Capsule

How to boost cancer immunotherapy

Why does our immune system protect us so well against infection but not against cancer? In part, this is because cancer cells use clever ways to escape immune responses designed to destroy them. A therapeutic strategy called "immune checkpoint blockade" thwarts these escape tactics and renders cancer cells vulnerable to immune attack. Although remarkably effective, only a subset of patients respond to it. Seeking possible explanations for this limited response, Kim et al. identified a specific immune cell population that interferes with the therapy in mouse tumor models. When the authors co-administered drugs that reduced the levels of these cells (called myeloid-derived suppressor cells), the efficacy of immune checkpoint blockade therapy improved considerably.

Proc Natl Acad Sci USA 2014; 10.1073/pnas.1410626111

Eitan Israeli

Capsule

When genetic diversity hurts the kids

Although we think of the genome as fixed, errors in DNA replication and recombination can cause changes. As the organism develops, individual nucleotides may mutate, or genetic material may duplicate or be deleted. Such "somatic mosaicism" means that different cells and tissues in the body may have different genomes. To determine whether this affects human disease, Campbell et al. took blood samples from 100 families with children who have genetic disorders. They found that approximately 4% of the parents (who were all healthy) exhibited somatic mosaicism, which suggests that the affected children inherited the mutation from a mosaic parent. These results suggest that somatic mosaicism is probably more common than previously thought and affects human health.

Am J Human Genet 2014; 10.1016/j.ajhg.2014.07.003

Eitan Israeli

Capsule

A breathtaking tale of sticky mucus in cystic fibrosis

Patients with cystic fibrosis have difficulty breathing because their airways are clogged with thick mucus. Does this mucus accumulate because there is a defect in the way it is produced? Or does it accumulate because of other disease features, such as dehydration or airway wall remodeling? Distinguishing between these possibilities is important for future drug development. In a study of piglets with cystic fibrosis, Hoegger and fellow-researchers identified mucus production as the primary defect. The airway glands of the piglets synthesized strands of mucus normally, but the strands were never released and stayed tethered to the gland ducts.

Science 2014; 345: 818

Eitan Israeli

Capsule

Antifungal drug resistance evoked via RNAi-dependent epimutations

Microorganisms evolve via a range of mechanisms that may include or involve sexual/parasexual reproduction, mutators, aneuploidy, Hsp90 and even prions. Mechanisms that may seem detrimental can be repurposed to generate diversity. Calo et al. show that the human fungal pathogen *Mucor circinelloides* develops spontaneous resistance to the antifungal drug FK506 (tacrolimus) via two distinct mechanisms. One involves Mendelian mutations that confer stable drug resistance; the other occurs via an epigenetic RNA interference (RNAi)-mediated pathway resulting in unstable drug resistance. The peptidylprolyl isomerase FKBP12 interacts with FK506 forming a complex that inhibits the protein phosphatase calcineurin. Calcineurin inhibition by FK506 blocks *M. circinelloides* transition to hyphae and enforces yeast growth. Mutations in the fkbA gene encoding FKBP12 or the calcineurin cnbR or cnaA genes confer FK506 resistance and restore hyphal growth. In parallel, RNAi is spontaneously triggered to silence the fkbA gene, giving rise to drug-resistant epimutants. FK506-resistant epimutants readily reverted to the drug-sensitive wild-type phenotype when grown without exposure to the drug. The establishment of these epimutants is accompanied by generation of abundant fkbA small RNAs and requires the RNAi pathway as well as other factors that constrain or reverse the epimutant state. Silencing involves the generation of a double-stranded RNA trigger intermediate using the fkbA mature mRNA as a template to produce antisense fkbA RNA. This study uncovers a novel epigenetic RNAi-based epimutation mechanism controlling phenotypic plasticity, with possible implications for antimicrobial drug resistance and RNAi-regulatory mechanisms in fungi and other eukaryotes.

Nature 2014; 513: 555

Eitan Israeli

Capsule

Chromatin state dynamics during blood formation

Chromatin modifications are crucial for development, yet little is known about their dynamics during differentiation. Hematopoiesis provides a well-defined model to study chromatin state dynamics; however, technical limitations impede profiling of homogeneous differentiation intermediates. Lara-Astiaso et al. developed a high sensitivity indexing-first chromatin immunoprecipitation approach to profile the dynamics of four chromatin modifications across 16 stages of hematopoietic differentiation. The authors identified 48,415 enhancer regions and characterized their dynamics. They found that lineage commitment involves de novo establishment of 17,035 lineage-specific enhancers. These enhancer repertoire expansions foreshadow transcriptional programs in differentiated cells. Combining our enhancer catalog with gene expression profiles, we elucidate the transcription factor network controlling chromatin dynamics and lineage specification in hematopoiesis. Together, these results provide a comprehensive model of chromatin dynamics during development.

