analysis illuminates a therapeutic strategy of combined targeting of the KRAS pathway and mitochondrial respiration to manage pancreatic cancer.

Nature 2014; 514: 628

Eitan Israeli

Capsule

Hunting for the effects of huntingtin

Huntington's disease (HD) is associated with a mutant form of the protein huntingtin (Htt). HD-associated symptoms are alleviated by inhibition of the kinase mTOR, which activates protein synthesis when amino acids are plentiful. In mouse striatal neurons, Pryor and colleagues found that wild-type Htt stimulated amino acid-induced mTOR signaling by enhancing its interaction with an activating protein. Mutant Htt promoted this interaction even when amino acid availability was not increased. In a mouse model of HD, activating mTOR in striatal neurons accelerated the onset of symptoms.

Sci Signal 2014; 7: ra103

Eitan Israeli

Capsule

High-fat diet mediated dysbiosis promotes intestinal carcinogenesis independently of obesity

Several features common to a Western lifestyle, including obesity and low levels of physical activity, are known risk factors for gastrointestinal cancers. There is substantial evidence suggesting that diet markedly affects the composition of the intestinal microbiota. Moreover, there is now unequivocal evidence linking dysbiosis to cancer development. However, the mechanisms by which high-fat diet (HFD)-mediated changes in the microbial community affect the severity of tumorigenesis in the gut remain to be determined. Schulz et al. demonstrate that an HFD promotes tumor progression in the small intestine of genetically susceptible, *K-ras*^{G12Dint}, mice independently of obesity. HFD consumption, in conjunction with *K-ras* mutation, mediated a shift in the composition of the gut microbiota, and this shift was associated with a decrease in Paneth cell-mediated antimicrobial host defense that compromised dendritic cell recruitment and MHC class II molecule presentation in the gut-associated lymphoid tissues. When butyrate was administered to HFD-fed *K-ras*^{G12Dint} mice, dendritic cell recruitment in the gut-associated lymphoid tissues was normalized, and tumor progression was attenuated. Importantly, deficiency in MYD88, a signaling adaptor for pattern recognition receptors and Toll-like receptors, blocked tumor progression. The transfer of fecal samples from HFD-fed mice with intestinal tumors to healthy adult *K-ras*^{G12Dint}mice was sufficient to transmit disease in the absence of an HFD. Furthermore, treatment with antibiotics completely blocked HFD-induced tumor progression, suggesting that distinct shifts in the microbiota have a pivotal role in aggravating disease. Collectively, these data underscore the importance of the reciprocal interaction between host and environmental factors in selecting a microbiota that favors carcinogenesis, and they suggest that tumorigenesis is transmissible among genetically predisposed individuals.

Nature 2014; 514: 508

Eitan Israeli

Capsule

A drug fights off ravages of aging in mice

Interested in a pill to extend life span and delay the onset of age-related diseases? The answer may lie in targeting the enzyme NAD-dependent deactylase sirtuin 1 (SIRT1): Animals with enhanced activity of SIRT1 show some of these effects. To study the effects of long-term SIRT1 activity, Mercken et al. fed mice a synthetic activator of SIRT1 from 6 months of age for the rest of their (∞3 year) life span. The treated mice had 5% and 10% increases in maximum and mean life span, respectively. They also resisted many problems associated with human aging. The mice had more stable blood glucose levels, better muscle endurance and balance, less fat, and suppressed inflammatory responses.

Aging Cell 2014; 10.1111/acel.12220

Eitan Israeli

Capsule

From single molecules to embryos in living color

Animation defines life, and the three-dimensional (3D) imaging of dynamic biological processes occurring within living specimens is essential to understand life. However, in vivo imaging, especially in 3D, involves inevitable tradeoffs of resolution, speed, and phototoxicity. Chen and team describe a microscope that can address these concerns. They used a class of non-diffracting beams, known as 2D optical lattices, which spread the excitation energy across the entire field of view while simultaneously eliminating out-of-focus excitation. Lattice light sheets increase the speed of image acquisition and reduce phototoxicity, which expands the range of biological problems that can be investigated. The authors illustrate the power of their approach using 20 distinct biological systems ranging from single-molecule binding kinetics to cell migration and division, immunology, and embryonic development.

