Capsule

A super-enhancer in leukemia development

Human cancer genome projects have provided a wealth of information about mutations that reside within the coding regions of genes and drive tumor growth by functionally altering protein products. However, this mutational portrait of cancer is incomplete: A growing number of mutations are being found within gene regulatory regions. Mansour and colleagues describe an intriguing example of this in a study of a childhood cancer, T cell acute lymphoblastic leukemia. An oncogene known to drive the growth of this cancer is expressed at high levels in the leukemic cells because the cells harbor mutations that create a powerful superenhancer (a DNA sequence that activates transcription) upstream of the oncogene.

Science 2014; 346: 1373

Eitan Israeli

Capsule

Endovascular therapy for ischemic stroke with perfusion-imaging selection

Trials of endovascular therapy for ischemic stroke have produced variable results. Campbell et al. conducted this study to test whether more advanced imaging selection, recently developed devices, and earlier intervention improve outcomes. They randomly assigned patients with ischemic stroke who were receiving 0.9 mg of alteplase per kg body weight less than 4.5 hours after the onset of ischemic stroke either to undergo endovascular thrombectomy with the Solitaire FR (Flow Restoration) stent retriever or to continue receiving alteplase alone. All the patients had occlusion of the internal carotid or middle cerebral artery and evidence of salvageable brain tissue and ischemic core of < 70 ml on computed tomographic (CT) perfusion imaging. The co-primary outcomes were reperfusion at 24 hours and early neurologic improvement (≥ 8 point reduction on the National Institutes of Health Stroke Scale or a score of 0 or 1 at day 3). Secondary outcomes included the functional score on the modified Rankin scale at 90 days. The trial was stopped early because of efficacy after 70 patients had undergone randomization (35 patients in each group). The percentage of ischemic territory that had undergone reperfusion at 24 hours was greater in the endovascular therapy group than in the alteplase-only group (median, 100% vs. 37%, $P < 0.001$). Endovascular therapy, initiated at a median of 210 minutes after the onset of stroke, increased early neurologic improvement at 3 days (80% vs. 37%, $P = 0.002$) and improved the functional outcome at 90 days, with more patients achieving functional independence (score of 0 to 2 on the modified Rankin scale, 71% vs. 40%, $P = 0.01$). There were no significant differences in rates of death or symptomatic intracerebral hemorrhage.

N Engl J Med 2015; 372: 1009

Eitan Israeli

Capsule

Evolution of multiple sclerosis in France since the beginning of hepatitis B vaccination

Since the implementation of the mass vaccination campaign against hepatitis B in France, the appearance of multiple sclerosis, sometimes occurring in the aftermath of vaccinations, led to the publication of epidemiological international studies. This was also justified by the sharp increase in the annual incidence of multiple sclerosis reported to the French health insurance in the mid-1990s. Almost 20 years later, a retrospective reflection can be sketched from these official data as well as from the national pharmacovigilance agency. Statistical data from these latter sources seem to show a significant correlation between the number of hepatitis B vaccinations performed and the declaration to the pharmacovigilance of multiple sclerosis occurring between 1 and 2 years later. The application of Hill's criteria to these data indicates that the correlation between hepatitis B vaccine and multiple sclerosis may be causal.

Immunol Res 2014; doi 10.1007/s12026-014-8574-4

Shelly Shachar

Capsule

NK cells link obesity-induced adipose stress to inflammation and insulin resistance

An important cause of obesity-induced insulin resistance is chronic systemic inflammation originating in visceral adipose tissue (VAT). VAT inflammation is associated with the accumulation of pro-inflammatory macrophages in adipose tissue, but the immunological signals that trigger their accumulation remain unknown. Wesveen et al. found that a phenotypically distinct population of tissue-resident natural killer (NK) cells represented a crucial link between obesity-induced adipose stress and VAT inflammation. Obesity drove the upregulation of ligands of the NK cell-activating receptor NCR1 on adipocytes; this stimulated NK cell proliferation and interferon-gamma (IFNγ) production, which in turn triggered the differentiation of pro-inflammatory macrophages and promoted insulin resistance. Deficiency of NK cells, NCR1 or IFNγ prevented the accumulation of pro-inflammatory macrophages in VAT and greatly ameliorated insulin sensitivity. Thus NK cells are key regulators of macrophage polarization and insulin resistance in response to obesity-induced adipocyte stress.

