Capsule

Metabolic reprogramming induces resistance to anti-NOTCH1 therapies in T cell acute lymphoblastic leukemia

Activating mutations in *NOTCH1* are common in T cell acute lymphoblastic leukemia (T-ALL). Herranz et al. identified glutaminolysis as a critical pathway for leukemia cell growth downstream of NOTCH1 and a key determinant of the response to anti-NOTCH1 therapies in vivo. Mechanistically, inhibition of NOTCH1 signaling in T-ALL induces a metabolic shut-down, with prominent inhibition of glutaminolysis and triggers autophagy as a salvage pathway supporting leukemia cell metabolism. Consequently, inhibition of glutaminolysis and inhibition of autophagy strongly and synergistically enhance the anti-leukemic effects of anti-NOTCH1 therapy in mice harboring T-ALL. Moreover, they demonstrate that *Pten* loss upregulates glycolysis and consequently rescues leukemic cell metabolism, thereby abrogating the anti-leukemic effects of NOTCH1 inhibition. Overall, these results identify glutaminolysis as a major node in cancer metabolism controlled by NOTCH1 and as a therapeutic target for the treatment of T-ALL.

Nature Med 2015; 21: 1182

Eitan Israeli

Capsule

Stable inhibitory activity of regulatory T cells requires the transcription factor Helios

The maintenance of immune homeostasis requires regulatory T cells (T_{regs}). Given their intrinsic self-reactivity, T_{regs} must stably maintain a suppressive phenotype to avoid autoimmunity. Kim et al. report that impaired expression of the transcription factor (TF) Helios by FoxP3$^+$ CD4 and Qa-1-restricted CD8 T_{regs} results in defective regulatory activity and autoimmunity in mice. Helios-deficient T_{regs} develop an unstable phenotype during inflammatory responses characterized by reduced FoxP3 expression and increased effector cytokine expression secondary to diminished activation of the STAT5 pathway. CD8 T_{regs} also require Helios-dependent STAT5 activation for survival and to prevent terminal T cell differentiation. The definition of Helios as a key transcription factor that stabilizes T_{regs} in the face of inflammatory responses provides a genetic explanation for a core property of T_{regs}.

Science 2015; 350: 334

Eitan Israeli

Capsule

Endogenous antigen processing drives the primary CD4+ T cell response to influenza

By convention, CD4+ T lymphocytes recognize foreign and self-peptides derived from internalized antigens in combination with major histocompatibility complex class II molecules. Alternative pathways of epitope production have been identified, but their contributions to host defense have not been established. Miller et al. show in a mouse infection model that the CD4+ T cell response to influenza, critical for durable protection from the virus, is driven principally by unconventional processing of antigen synthesized within the infected antigen-presenting cell, not by classical processing of endocytosed virions or material from infected cells. Investigation of the cellular components involved, including the H2-M molecular chaperone, the proteasome and interferon gamma-inducible lysosomal thiol reductase revealed considerable heterogeneity in the generation of individual epitopes, an arrangement that ensures peptide diversity and broad CD4+ T cell engagement. These results could fundamentally revise strategies for rational vaccine design and may lead to key insights into the induction of autoimmune and anti-tumor responses.

Nature Med 2015; 21: 1216

Eitan Israeli

Capsule

Anticoagulant "morfs" into pneumonia therapy

Pneumonia can cause lung cell death, yet the mechanisms by which infection reduces cell viability are unclear. Zou et al. found that a poorly described protein, Morf4l1, triggers cell death in mice with pneumonia. The half-life of Morf4l1 – normally a short-lived protein – was increased in the context of pneumonia. The anticoagulant drug Argatroban blocked half-life extension as well as the injurious actions of Morf4l1, thus prolonging the survival of mice with experimental pneumonia.