Science 2014; 346: 10.1126/science.1257998

Eitan Israeli

Capsule

Pre-Columbian mycobacterial genomes reveal seals as a source of New World human tuberculosis

Modern strains of *Mycobacterium tuberculosis* from the Americas are closely related to those from Europe, supporting the assumption that human tuberculosis was introduced post-contact. This notion, however, is incompatible with archaeological evidence of pre-contact tuberculosis in the New World. Comparative genomics of modern isolates suggests that *M. tuberculosis* attained its worldwide distribution following human dispersals out of Africa during the Pleistocene epoch, although this has yet to be confirmed with ancient calibration points. Bos et al. present three 1000 year old mycobacterial genomes from Peruvian human skeletons, revealing that a member of the *M. tuberculosis* complex caused human disease before contact. The ancient strains are distinct from known human-adapted forms and are most closely related to those adapted to seals and sea lions. Two independent dating approaches suggest a most recent common ancestor for the *M. tuberculosis* complex less than 6000 years ago, which supports a Holocene dispersal of the disease. These results implicate sea mammals as having played a role in transmitting the disease to humans across the ocean.

Nature 2014; 514: 494

Eitan Israeli

Capsule

Mesenchymal-endothelial transition contributes to cardiac neovascularization

Endothelial cells contribute to a subset of cardiac fibroblasts by undergoing endothelial-to-mesenchymal transition, but whether cardiac fibroblasts can adopt an endothelial cell fate and directly contribute to neovascularization after cardiac injury is not known. Ubil et al. used genetic fate map techniques to demonstrate that cardiac fibroblasts rapidly adopt an endothelial cell-like phenotype after acute ischemic cardiac injury. Fibroblast-derived endothelial cells exhibit anatomical and functional characteristics of native endothelial cells. The authors show that the transcription factor p53 regulates such a switch in cardiac fibroblast fate. Loss of p53 in cardiac fibroblasts severely decreases the formation of fibroblast-derived endothelial cells, reduces post-infarct vascular density and worsens cardiac function. Conversely, stimulation of the p53 pathway in cardiac fibroblasts augments mesenchymal-to-endothelial transition, enhances vascularity and improves cardiac function. These observations demonstrate that mesenchymal-to-endothelial transition contributes to neovascularization of the injured heart and represents a potential therapeutic target for enhancing cardiac repair.

Nature 2014; 514: 585

Eitan Israeli

Capsule

For radiotherapy, less can be more

Radionuclides attached to antibodies have the potential to target radiation specifically to cancer cells, reducing the damage to non-cancerous cells and the side effects of radiotherapy. Clinical trials evaluating antibodies labeled with actinium-225, a radionuclide that emits high energy α-particles, are currently underway. However, the two-step method used to label antibodies with actinium-225 is inefficient and expensive. Maguire et al. describe an improved one-step method for producing stable and therapeutically active actinium-225 antibodies. They report increases in yield and specific activity of up to 10- and 30-fold, respectively. Through lowering the cost and dose required for actinium-225 targeted therapy, this method may help to expand the clinical use of actinium-225-labeled antibodies.

J Nucl Med 2014; 10.2967/jnumed.114.138347

Eitan Israeli

Capsule

Dendritic cells control fibroblastic reticular network tension and lymph node expansion

After immunogenic challenge, infiltrating and dividing lymphocytes markedly increase lymph node cellularity, leading to organ expansion. Acton et al. report that the physical elasticity of lymph nodes is maintained in part by podoplanin (PDPN) signaling in stromal fibroblastic reticular cells (FRCs) and its modulation by CLEC-2 expressed on dendritic cells. They show in mouse cells that PDPN induces actomyosin contractility in FRCs via activation of RhoA/C and downstream Rho-associated protein kinase (ROCK). Engagement by CLEC-2 causes PDPN clustering and rapidly uncouples PDPN from RhoA/C activation, relaxing the actomyosin cytoskeleton and permitting FRC stretching. Notably, administration of CLEC-2 protein to immunized mice augments lymph node expansion. In contrast, lymph node expansion is significantly constrained in mice selectively lacking CLEC-2 expression in dendritic cells. Thus, the same dendritic cells that initiate immunity by presenting antigens to T lymphocytes also initiate remodeling of lymph nodes by delivering CLEC-2 to FRCs. CLEC-2 modulation of PDPN signaling permits FRC network stretching and allows for the rapid lymph node expansion – driven by lymphocyte influx and proliferation – that is the critical hallmark of adaptive immunity.