Science 2014; 345: 942

Eitan Israeli

Capsule

Parasites make it hard to fight viruses

Microbial co-infections challenge the immune system – different pathogens often require different flavors of immune responses for their elimination. Two teams studied what happens when parasitic worms and viruses infect mice at the same time. Reese et al. (*Science* 2014; 345: 73) found that parasite co-infection woke up a dormant virus. Osborne et al. (*Science* p. 517) found that mice already infected with parasitic worms were worse at fighting off viruses. In both cases, worms skewed the immune response so that the immune cells and the molecules they secreted created an environment favorable for the worm at the expense of antiviral immunity.

Eitan Israeli

Capsule

Angiotensin-neprilysin inhibition versus enalapril in heart failure

McMurray et al. compared the angiotensin receptor-neprilysin inhibitor LCZ696 with enalapril in patients who had heart failure with a reduced ejection fraction. In previous studies, enalapril improved survival in such patients. In this double-blind trial, the authors randomly assigned 8442 patients with class II, III, or IV heart failure and an ejection fraction of 40% or less to receive either LCZ696 (at a dose of 200 mg twice daily) or enalapril (at a dose of 10 mg twice daily) in addition to recommended therapy. The primary outcome was a composite of death from cardiovascular causes or hospitalization for heart failure, but the trial was designed to detect a difference in the rates of death from cardiovascular causes. The trial was stopped early, according to prespecified rules, after a median follow-up of 27 months, because the boundary for an overwhelming benefit with LCZ696 had been crossed. At the time of study closure, the primary outcome had occurred in 914 patients (21.8%) in the LCZ696 group and 1117 patients (26.5%) in the enalapril group [hazard ratio in the LCZ696 group 0.80, 95% confidence interval (CI) 0.73–0.87, $P < 0.001$]. A total of 711 patients (17.0%) receiving LCZ696 and 835 patients (19.8%) receiving enalapril died (hazard ratio for death from any cause 0.84, 95%CI 0.76–0.93, $P < 0.001$); of these patients, 558 (13.3%) and 693 (16.5%), respectively, died from cardiovascular causes (hazard ratio 0.80, 95%CI 0.71–0.89, $P < 0.001$). As compared with enalapril, LCZ696 also reduced the risk of hospitalization for heart failure by 21% ($P < 0.001$) and decreased the symptoms and physical limitations of heart failure ($P = 0.001$). The LCZ696 group had higher proportions of patients with hypotension and nonserious angioedema but lower proportions with renal impairment, hyperkalemia, and cough than the enalapril group.

N Engl J Med 2014; 371: 993

Eitan Israeli

Capsule

A neuropeptide kills patient's motivation

Chronic pain is not only extremely disturbing and unpleasant, it can also make people depressed and demotivated. What causes these effects? Schwartz and co-researchers discovered that chronic pain causes changes in the way a neuropeptide called galanin affects certain neurons in a brain region called the nucleus accumbens. Galanin influences a variety of behaviors, including feeding and certain aspects of pain. In this case, it depresses synaptic transmission at specific excitatory synapses. It does so, in part, by changing the ratio of subunits of an important receptor protein.

Science 2014; 345: 535

Eitan Israeli

Capsule

Combinations of antibiotics to fight bacteria

Is it possible to streamline the complex task of finding new drugs to fight resistant bacteria and other disease targets? Most biological processes are controlled by complicated regulatory networks, so combinations of two or more drugs are likely to be more effective than any single agent. Finding combinations that work means first screening enormous numbers of possibilities. Cheng et al. examined mixtures of genetic elements in millions of different combinations. Those combinations with the desired effect in a biological test could be identified afterward by highthroughput sequencing capable of detecting associated DNA "barcode" identifier sequences. Results are promising and revealed combinations of transcription factors that enhanced lethal effects of an antibiotic by a millionfold.