Sci Transl Med 2015; 7: 311ra171

Eitan Israeli

Capsule

A close-up view of retrovirus spreading

Viral infections typically begin with a small number of viral particles gaining access to the host at a specific tissue site. But how do viruses that cause systemic infections, such as HIV, spread more widely? Sewald et al. visualized how the retroviruses murine leukemia virus (MLV) and HIV spread within lymph nodes in mice. Specific macrophages that line the lymph-draining sinuses in lymph nodes first captured the virus using the carbohydrate-binding protein CD169. These macrophages subsequently transferred virus to the B1 subclass of B lymphocytes, which migrated further into the lymph node, disseminating the virus more widely.

Science 2015; 350: 563

Eitan Israeli

Capsule

Emergency department visits related to dietary supplements

Dietary supplements, such as herbal or complementary nutritional products and micronutrients (vitamins and minerals), are commonly used in the United States, yet national data on adverse effects are limited. Geller et al. used nationally representative surveillance data from 63 emergency departments obtained from 2004 through 2013 to describe visits to U.S. emergency departments because of adverse events related to dietary supplements. Based on 3667 cases, they estimated that 23,005 emergency department visits per year were attributed to adverse events related to dietary supplements. These visits resulted in an estimated 2154 hospitalizations annually. Such visits frequently involved young adults between the ages of 20 and 34 years (28.0% of visits) and unsupervised children (21.2% of visits). After the exclusion of unsupervised ingestion of dietary supplements by children, 65.9% of emergency department visits for single-supplement-related adverse events involved herbal or complementary nutritional products; 31.8% involved micronutrients. Herbal or complementary nutritional products for weight loss (25.5%) and increased energy (10.0%) were commonly implicated. Weight loss or energy products caused 71.8 of supplement-related adverse events involving palpitations, chest pain, or tachycardia, and 58.0% involved persons aged 20–34 years. Among adults 65 years of age or older, choking or pill-induced dysphagia or globus caused 37.6% of all emergency department visits for supplement-related adverse events; micronutrients were implicated in 83.1% of these visits.

N Engl J Med 2015; 373: 1531

Eitan Israeli

Capsule

Skin cell-derived neurons act their age

The main risk factor for neurodegenerative disorders is aging. To better understand cellular aging, scientists seek to model it using human neurons in tissue culture. Given the difficulty of obtaining neurons directly from human donors, scientists can derive them from either induced pluripotent stem cells (iPSCs) or by directly inducing them from another cell type. Mertens et al. compared the gene signatures of neurons obtained by these two methods and found that although the iPSC-derived neurons erased their signatures of aging, the induced neurons retained their original aged characteristics. Thus, directly converted induced neurons could provide a key resource for modeling neuronal aging.

Cell Stem Cell 2015; 10.1016/j.stem.2015.09.001

Eitan Israeli

Capsule

A trial of calcium and vitamin D for the prevention of colorectal adenomas

Epidemiologic and preclinical data suggest that higher intake and serum levels of vitamin D and higher intake of calcium reduce the risk of colorectal neoplasia. To further study the chemopreventive potential of these nutrients, Baron et al. conducted a randomized, double-blind, placebo-controlled trial of supplementation with vitamin D, calcium, or both for the prevention of colorectal adenomas. Participants were patients with recently diagnosed adenomas and no known colorectal polyps remaining after complete colonoscopy. They randomly assigned 2259 participants to receive daily vitamin D3 (1000 IU), calcium as carbonate (1200 mg), both, or neither in a partial 2×2 factorial design. Women could elect to receive calcium plus random assignment to vitamin D or placebo. Follow-up colonoscopy was anticipated to be performed 3 or 5 years after the baseline examinations, according to the endoscopist's recommendation. The primary end-point was adenomas diagnosed in the interval from randomization through the anticipated surveillance colonoscopy. Participants who were randomly assigned to receive vitamin D had a mean net increase in serum 25-hydroxyvitamin D levels of 7.83 ng/ml, relative to participants given placebo. Overall, 43% of participants had one or more adenomas diagnosed during follow-up. The adjusted risk ratios for recurrent adenomas were 0.99 with vitamin D versus no vitamin D, 0.95 with calcium versus no calcium, and with both agents versus neither agent. The findings for advanced adenomas were similar. There were few serious adverse events. The authors conclude that daily supplementation with vitamin D3 (1000 IU), calcium (1200 mg), or both, after removal of colorectal adenomas did not significantly reduce the risk of recurrent colorectal adenomas over a period of 3 to 5 years.