Nature Immunol 2015; 16: 376

Eitan Israeli

Capsule

Escape from bacterial iron piracy through rapid evolution of transferrin

Iron sequestration provides an innate defense, termed nutritional immunity, leading pathogens to scavenge iron from hosts. Although the molecular basis of this battle for iron is established, its potential as a force for evolution at host-pathogen interfaces is unknown. Barber & Elde have shown that the iron transport protein transferrin is engaged in ancient and ongoing evolutionary conflicts with TbpA, a transferrin surface receptor from bacteria. Single substitutions in transferrin at rapidly evolving sites reverse TbpA binding, providing a mechanism to counteract bacterial iron piracy among great apes. Furthermore, the C2 transferrin polymorphism in humans evades TbpA variants from *Haemophilus influenzae*, revealing a functional basis for standing genetic variation. These findings identify a central role for nutritional immunity in the persistent evolutionary conflicts between primates and bacterial pathogens.

Science 2014; 346: 1362

Eitan Israeli

Capsule

Intestinal FXR agonism promotes adipose tissue browning and reduces obesity and insulin resistance

The systemic expression of the bile acid (BA) sensor farnesoid X receptor (FXR) has led to promising new therapies targeting cholesterol metabolism, triglyceride production, hepatic steatosis and biliary cholestasis. In contrast to systemic therapy, bile acid release during a meal selectively activates intestinal FXR. By mimicking this tissue-selective effect, the gut-restricted FXR agonist fexaramine (Fex) robustly induces enteric fibroblast growth factor 15 (FGF15), leading to alterations in BA composition, but does so without activating FXR target genes in the liver. However, unlike systemic agonism, Fang et al. found that Fex reduces diet-induced weight gain, body-wide inflammation and hepatic glucose production, while enhancing thermogenesis and browning of white adipose tissue (WAT). These pronounced metabolic improvements suggest tissue-restricted FXR activation as a new approach in the treatment of obesity and metabolic syndrome.

Nature Med 2015; 21: 159

Eitan Israeli

Capsule

A human tRNA synthetase is a potent PARP1-activating effector target for resveratrol

Resveratrol is reported to extend lifespan and provide cardio-neuro-protective, anti-diabetic, and anti-cancer effects by initiating a stress response that induces survival genes. Because human tyrosyl transfer-RNA (tRNA) synthetase (TyrRS) translocates to the nucleus under stress conditions, we considered the possibility that the tyrosine-like phenolic ring of resveratrol might fit into the active site pocket to effect a nuclear role. Sajish et al. present a 2.1 Å co-crystal structure of resveratrol bound to the active site of TyrRS. Resveratrol nullifies the catalytic activity and redirects TyrRS to a nuclear function, stimulating NAD+-dependent auto-poly-ADP-ribosylation of poly(ADP-ribose) polymerase 1 (PARP1). Downstream activation of key stress signaling pathways are causally connected to TyrRS–PARP1–NAD+ collaboration. This collaboration is also demonstrated in the mouse, and is specifically blocked in vivo by a resveratrol-displacing tyrosyl adenylate analogue. In contrast to functionally diverse tRNA synthetase catalytic nulls created by alternative splicing events that ablate active sites, here a non-spliced TyrRS catalytic null reveals a new PARP1- and NAD+-dependent dimension to the physiological mechanism of resveratrol.