Proc Natl Acad Sci USA 2014;10.1073/pnas.1400093111

Eitan Israeli

Capsule

Comprehensive molecular characterization of gastric adenocarcinoma

Gastric cancer is a leading cause of cancer deaths, but analysis of its molecular and clinical characteristics has been complicated by histological and etiological heterogeneity. The Cancer Genome Atlas Research Network describe a comprehensive molecular evaluation of 295 primary gastric adenocarcinomas as part of The Cancer Genome Atlas (TCGA) project. The authors propose a molecular classification dividing gastric cancer into four subtypes: tumors positive for Epstein-Barr virus, which display recurrent PIK3CA mutations, extreme DNA hypermethylation, and amplification of JAK2, CD274 (also known as PD-L1) and PDCD1LG2 (also known as PD-L2); microsatellite unstable tumors, which show elevated mutation rates, including mutations of genes encoding targetable oncogenic signaling proteins; genomically stable tumors, which are enriched for the diffuse histological variant and mutations of RHOA or fusions involving RHO-family GTPase-activating proteins; and tumors with chromosomal instability, which show marked aneuploidy and focal amplification of receptor tyrosine kinases. Identification of these subtypes provides a roadmap for patient stratification and trials of targeted therapies.

Nature 2014; 513: 202

Eitan Israeli

Capsule

AR-V7 and resistance to enzalutamide and abiraterone in prostate cancer

The androgen-receptor isoform encoded by splice variant 7 lacks the ligand-binding domain, which is the target of enzalutamide and abiraterone, but remains constitutively active as a transcription factor. We hypothesized that detection of androgen-receptor splice variant 7 messenger RNA (AR-V7) in circulating tumor cells from men with advanced prostate cancer would be associated with resistance to enzalutamide and abiraterone. Antonarakis et al. used a quantitative reverse-transcriptase-polymerase chain reaction assay to evaluate AR-V7 in circulating tumor cells from prospectively enrolled patients with metastatic castration-resistant prostate cancer who were initiating treatment with either enzalutamide or abiraterone. We examined associations between AR-V7 status (positive vs. negative) and prostate-specific antigen (PSA) response rates (the primary end-point), freedom from PSA progression (PSA progression-free survival), clinical or radiographic progression-free survival, and overall survival. A total of 31 enzalutamide-treated patients and 31 abiraterone-treated patients were enrolled, of whom 39% and 19%, respectively, had detectable AR-V7 in circulating tumor cells. Among men receiving enzalutamide, AR-V7-positive patients had lower PSA response rates than AR-V7-negative patients (0% vs. 53%, $P = 0.004$) and shorter PSA progression-free survival (median 1.4 months vs. 6.0 months, $P < 0.001$), clinical or radiographic progression-free survival (median 2.1 vs. 6.1 months, $P < 0.001$), and overall survival (median 5.5 months vs. not reached, $P = 0.002$). Similarly, among men receiving abiraterone, AR-V7-positive patients had lower PSA response rates than AR-V7-negative patients (0% vs. 68%, $P = 0.004$) and shorter PSA progression-free survival (median 1.3 months vs. not reached, $P < 0.001$), clinical or radiographic progression-free survival (median 2.3 months vs. not reached, $P < 0.001$), and overall survival (median 10.6 months vs. not reached, $P = 0.006$). The association between AR-V7 detection and therapeutic resistance was maintained after adjustment for expression of full-length androgen receptor messenger RNA.

N Engl J Med 2014; 371:1028

Eitan Israeli

Capsule

Evolution of Ebola virus over time

The high rate of mortality in the current Ebola epidemic has made it difficult for researchers to collect samples of the virus and study its evolution. Gire et al. describe Ebola epidemiology on the basis of 99 whole-genome sequences, including samples from 78 affected individuals. The authors analyzed changes in the viral sequence and conclude that the current outbreak probably resulted from the spread of the virus from central Africa in the past decade. The outbreak started from a single transmission event from an unknown animal reservoir into the human population. Two viral lineages from Guinea then spread from person to person into Sierra Leone.

Science 2014; 345: 1369

Eitan Israeli

Capsule

Loss of oncogenic Notch1 with resistance to a PI3K inhibitor in T cell leukemia

Mutations that deregulate Notch1 and Ras/phosphoinositide 3 kinase (PI3K)/Akt signaling are prevalent in T cell acute lymphoblastic leukemia (T-ALL), and often coexist. Dail and colleagues show that the PI3K inhibitor GDC-0941 is active against primary T-ALLs from wild-type and KrasG12D mice, and addition of the MEK inhibitor PD0325901 increases its efficacy. Mice invariably relapsed after treatment with drug-resistant clones, most of which unexpectedly had reduced levels of activated Notch1 protein, down-regulated many Notch1 target genes, and exhibited cross-resistance to γ-secretase inhibitors. Multiple resistant primary T-ALLs that emerged in vivo did not contain somatic Notch1 mutations present in the parental leukemia. Importantly, resistant clones up-regulated PI3K signaling. Consistent with these data, inhibiting Notch1 activated the PI3K pathway, providing a likely mechanism for selection against oncogenic Notch1 signaling. These studies validate PI3K as a therapeutic target in T-ALL and raise the unexpected possibility that dual inhibition of PI3K and Notch1 signaling could promote drug resistance in T-ALL.