N Eng J Med 2015; 373: 1519

Eitan Israeli

Capsule

Selective small-molecule inhibition of an RNA structural element

Riboswitches are non-coding RNA structures located in messenger RNAs that bind endogenous ligands, such as a specific metabolite or ion, to regulate gene expression. As such, riboswitches serve as a novel, yet largely unexploited, class of emerging drug targets. Demonstrating this potential, however, has proven difficult and is restricted to structurally similar antimetabolites and semi-synthetic analogues of their cognate ligand, thus greatly restricting the chemical space and selectivity sought for such inhibitors. Howe et al. report the discovery and characterization of ribocil, a highly selective chemical modulator of bacterial riboflavin riboswitches, which was identified in a phenotypic screen and acts as a structurally distinct synthetic mimic of the natural ligand, flavin mononucleotide, to repress riboswitch-mediated *ribB* gene expression and inhibit bacterial cell growth. These findings indicate that non-coding RNA structural elements may be more broadly targeted by synthetic small molecules than previously expected.

Nature 2015; 526: 672

Eitan Israeli

Capsule

A naturally occurring variant of the human prion protein completely prevents prion disease

Mammalian prions, transmissible agents causing lethal neurodegenerative diseases, are composed of assemblies of misfolded cellular prion protein (PrP). A novel PrP variant, G127V, was under positive evolutionary selection during the epidemic of kuru – an acquired prion disease epidemic of the Fore population in Papua New Guinea – and appeared to provide strong protection against disease in the heterozygous state. Asante and co-workers investigated the protective role of this variant and its interaction with the common, worldwide M129V PrP polymorphism. V127 was seen exclusively on a M129 *PRNP* allele. We demonstrate that transgenic mice expressing both variant and wild-type human PrP are completely resistant to both kuru and classical Creutzfeldt-Jakob disease (CJD) prions (which are closely similar) but can be infected with variant CJD prions, a human prion strain resulting from exposure to bovine spongiform encephalopathy prions to which the Fore were not exposed. Notably, mice expressing only PrP V127 were completely resistant to all prion strains, demonstrating a different molecular mechanism to M129V, which provides its relative protection against classical CJD and kuru in the heterozygous state. Indeed, this single amino acid substitution (GV) at a residue invariant in vertebrate evolution is as protective as deletion of the protein. Further study in transgenic mice expressing different ratios of variant and wild-type PrP indicates that not only is PrP V127 completely refractory to prion conversion but acts as a potent dose-dependent inhibitor of wild-type prion propagation.

Nature 2015; 522: 478

Eitan Israeli

Capsule

Non-coding recurrent mutations in chronic lymphocytic leukemia

Chronic lymphocytic leukemia (CLL) is a frequent disease in which the genetic alterations determining the clinicobiological behavior are not fully understood. Puente and fellow researchers describe a comprehensive evaluation of the genomic landscape of 452 CLL cases and 54 patients with monoclonal B lymphocytosis, a precursor disorder. The authors extend the number of CLL driver alterations, including changes in *ZNF292*, *ZMYM3*, *ARID1A* and *PTPN11*. They also identify novel recurrent mutations in non-coding regions, including the 3' region of NOTCH1, which cause aberrant splicing events, increase NOTCH1 activity and result in a more aggressive disease. In addition, mutations in an enhancer located on chromosome 9p13 result in reduced expression of the B cell-specific transcription factor PAX5. The accumulative number of driver alterations (0 to ≥ 4) discriminated between patients with differences in clinical behavior. This study provides an integrated portrait of the CLL genomic landscape, identifies new recurrent driver mutations of the disease, and suggests clinical interventions that may improve the management of this neoplasia.