Nature 2015; 519: 370

Eitan Israeli

Capsule

Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults

Pneumococcal polysaccharide conjugate vaccines prevent pneumococcal disease in infants, but their efficacy against pneumococcal community-acquired pneumonia in adults 65 years of age or older is unknown. Bonten et al. evaluated the efficacy of 13-valent polysaccharide conjugate vaccine (PCV13) in preventing first episodes of vaccine-type strains of pneumococcal community-acquired pneumonia, non-bacteremic and non-invasive pneumococcal community-acquired pneumonia, and invasive pneumococcal disease. Standard laboratory methods and a serotype-specific urinary antigen detection assay were used to identify community-acquired pneumonia and invasive pneumococcal disease. In the per-protocol analysis of first episodes of infections due to vaccine-type strains, community-acquired pneumonia occurred in 49 persons in the PCV13 group and 90 persons in the placebo group (vaccine efficacy 45.6%, 95.2% confidence interval 21.8–62.5), non-bacteremic and non-invasive community-acquired pneumonia occurred in 33 persons in the PCV13 group and 60 persons in the placebo group (vaccine efficacy 45.0%, 95.2% CI 14.2–65.3), and invasive pneumococcal disease occurred in 7 persons in the PCV13 group and 28 persons in the placebo group (vaccine efficacy 75.0%, 95% CI 41.4–90.8). Efficacy persisted throughout the trial (mean follow-up 3.97 years). In the modified intention-to-treat analysis, similar efficacy was observed (vaccine efficacy 37.7%, 41.1%, and 75.8%, respectively), and community-acquired pneumonia occurred in 747 persons in the PCV13 group and 787 persons in the placebo group (vaccine efficacy 5.1%, 95% CI -5.1–14.2). Numbers of serious adverse events and deaths were similar in the two groups, but there were more local reactions in the PCV13 group.

N Engl J Med 2015; 372: 1114

Eitan Israeli

Capsule

Synthetic lethality by targeting EZH2 methyltransferase activity in *ARID1A*-mutated cancers

The gene encoding ARID1A, a chromatin remodeler, shows one of the highest mutation rates across many cancer types. Notably, ARID1A is mutated in over 50% of ovarian clear cell carcinomas, which currently have no effective therapy. To date, clinically applicable targeted cancer therapy based on *ARID1A* mutational status has not been described. Bitler and colleagues show that inhibition of the EZH2 methyltransferase acts in a synthetic lethal manner in *ARID1A*-mutated ovarian cancer cells and that *ARID1A* mutational status correlated with response to the EZH2 inhibitor. They identified *PIK3IP1* as a direct target of *ARID1A* and EZH2 that is upregulated by EZH2 inhibition and contributed to the observed synthetic lethality by inhibiting PI3K-AKT signaling. Importantly, EZH2 inhibition caused regression of *ARID1A*-mutated ovarian tumors in vivo. To our knowledge, this is the first data set to demonstrate a synthetic lethality between *ARID1A* mutation and EZH2 inhibition. These data indicate that pharmacological inhibition of EZH2 represents a novel treatment strategy for cancers involving ARID1A mutations.

Nature Med 2015; 21: 231

Eitan Israeli

Capsule

Liberal or restrictive transfusion after cardiac surgery

Whether a restrictive threshold for hemoglobin level in red cell transfusions, as compared with a liberal threshold, reduces postoperative morbidity and health care costs after cardiac surgery is uncertain. A total of 2007 patients underwent randomization; 4 participants withdrew, leaving 1000 in the restrictive threshold group and 1003 in the liberal threshold group. Transfusion rates after randomization were 53.4% and 92.2% in the two groups, respectively. The primary outcome occurred in 35.1% of the patients in the restrictive threshold group and 33.0% of the patients in the liberal threshold group (odds ratio 1.11, 95% confidence interval 0.91–1.34, $P = 0.30$); there was no indication of heterogeneity according to subgroup. There were more deaths in the restrictive threshold group than in the liberal threshold group (4.2% vs. 2.6%, hazard ratio 1.64, 95% CI 1.00–2.67, $P = 0.045$). Serious postoperative complications, excluding primary outcome events, occurred in 35.7% of participants in the restrictive threshold group and 34.2% of participants in the liberal threshold group. Total costs did not differ significantly between the groups.