Nature 2014; 513: 512

Eitan Israeli

Capsule

Statin treatment rescues *FGFR3* skeletal dysplasia phenotypes

Gain-of-function mutations in the fibroblast growth factor receptor 3 gene (*FGFR3*) result in skeletal dysplasias, such as thanatophoric dysplasia and achondroplasia (ACH). The lack of disease models using human cells has hampered the identification of a clinically effective treatment for these diseases. Yamashita et al. show that statin treatment can rescue patient-specific induced pluripotent stem cell (iPSC) models and a mouse model of *FGFR3* skeletal dysplasia. The authors converted fibroblasts from thanatophoric dysplasia type I (TD1) and ACH patients into iPSCs. The chondrogenic differentiation of TD1 iPSCs and ACH iPSCs resulted in the formation of degraded cartilage. They found that statins could correct the degraded cartilage in both chondrogenically differentiated TD1 and ACH iPSCs. Treatment of ACH model mice with statin led to a significant recovery of bone growth. These results suggest that statins could represent a medical treatment for infants and children with TD1 and ACH.

Nature 2014; 513: 507

Eitan Israeli

Capsule

Refilling drug delivery devices

Drugs delivered throughout the body often cause collateral damage to healthy tissues. When disease or injury is localized, patients can avoid this problem by using a drug delivery device implanted in the target tissue. However, such devices eventually run out of drugs and must be removed surgically and refilled. Brudno et al. designed a drug-delivery device that can be refilled non-invasively and tested it in a mouse tumor model. They made the device from a gel tethered to short DNA sequences. To refill it, they coupled gel strands to drugs and tethered them to complementary DNA sequences, then injected the strands intravenously into the mice. Because of the complementary DNA sequences, the strands homed directly to the device.

Proc Natl Acad Sci USA 2014;10.1073/pnas.1413027111

Eitan Israeli

Capsule

Flu survivors are an inflammatory club

Kill it: That is the immune system's response to most viral infections, including influenza. Eliminating infected cells rids the body of the infection. Heaton and group report that a special type of epithelial cell in the lungs of mice – called club cells – survive influenza infection. How do they do it? Gene expression analysis suggests that club cells express high amounts of antiviral genes in response to infection. Although this process probably helps the animal contain the virus during early infection, club cells also produced pro-inflammatory molecules that cause lung pathology. Whether club cells play a role in inflammation-induced mortality, as seen in the H5N1 and H1N1 influenza pandemics, remains to be seen.

J Exp Med 2014;10.1084/jem.20140488

Eitan Israeli

Capsule

An acetate switch regulates stress erythropoiesis

The hormone erythropoietin (EPO), which is synthesized in the kidney or liver of adult mammals, controls erythrocyte production and is regulated by the stress-responsive transcription factor hypoxia-inducible factor-2 (HIF-2). Xu and co-authors previously reported that the lysine acetyltransferase CREB-binding protein (CBP) is required for HIF-2α acetylation and efficient HIF-2-dependent EPO induction during hypoxia. Now the authors (show that these processes require acetate-dependent acetyl CoA synthetase 2 (ACSS2). In human Hep3B hepatoma cells and in EPO-generating organs of hypoxic or acutely anemic mice, acetate levels rise and ACSS2 is required for HIF-2αacetylation, CBP-HIF-2α complex formation, CBP-HIF-2α recruitment to the EPO enhancer and efficient induction of EPO gene expression. In acutely anemic mice, acetate supplementation augments stress erythropoiesis in an ACSS2-dependent manner. Moreover, in acquired and inherited chronic anemia mouse models, acetate supplementation increases EPO expression and the resting hematocrit. Thus, a mammalian stress-responsive acetate switch controls HIF-2 signaling and EPO induction during pathophysiological states marked by tissue hypoxia.