Nature 2015; 526: 519

Eitan Israeli

Capsule

Parental olfactory experience influences behavior and neural structure in subsequent generations

Using olfactory molecular specificity, Dias et al. examined the inheritance of parental traumatic exposure, a phenomenon that has been frequently observed but not understood. They subjected F0 mice to odor fear conditioning before conception and found that subsequently conceived F1 and F2 generations had an increased behavioral sensitivity to the F0-conditioned odor, but not to other odors. When an odor (acetophenone) that activates a known odorant receptor (*Olfr151*) was used to condition F0 mice, the behavioral sensitivity of the F1 and F2 generations to acetophenone was complemented by an enhanced neuroanatomical representation of the Olfr151 pathway. Bisulfite sequencing of sperm DNA from conditioned F0 males and F1 naive offspring revealed CpG hypomethylation in the *Olfr151* gene. In addition, in vitro fertilization, F2 inheritance and cross-fostering revealed that these transgenerational effects are inherited via parental gametes. These findings provide a framework for addressing how environmental information may be inherited transgenerationally at behavioral, neuroanatomical and epigenetic levels.

Nature Neurosci 2014; 17: 89

Eitan Israeli

Capsule

Stopping aneurysms before they start

The smooth muscle cells in aortas are connected to the extracellular matrix. Mutations in components of the extracellular matrix, such as fibulin-4, can lead to the enlargement of the aortic lumen, otherwise known as an aneurysm. Yamashiro and coauthors found that mice lacking fibulin-4 in smooth muscle cells had disrupted connections with the extracellular matrix. The mice also had abnormal increases in mechanosensitive proteins and enhanced activity of an actin cytoskeleton-remodeling enzyme called cofilin. Inhibiting the activity of cofilin or its upstream activators could therefore prevent the development of aneurysms.

Sci Signal 2016; 8, ra105

Eitan Israeli

Capsule

RIPK1 and NF-κB signaling in dying cells determines cross-priming of CD8+T cells

Dying cells initiate adaptive immunity by providing both antigens and inflammatory stimuli for dendritic cells, which in turn activate CD8+ T cells through a process called antigen cross-priming. To define how different forms of programmed cell death influence immunity, Yatim et al. established models of necroptosis and apoptosis, in which dying cells are generated by receptor-interacting protein kinase-3 and caspase-8 dimerization, respectively. The authors found that the release of inflammatory mediators, such as damage-associated molecular patterns, by dying cells was not sufficient for CD8+ T cell cross-priming. Instead, robust cross-priming required receptor-interacting protein kinase-1 (RIPK1) signaling and nuclear factor κB (NF-κB)-induced transcription within dying cells. Decoupling NF-κB signaling from necroptosis or inflammatory apoptosis reduced priming efficiency and tumor immunity. These results reveal that coordinated inflammatory and cell death signaling pathways within dying cells orchestrate adaptive immunity.

Science 2015; 350: 328

Eitan Israeli

Capsule

T cell receptor reversed polarity recognition of a self-antigen major histocompatibility complex

Central to adaptive immunity is the interaction between the αβ T cell receptor (TCR) and peptide presented by the major histocompatibility complex (MHC) molecule. Presumably reflecting TCR-MHC bias and T cell signaling constraints, the TCR universally adopts a canonical polarity atop the MHC. Beringer et al. report the structures of two TCRs, derived from human induced T regulatory (iTreg) cells, complexed to an MHC class II molecule presenting a proinsulin-derived peptide. The ternary complexes revealed a 180° polarity reversal compared to all other TCR-peptide-MHC complex structures. Namely, the iTreg TCR α-chain and β-chain are overlaid with the α-chain and β-chain of MHC class II, respectively. Nevertheless, this TCR interaction elicited a peptide-reactive, MHC-restricted T cell signal. Thus TCRs are not 'hardwired' to interact with MHC molecules in a stereotypic manner to elicit a T cell signal, a finding that fundamentally challenges our understanding of TCR recognition.