N Engl J Med 2015; 372: 997

Eitan Israeli

Capsule

Tetanus toxoid and CCL3 improve dendritic cell vaccines in mice and glioblastoma patients

After stimulation, dendritic cells (DCs) mature and migrate to draining lymph nodes to induce immune responses. As such, autologous DCs generated ex vivo have been pulsed with tumor antigens and injected back into patients as immunotherapy. While DC vaccines have shown limited promise in the treatment of patients with advanced cancers including glioblastoma, the factors dictating DC vaccine efficacy remain poorly understood. Mitchell et al. show that preconditioning the vaccine site with a potent recall antigen such as tetanus/diphtheria (Td) toxoid can significantly improve the lymph node homing and efficacy of tumor antigen-specific DCs. To assess the effect of vaccine site preconditioning in humans, the authors randomized patients with glioblastoma to preconditioning with either mature DCs or Td unilaterally before bilateral vaccination with DCs pulsed with Cytomegalovirus phosphoprotein 65 (pp65) RNA. The authors and other laboratories have shown that pp65 is expressed in more than 90% of glioblastoma specimens but not in surrounding normal brain, providing an unparalleled opportunity to subvert this viral protein as a tumor-specific target. Patients given Td had enhanced DC migration bilaterally and significantly improved survival. In mice, Td preconditioning also enhanced bilateral DC migration and suppressed tumor growth in a manner dependent on the chemokine CCL3. These clinical studies and corroborating investigations in mice suggest that preconditioning with a potent recall antigen may represent a viable strategy to improve anti-tumor immunotherapy.

Nature 2015; 519: 366

Eitan Israeli

Capsule

When cognitive control shuts down in OCD

People with obsessive-compulsive disorder (OCD) cannot control their thoughts, engage in compulsive actions and perform repetitive behaviors to reduce their anxiety. To better understand the neurological basis of these symptoms, Banca et al. used individually tailored stimuli to provoke and alleviate symptoms in people with OCD while scanning their brains with functional magnetic resonance imaging. When provoked, the caudate-prefrontal brain circuits involved in cognitive control and goal-directed behavior shut down in OCD patients. This was accompanied by hyperactivation of a brain region called the putamen, which controls repetitive behavior. These insights may pave the way for novel therapeutic approaches to treating OCD.

Brain 2015; 138: 798

Eitan Israeli

Capsule

Mongersen, an oral *SMAD7* antisense oligonucleotide, and Crohn's disease

Crohn's disease-related inflammation is characterized by reduced activity of the immunosuppressive cytokine transforming growth factor-beta 1 (TGFβ1) due to high levels of *SMAD7*, an inhibitor of TGFβ1 signaling. Preclinical studies and a phase 1 study have shown that an oral SMAD7 antisense oligonucleotide, mongersen, targets ileal and colonic SMAD7. In a double-blind, placebo-controlled, phase 2 trial, Monteleone et al. evaluated the efficacy of mongersen for the treatment of persons with active Crohn's disease. Patients were randomly assigned to receive 10, 40, or 160 mg of mongersen or placebo per day for 2 weeks. The primary outcomes were clinical remission at day 15, defined as a Crohn's Disease Activity Index (CDAI) score of less than 150, with maintenance of remission for at least 2 weeks, and the safety of mongersen treatment. A secondary outcome was clinical response (defined as a reduction of 100 points or more in the CDAI score) at day 28. The proportions of patients who reached the primary end-point were 55% and 65% for the 40 mg and 160 mg mongersen groups, respectively, as compared with 10% for the placebo group ($P < 0.001$). There was no significant difference in the percentage of participants reaching clinical remission between the 10 mg group (12%) and the placebo group. The rate of clinical response was significantly greater among patients receiving 10 mg (37%), 40 mg (58%), or 160 mg (72%) of mongersen than among those receiving placebo (17%) ($P = 0.04$, $P < 0.001$, and $P < 0.001$, respectively). Most adverse events were related to complications and symptoms of Crohn's disease.

N Engl J Med 2015; 372: 1104

Eitan Israeli

Capsule

Yersinia disarm a cellular defense system

Macrophages are cells that engulf and destroy foreign substances in a process called phagocytosis. Lee et al. now show how a bacterium from the Yersinia family, which includes the bacteria that causes bubonic plague, acts to disable phagocytosis. *Yersinia enterocolitica* injects a protein called YopO into macrophages. A crystal structure shows that YopO binds to single host actin proteins in a way that prevents them from adding to actin filaments that form the skeleton of the cell. Moreover, the complex sequesters and phosphorylates proteins required for remodeling the actin skeleton, probably preventing the remodeling required for phagocytosis.