Nature Med 2014; 20: 1018

Eitan Israeli

Capsule

A BLUEPRINT of immune cell development

To determine the epigenetic mechanisms that direct blood cells to develop into the many components of our immune system, the BLUEPRINT consortium examined the regulation of DNA and RNA transcription to dissect the molecular traits that govern blood cell differentiation. By inducing immune responses, Saeed et al. document the epigenetic changes in the genome that underlie immune cell differentiation. Cheng et al. demonstrate that trained monocytes are highly dependent on the breakdown of sugars in the presence of oxygen, which allows cells to produce the energy needed to mount an immune response. Chen's group examined RNA transcripts and found that specific cell lineages use RNA transcripts of different length and composition (isoforms) to form proteins. Together, the studies reveal how epigenetic effects can drive the development of blood cells involved in the immune system.

Science 2014; 10.1126.1251086, 1250684, 1251033

Eitan Israeli

Capsule

Practice makes perfect — or does it?

How do we learn from past errors? Herzfeld et al. found that when we practice a movement, the human brain has a memory for errors that is then used to learn faster in new conditions. This memory for error exists in parallel with motor memory's two traditional forms: memory of actions and memory of external perturbations. They also proposed a mathematical model for learning from errors. This model explained previous experimental results and predicted other major findings that they later verified experimentally.

Science 2014; 345: 1349

Eitan Israeli

Capsule

The alarmin IL-33 promotes regulatory T cell function in the intestine

FOXP3+ regulatory T cells (Treg cells) are abundant in the intestine, where they prevent dysregulated inflammatory responses to self and environmental stimuli. It is now appreciated that Treg cells acquire tissue-specific adaptations that facilitate their survival and function; however, key host factors controlling the Treg response in the intestine are poorly understood. The interleukin (IL)-1 family member IL-33 is constitutively expressed in epithelial cells at barrier sites, where it functions as an endogenous danger signal, or alarmin, in response to tissue damage. Recent studies in humans have described high levels of IL-33 in inflamed lesions of inflammatory bowel disease patients, suggesting a role for this cytokine in disease pathogenesis. In the intestine, both protective and pathological roles for IL-33 have been described in murine models of acute colitis, but its contribution to chronic inflammation remains ill defined. Schiering and team show in mice that the IL-33 receptor ST2 is preferentially expressed on colonic Treg cells, where it promotes Treg function and adaptation to the inflammatory environment. IL-33 signaling in T cells stimulates Treg responses in several ways. First, it enhances transforming growth factor (TGF)-β1-mediated differentiation of Treg cells and, second, it provides a necessary signal for Treg cell accumulation and maintenance in inflamed tissues. Strikingly, IL-23, a key pro-inflammatory cytokine in the pathogenesis of inflammatory bowel disease, restrained Treg responses through inhibition of IL-33 responsiveness. These results demonstrate a hitherto unrecognized link between an endogenous mediator of tissue damage and a major anti-inflammatory pathway, and suggest that the balance between IL-33 and IL-23 may be a key controller of intestinal immune responses.

Nature 2014; 513: 564

Eitan Israeli

Capsule

Moral homeostasis in real life vs. the lab

Individuals who witnessed a moral deed are more likely than non-witnesses to perform a moral deed themselves and are also more likely to allow themselves to act immorally. Hofmann et al. asked smartphone users to report their encounters with morality. Most moral judgment experiments are lab-based and don't allow for conclusions based on what people experience in their daily lives. This field experiment revealed that people experience moral events frequently in daily life. A respondent's ideology influenced the kind of event reported and the frequency, which is consistent with moral foundations theory.

Science 2014; 345: 1340

Eitan Israeli

Capsule

Origin of the spine lies in a worm

The notochord, the developmental backbone precursor, defines chordates – the group of animals to which humans belong. The origin of the notochord remains mysterious. Lauri and co-workers report the identification of a longitudinal muscle in an annelid worm that displays striking similarities to the notochord regarding position, developmental origin, and expression profile. Similar muscles, termed axochords, are found in various invertebrate phyla. These data suggest that the last common ancestor of bilaterians already possessed contractile midline tissue that, via stiffening, developed into a cartilaginous rod in the chordate line.