Nature 2014; 514: 498

Eitan Israeli

Capsule

Cleavage of tau by asparagine endopeptidase mediates the neurofibrillary pathology in Alzheimer's disease

Neurofibrillary tangles (NFTs), composed of truncated and hyperphosphorylated tau, are a common feature of numerous aging-related neurodegenerative diseases, including Alzheimer's disease (AD). However, the molecular mechanisms mediating tau truncation and aggregation during aging remain elusive. Zhang et al. show that asparagine endopeptidase (AEP), a lysosomal cysteine proteinase, is activated during aging and proteolytically degrades tau, abolishes its microtubule assembly function, induces tau aggregation and triggers neurodegeneration. AEP is upregulated and active during aging and is activated in human AD brain and tau P301S-transgenic mice with synaptic pathology and behavioral impairments, leading to tau truncation in NFTs. Tau P301S-transgenic mice with deletion of the gene encoding AEP show substantially reduced tau hyperphosphorylation, less synapse loss and rescue of impaired hippocampal synaptic function and cognitive deficits. Mice infected with adeno-associated virus encoding an uncleavable tau mutant showed attenuated pathological and behavioral defects compared to mice injected with adeno-associated virus encoding tau P301S. Together, these observations indicate that AEP acts as a crucial mediator of tau-related clinical and neuropathological changes. Inhibition of AEP may be therapeutically useful for treating tau-mediated neurodegenerative diseases.

Nature Med 2014; 20: 1254

Eitan Israeli

Capsule

Diabetes recovery by age-dependent conversion of pancreatic δ cells into insulin producers

Total or near-total loss of insulin-producing β cells occurs in type 1 diabetes. Restoration of insulin production in type 1 diabetes is thus a major medical challenge. Chera et al. previously observed in mice in which β cells are completely ablated that the pancreas reconstitutes new insulin-producing cells in the absence of autoimmunity. The process involves the contribution of islet non-β cells; specifically, glucagon-producing α cells begin producing insulin by a process of reprogramming (transdifferentiation) without proliferation. Now the authors show the influence of age on β cell reconstitution from heterologous islet cells after near-total β cell loss in mice. The authors found that senescence does not alter α cell plasticity: α cells can reprogram to produce insulin from puberty through to adulthood, and also in aged individuals, even a long time after β cell loss. In contrast, before puberty there is no detectable α cell conversion, although β cell reconstitution after injury is more efficient, always leading to diabetes recovery. This process occurs through a newly discovered mechanism: the spontaneous en masse reprogramming of somatostatin-producing δ cells. The juveniles display 'somatostatin-to-insulin' δ cell conversion, involving dedifferentiation, proliferation and re-expression of islet developmental regulators. This juvenile adaptability relies, at least in part, upon the combined action of FoxO1 and downstream effectors. Restoration of insulin-producing cells from non-β cell origins is thus enabled throughout life via δ or α cell spontaneous reprogramming. A landscape with multiple intra-islet cell interconversion events is emerging, offering new perspectives for therapy.

Nature 2014; 514: 503

Eitan Israeli

Capsule

Disease biomarkers: What's the risk?

With approximately 60% of cardiac events occurring in patients of low or moderate risk, doctors need new biomarkers to accurately predict which of their patients will develop disease. Antibodies targeting the protein apolipoprotein A-1 (apoA-1), which plays a role in lipid metabolism, are one such candidate. Some of these antibodies may confer more risk than others, depending where on apoA-1 they bind. Using serum samples from cardiac patients, Teixeira et al. identified the peptides within apoA-1 where antibodies bound. These findings may point toward new therapeutic opportunities and improved biomarkers for predicting the risk of cardiovascular disease.

J Biol Chem 2014; 10.1074/jbc.M114.589002

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

The dark side of protective genes

Aberrant antibody deposits in the kidney characterize immunoglobulin A nephropathy (IgAN), a disease most prevalent in East Asians. Kiryluk et al. studied the underlying genetics of IgAN and found that variants of genes with roles in maintaining the intestinal epithelial barrier or in the immune response to mucosal pathogens conferred an elevated risk of IgAN. People living in areas with the greatest diversity of helminthes showed the highest genetic risk for developing IgAN. This intriguing correlation suggests that the high incidence of IgAN in certain regions might be a consequence of protective adaptation to mucosal pathogens.

Nat Genet 2014; 10.1038/ng.3118

Eitan Israeli

Capsule

Nanoparticles for molecular cancer imaging

Tiny particles can be coated with antibodies or peptides to target a molecule specific to cancer, improving diagnostic accuracy and patient stratification. Yet these decorated nanoparticles have been slow in making it to clinical trials. Phillips et al. describe the translation of ultrasmall (< 10 nm) inorganic nanoparticles, called "C dots," from animals to patients. The nanoparticles were not toxic in a small group of five patients with metastatic melanoma and were excreted intact via the kidneys and bladder. In contrast, larger or uncoated particles often get lodged in the liver. Many more studies in patients will be needed to confirm lack of toxicity and to optimize tumor targeting, but now that such ultrasmall nanoparticles can be tested in people, a new era of molecular cancer imaging has begun.

Sci Transl Med 2014; 6: 260ra149

Eitan Israeli