Nat Struct Mol Biol 2015;10.1038/nsmb.2964

Eitan Israeli

Capsule

Ribosomes regulate stem cell fate

The use of stem cells in regenerative medicine holds enormous therapeutic potential. However, scientists still need to fully understand the molecular signals that control the ability of stem cells to self-renew and differentiate. To identify genes that may regulate this, Fortier and collaborators screened a library of mouse embryonic stem cells (ESCs) containing chromosomal deletions. They found that the loss of a single copy of several genes encoding protein subunits of the ribosome, a large protein complex that translates mRNA into proteins, resulted in impaired ESC differentiation but did not affect self-renewal.

Proc Natl Acad Sci USA 2015;10.1073/pnas.1418845112.

Eitan Israeli

Capsule

Weaning means more than no more milk but also jump starts beta cells

Nursing mothers provide much needed nutrition to offspring, but the full effects of weaning on offspring's physiology is unknown. Stolovich-Rain and team now show that in mice, weaning affects the function of insulin-producing beta cells in the pancreas. The ability of beta cells to regenerate after injury or to modulate their insulin secretion decreases with age. However, beta cells also regenerated poorly in response to injury in very young mice and only gained this function upon weaning. These results suggest that at least for mouse beta cells, weaning jump starts the cell cycle and modulates insulin production in response to glucose.

Curr Biol 2014; 24: 2733

Eitan Israeli

Capsule

LTB4 promotes insulin resistance in obese mice by acting on macrophages, hepatocytes and myocytes

Insulin resistance results from several pathophysiologic mechanisms, including chronic tissue inflammation and defective insulin signaling. Li et al. found that liver, muscle and adipose tissue exhibit higher levels of the chemotactic eicosanoid LTB4 in obese high fat diet (HFD)-fed mice. Inhibition of the LTB4 receptor Ltb4r1, through either genetic or pharmacologic loss of function, led to an anti-inflammatory phenotype with protection from insulin resistance and hepatic steatosis. In vitro treatment with LTB4 directly enhanced macrophage chemotaxis, stimulated inflammatory pathways, reduced insulin-stimulated glucose uptake in L6 myocytes, and impaired insulin-mediated suppression of hepatic glucose output in primary mouse hepatocytes. This was accompanied by lower insulin-stimulated Akt phosphorylation and higher Irs-1/2 serine phosphorylation, and all of these events were dependent on Gαi and Jnk1, two downstream mediators of Ltb4r1 signaling. These observations elucidate a novel role of the LTB4-Ltb4r1 signaling pathway in hepatocyte and myocyte insulin resistance, and they show that in vivo inhibition of Ltb4r1 leads to robust insulin-sensitizing effects.

Nature Med 2015; 21: 239

Eitan Israeli

Capsule

Pro-inflammatory microenvironments within the intestine regulate the differentiation of tissue-resident CD8+ T cells responding to infection

Bergsbaken and co-authors report that oral infection with *Yersinia pseudotuberculosis* results in the development of two distinct populations of pathogen-specific CD8+ tissue-resident memory T cells (TRM cells) in the lamina propria. CD103– T cells did not require transforming growth factor-beta (TGFβ) signaling but were true resident memory cells. Unlike CD103+CD8+ T cells, which were TGF-β dependent and were scattered in the tissue, CD103–CD8+ T cells clustered with CD4+ T cells and CX3CR1+macrophages and/or dendritic cells around areas of bacterial infection. CXCR3-dependent recruitment of cells to inflamed areas was critical for development of the CD103– population and pathogen clearance. These studies have identified the 'preferential' development of CD103– T_{RM}cells in inflammatory microenvironments within the lamina propria and suggest that this subset has a critical role in controlling infection.

Nature Immunol 2015; 16: 406

Eitan Israeli

Capsule

Toward broad-spectrum antiviral drugs

For many emerging viruses such as Ebola and dengue, no licensed drug treatments exist. In a perspective, Bekerman and Einav argue that broad-spectrum antiviral drugs could play a key role in treating infections caused by these and other viruses. These drugs can either target the virus or the host cell. Drugs licensed for treating other diseases, including several cancer drugs, are also showing promise as possible antiviral treatments. If challenges such as toxicity and drug resistance can be addressed, broad-spectrum antiviral drugs will be a useful complement to existing narrow-spectrum approaches.