Science 2014; 345: 1365

Eitan Israeli

Capsule

Rationale for co-targeting IGF-1R and ALK in ALK fusion-positive lung cancer

Crizotinib, a selective tyrosine kinase inhibitor (TKI), shows marked activity in patients whose lung cancers harbor fusions in the gene encoding anaplastic lymphoma receptor tyrosine kinase (ALK), but its efficacy is limited by variable primary responses and acquired resistance. In work arising from the clinical observation of a patient with ALK fusion-positive lung cancer who had an exceptional response to an insulin-like growth factor 1 receptor (IGF-1R)-specific antibody, Lovly and fellow researchers define a therapeutic synergism between ALK and IGF-1R inhibitors. Similar to IGF-1R, ALK fusion proteins bind to the adaptor insulin receptor substrate 1 (IRS-1), and IRS-1 knockdown enhances the antitumor effects of ALK inhibitors. In models of ALK TKI resistance, the IGF-1R pathway is activated, and combined ALK and IGF-1R inhibition improves therapeutic efficacy. Consistent with this finding, the levels of IGF-1R and IRS-1 are increased in biopsy samples from patients progressing on crizotinib monotherapy. Collectively these data support a role for the IGF-1R–IRS-1 pathway in both ALK TKI-sensitive and ALK TKI-resistant states and provide a biological rationale for further clinical development of dual ALK and IGF-1R inhibitors.

Nature Med 2014; 20: 1027

Eitan Israeli

Capsule

Alopecia areata is driven by cytotoxic T lymphocytes and is reversed by JAK inhibition

Alopecia areata (AA) is a common autoimmune disease resulting from damage of the hair follicle by T cells. The immune pathways required for autoreactive T cell activation in AA are not defined, limiting clinical development of rational targeted therapies. Genome-wide association studies (GWAS) implicated ligands for the NKG2D receptor (product of the *KLRK1* gene) in disease pathogenesis. Xing et al. show that cytotoxic CD8+NKG2D+ T cells are both necessary and sufficient for the induction of AA in mouse models of disease. Global transcriptional profiling of mouse and human AA skin revealed gene expression signatures indicative of cytotoxic T cell infiltration, an interferon-gamma (IFNγ) response and up-regulation of several γ-chain (γc) cytokines known to promote the activation and survival of IFNγ-producing CD8+NKG2D+ effector T cells. Therapeutically, antibody-mediated blockade of IFNγ, interleukin-2 (IL-2) or interleukin-15 receptor β (IL-15Rβ) prevented disease development, reducing the accumulation of CD8+NKG2D+ T cells in the skin and the dermal IFN response in a mouse model of AA. Systemically administered pharmacological inhibitors of Janus kinase (JAK) family protein tyrosine kinases, downstream effectors of the IFNγ and γc cytokine receptors, eliminated the IFN signature and prevented the development of AA, while topical administration promoted hair regrowth and reversed established disease. Notably, three patients treated with oral ruxolitinib, an inhibitor of JAK1 and JAK2, achieved near-complete hair regrowth within 5 months of treatment, suggesting the potential clinical utility of JAK inhibition in human AA.

Nature Med 2014; 20: 1043

Eitan Israeli

Capsule

Endothelial cell FAK targeting sensitizes tumors to DNA-damaging therapy

Chemoresistance is a serious limitation of cancer treatment. Until recently, almost all the work done to study this limitation has been restricted to tumor cells. Tavora et al. have identified a novel molecular mechanism by which endothelial cells regulate chemosensitivity. The authors established that specific targeting of focal adhesion kinase (FAK, also known as PTK2) in endothelial cells is sufficient to induce tumor cell sensitization to DNA-damaging therapies and thus inhibit tumor growth in mice. The clinical relevance of this work is supported by our observations that low blood vessel FAK expression is associated with complete remission in human lymphoma. This study shows that deletion of FAK in endothelial cells has no apparent effect on blood vessel function per se, but induces increased apoptosis and decreased proliferation within perivascular tumor cell compartments of mice treated with doxorubicin and radiotherapy. Mechanistically, we demonstrate that endothelial cell FAK is required for DNA damage-induced NF-κB activation in vivo and in vitro, and the production of cytokines from endothelial cells. Moreover, loss of endothelial cell FAK reduces DNA damage-induced cytokine production, thus enhancing chemosensitization of tumor cells to DNA-damaging therapies in vitro and in vivo. Overall, their data identified endothelial cell FAK as a regulator of tumor chemosensitivity. Furthermore, the authors anticipate that this proof-of-principle data will be a starting point for the development of new possible strategies to regulate chemosensitization by targeting endothelial cell FAK specifically.

Nature 2014; 514: 112

Eitan Israeli

Capsule

A long non-coding RNA protects the heart from pathological hypertrophy

The role of long non-coding RNA (lncRNA) in adult hearts is unknown; also unclear is how lncRNA modulates nucleosome remodeling. An estimated 70% of mouse genes undergo antisense transcription, including myosin heavy chain 7 (Myh7), which encodes molecular motor proteins for heart contraction. Han and group identified a cluster of lncRNA transcripts from Myh7 loci and demonstrated a new lncRNA-chromatin mechanism for heart failure. In mice, these transcripts, which they named myosin heavy chain-associated RNA transcripts (Myheart, or Mhrt), are cardiac-specific and abundant in adult hearts. Pathological stress activates the Brg1-Hdac-Parp chromatin repressor complex to inhibit Mhrt transcription in the heart. Such stress-induced Mhrt repression is essential for cardiomyopathy to develop: restoring Mhrt to the pre-stress level protects the heart from hypertrophy and failure. Mhrt antagonizes the function of Brg1, a chromatin-remodeling factor that is activated by stress to trigger aberrant gene expression and cardiac myopathy. Mhrt prevents Brg1 from recognizing its genomic DNA targets, thus inhibiting chromatin targeting and gene regulation by Brg1. It does so by binding to the helicase domain of Brg1, a domain that is crucial for tethering Brg1 to chromatinized DNA targets. Brg1 helicase has dual nucleic-acid-binding specificities: it is capable of binding lncRNA (Mhrt) and chromatinized – but not naked – DNA. This dual-binding feature of helicase enables a competitive inhibition mechanism by which Mhrt sequesters Brg1 from its genomic DNA targets to prevent chromatin remodeling. A Mhrt-Brg1 feedback circuit is thus crucial for heart function. Human MHRT also originates from MYH7 loci and is repressed in various types of myopathic hearts, suggesting a conserved lncRNA mechanism in human cardiomyopathy. These studies identified a cardioprotective lncRNA, defined a new targeting mechanism for ATP-dependent chromatin-remodeling factors, and established a new paradigm for lncRNA-chromatin interaction.

Nature 2014; 514: 102

Eitan Israeli

Capsule

Animal behavior follows dopamine rewards

In auditory fear conditioning, mice learn to associate auditory cues, such as a tone, with mild footshocks. Forming associations like this, then remembering them long-term (called fear memory consolidation), is an important strategy for navigating one's environment. To understand the molecular basis of fear memory consolidation, Dias et al. investigated the contribution of microRNAs, small bits of RNA that modulate gene expression. They discovered an important role for the microRNA-34a, which targeted components of a particular signaling pathway (the so-called Notch pathway) that is normally involved in development. MicroRNA-34a caused a transient decrease in Notch-dependent signaling in the amygdala, which was important for fear memory consolidation.

Neuron 2014; 83: 906

Eitan Israeli

Capsule

The G protein α subunit Gαs is a tumor suppressor in Sonic hedgehog-driven medulloblastoma

Medulloblastoma, the most common malignant childhood brain tumor, exhibits distinct molecular subtypes and cellular origins. Genetic alterations driving medulloblastoma initiation and progression remain poorly understood. He et al. identified GNAS, encoding the G protein Gαs, as a potent tumor suppressor gene that, when expressed at low levels, defines a subset of aggressive Sonic hedgehog (SHH)-driven human medulloblastomas. Ablation of the single *Gnas* gene in anatomically distinct progenitors in mice is sufficient to induce Shh-associated medulloblastomas, which recapitulate their human counterparts. Gαs is highly enriched at the primary cilium of granule neuron precursors and suppresses Shh signaling by regulating both the cAMP-dependent pathway and ciliary trafficking of Hedgehog pathway components. Elevation in levels of a Gαs effector, cAMP, effectively inhibits tumor cell proliferation and progression in *Gnas*-ablated mice. Thus, these gain- and loss-of-function studies identify a previously unrecognized tumor suppressor function for Gαs that can be found consistently across Shh-group medulloblastomas of disparate cellular and anatomical origins, highlighting G protein modulation as a potential therapeutic avenue.

Nature Med 2014; 20: 1035

Eitan Israeli

Capsule

Reversion of advanced Ebola virus disease in non-human primates with ZMapp

Without an approved vaccine or treatments, Ebola outbreak management has been limited to palliative care and barrier methods to prevent transmission. These approaches, however, have yet to end the 2014 outbreak of Ebola after its prolonged presence in West Africa. Qiu et al. show that a combination of monoclonal antibodies (ZMapp), optimized from two previous antibody cocktails, is able to rescue 100% of rhesus macaques when treatment is initiated up to 5 days post-challenge. High fever, viremia and abnormalities in blood count and blood chemistry were evident in many animals before ZMapp intervention. Advanced disease, as indicated by elevated liver enzymes, mucosal hemorrhages and generalized petechia could be reversed, leading to full recovery. ELISA and neutralizing antibody assays indicate that ZMapp is cross-reactive with the Guinean variant of Ebola. ZMapp exceeds the efficacy of any other therapeutics described so far, and results warrant further development of this cocktail for clinical use.