Science 2015; 348: 282

Eitan Israeli

Capsule

Axonal regeneration: progress toward fixing a broken back?

Axon regeneration after a spinal cord injury requires interference with neuronal mechanisms to promote axon extension and early suppression of scar formation. Microtubule stabilization could provide, in principle, a basis for such intervention. Ruschel et al. used animal models of spinal cord injury, time-lapse imaging in vivo, primary neuronal cultures, and behavioral studies to tackle this challenge. They showed that epothilone B, a U.S. Food and Drug Administration-approved microtubule-stabilizing drug that can cross the blood-brain barrier, does promote functional axon regeneration, even after injury.

Science 2015; 348: 347

Eitan Israeli

Capsule

Characterization of pancreatic NMDA receptors as possible drug targets for diabetes treatment

In the nervous system, NMDA receptors (NMDARs) participate in neurotransmission and modulate the viability of neurons. In contrast, little is known about the role of NMDARs in pancreatic islets and the insulin-secreting beta cells whose functional impairment contributes to diabetes mellitus. Marquard et al. found that inhibition of NMDARs in mouse and human islets enhanced their glucose-stimulated insulin secretion (GSIS) and survival of islet cells. Further, NMDAR inhibition prolonged the amount of time that glucose-stimulated beta cells spent in a depolarized state with high cytosolic Ca2+ concentrations. The authors also noticed that, in vivo, the NMDAR antagonist dextromethorphan (DXM) enhanced glucose tolerance in mice, and that in vitro dextrorphan, the main metabolite of DXM, amplified the stimulatory effect of exendin-4 on GSIS. In a mouse model of type 2 diabetes mellitus (T2DM), long-term treatment with DXM improved islet insulin content, islet cell mass and blood glucose control. Further, in a small clinical trial they found that individuals with T2DM treated with DXM showed enhanced serum insulin concentrations and glucose tolerance. These data highlight the possibility that antagonists of NMDARs may provide a useful adjunct treatment for diabetes.

Nature Med 2015; 21: 363

Eitan Israeli

Capsule

Ocular involvement in monogenic autoinflammatory diseases

Monogenic autoinflammatory disorders (AIDs) are an expanding group of diseases of the innate immune system characterized by unprovoked attacks of systemic inflammation, which typically present in the absence of autoantibodies and autoreactive T cells. The family of monogenic AIDs includes periodic fever syndromes, pyogenic and granulomatous disorders, all characterized by recurrent fever attacks with localized inflammation involving various districts, such as skin, serosal membranes, joints, gastrointestinal tube, central nervous system and eye. Their heterogeneous clinical spectrum is caused by mutations in genes involved in the regulation of inflammatory and apoptotic signals, mostly components of the inflammasome, cytokine receptors, or receptor antagonists, and culminating with the aberrant release of pro-inflammatory cytokines such as interleukin-1beta (IL-1β) and tumor necrosis factor-alpha (TNFα). Bascherini et al. summarize the most relevant monogenic AIDs affecting the eye. They reviewed all the medical literature regarding the protean ocular involvement in AIDs, mainly considering granulomatous disorders, familial Mediterranean fever (FMF), TNF receptor-associated periodic syndrome (TRAPS), mevalonate kinase deficiency (MKD) and cryopyrin-associated periodic fever syndromes (CAPS). The review underlines how eye involvement may be relevant and represent, if untreated, a serious condition with long-term complications and risk of potential blindness, particularly in Blau and CINCA syndrome. They suggest managing ocular disease with topical application and/or systemic administration of corticosteroids, including the use of immunosuppressive drugs in the case of disease reactivations or other complications. In refractory cases, although more data from observational and experimental studies are needed, biologic agents inhibiting IL-1 or TNFα appear to be a new and potent tool in the management of eye involvement in AIDs patients.

Clin Rheumatol 2015, Epub ahead of print

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