Nature 2014; 514: 47

Eitan Israeli

Capsule

Bring out your dead — hungry receptors await

Every day billions of cells die within the body. Specialized cells called phagocytes patrol the blood and act as cellular garbage collectors, clearing dead cells to prevent tissue damage and inflammation. Phagocytes recognize dead cells because they express molecular "eat me" signals on their surfaces. Zagórska and group examined how mouse phagocytes use different cellular protein receptors, called TAMs, during this process. The TAM receptors Mer and Axl recognize the "eat me" signals on the surface of dead cells. Mer kept the peace by removing the dead cells that accumulate during normal wear and tear. In contrast, during inflammation, Axl protein expression increased and it took over the removal process from Mer.

Nat Immunol 2014; 10.1038/ni.2986

Eitan Israeli

Capsule

DNA damage induced differentiation of leukemic cells as an anti-cancer barrier

Self-renewal is the hallmark feature both of normal stem cells and cancer stem cells. Since the regenerative capacity of normal hematopoietic stem cells is limited by the accumulation of reactive oxygen species and DNA double-strand breaks, scientists speculated that DNA damage might also constrain leukemic self-renewal and malignant hematopoiesis, and here Santos et al. show that the histone methyl-transferase MLL4, a suppressor of B cell lymphoma, is required for stem cell activity and an aggressive form of acute myeloid leukemia harboring the MLL-AF9 oncogene. Deletion of MLL4 enhances myelopoiesis and myeloid differentiation of leukemic blasts, which protects mice from death related to acute myeloid leukemia. MLL4 exerts its function by regulating transcriptional programs associated with the antioxidant response. Addition of reactive oxygen species scavengers or ectopic expression of FOXO3 protects MLL4$^{-/-}$ MLL-AF9 cells from DNA damage and inhibits myeloid maturation. Similar to MLL4 deficiency, loss of *ATM* or *BRCA1* sensitizes transformed cells to differentiation, suggesting that myeloid differentiation is promoted by loss of genome integrity. Indeed, the authors show that restriction enzyme-induced double-strand breaks are sufficient to induce differentiation of MLL-AF9 blasts, which requires cyclin-dependent kinase inhibitor p21Cip1 (Cdkn1a) activity. In summary, they uncovered an unexpected tumor-promoting role of genome guardians in enforcing the oncogene-induced differentiation blockade in acute myeloid leukemia.

Nature 2014; 514: 107

Eitan Israeli

MMWR Early Release on the Ebola outbreak

Ebola Virus Disease Outbreak – West Africa, September 2014
Updated data on the Ebola virus disease outbreak in West Africa indicate that, as of September 23, a total of 6574 cases had been reported from five West African countries (Guinea, Liberia, Nigeria, Senegal, and Sierra Leone). The highest reported case counts were from Liberia (3458 cases), Sierra Leone (2021) and Guinea (1074).

Incident Management System Ebola Epidemiology Team, CDC; Ministries of Health of Guinea, Sierra Leone, Liberia, Nigeria, and Senegal; Viral Special Pathogens Branch, National Center for Emerging and Zoonotic Infectious Diseases, CDC.

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Ebola Virus Disease Outbreak – Nigeria, July-September 2014
On July 20, an acutely ill traveler from Liberia arrived at the international airport in Lagos, Nigeria, and was confirmed to have Ebola virus disease after being admitted to a private hospital. The Federal Ministry of Health, with the Lagos State government and international partners, activated an Ebola Incident Management Center as a precursor to the current Emergency Operations Center to rapidly respond to this outbreak. The index patient died on July 25; as of September 24, there were 19 laboratory-confirmed Ebola cases and one probable case in two states, with 894 contacts identified and followed during the response.

Shuaib et al. *MMWR* 2014;63(Early Release):1-6

Importation and Containment of Ebola Virus Disease – Senegal, August-September 2014
On 29 August 2014, Senegal confirmed its first case of Ebola virus disease in a Guinean man, aged 21 years, who had traveled from Guinea to Dakar, Senegal, in mid-August to visit family. Senegalese medical and public health personnel were alerted about this patient after public health staff in Guinea contacted his family in Senegal on August 27. This report describes the investigation and containment measures that followed.

Mirkovic et al. *MMWR* 2014;63 (Early Release):1-2

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