Nature Immunol 2015; 16: 1153

Eitan Israeli

Capsule

The benefits of *Escherichia coli*

Infection and intestinal damage can trigger severe muscle wasting and loss of fat in mice. How this happens is poorly understood. Palaferri Schieber et al. discovered a protective *Escherichia coli* strain in their mouse colony. Mice intestinally colonized with the *E. coli* and infected with the food-poisoning bug *Salmonella* or with the lung pathogen *Burkholderia* did not waste away. Without the *E. coli*, similarly infected mice became fatally ill. The protective *E. coli* stimulated an innate immune mechanism that ensured that muscle-signaling pathways were not damaged by infection. Thus, the friendly *E. coli* allowed its host to tolerate and survive the pathogens.

Science 2015; 350: 558

Eitan Israeli

Capsule

Inflammasomes take the wheel of unfortune...

Cells require microbial ligand binding to sense pathogens. Binding to the family of NOD-like receptors triggers the assembly of large protein signaling complexes called inflammasomes, leading infected cells to die and produce inflammatory mediators. Hu et al. and Zhang et al. used cryo-electron microscopy to uncover the structural and biochemical basis of two such receptors: NAIP2, which directly binds microbial ligands, and NLRC4, a protein functioning directly downstream. A self-propagating activation mechanism of downstream inflammasome signaling starts with one molecule of NAIP4 directly binding its microbial ligand. NAIP4 then catalyzes the activation of 10 to 12 NLRC4 molecules to form a wheel-like structure.

Science 2015; 350: 399, 404

Eitan Israeli

Capsule

The Ro60 autoantigen binds endogenous retroelements and regulates inflammatory gene expression

Autoantibodies target the RNA binding protein Ro60 in systemic lupus erythematosus (SLE) and Sjögren's syndrome. However, it is unclear whether Ro60 and its associated RNAs contribute to disease pathogenesis. Huang et al. catalogued the Ro60-associated RNAs in human cell lines and found that among other RNAs, Ro60 bound an RNA motif derived from endogenous Alu retroelements. Alu transcripts were induced by type I interferon and stimulated pro-inflammatory cytokine secretion by human peripheral blood cells. Ro60 deletion resulted in enhanced expression of Alu RNAs and interferon-regulated genes. Anti-Ro60-positive SLE immune complexes contained Alu RNAs, and Alu transcripts were up-regulated in SLE whole blood samples relative to controls. These findings establish a link among the lupus autoantigen Ro60, Alu retroelements, and type I interferon. Short interspersed nuclear elements (SINEs) are short DNA sequences (‹ 500 bases) that represent reverse-transcribed RNA molecules originally transcribed by RNA polymerase III into tRNA, 5S ribosomal RNA, and other small nuclear RNAs. The mechanism of retrotransposition of these elements is more complicated than LINEs, and less dependent solely on the actual elements that they encode. SINEs do not encode a functional reverse transcriptase protein and rely on other mobile elements for transposition. In some cases they may have their own endonuclease that will allow them to cleave their way onto genome, but the majority of SINEs integrate at chromosomal breaks by using random DNA breaks to prime reverse transcriptase. The most common SINEs in primates are called Alu sequences. Alu elements are approximately 350 base pairs long, do not contain any coding sequences, and can be recognized by the restriction enzyme AluI (hence the name).

Science 2015; 350: 455

Eitan Israeli

Capsule

Excess TGFβ mediates muscle weakness associated with bone metastases in mice

Cancer-associated muscle weakness is a poorly understood phenomenon, and there is no effective treatment. Waning et al. found that seven different mouse models of human osteolytic bone metastases – representing breast, lung and prostate cancers, as well as multiple myeloma – exhibited impaired muscle function, implicating a role for the tumor-bone microenvironment in cancer-associated muscle weakness. The authors found that transforming growth factor-beta (TGFβ), released from the bone surface as a result of metastasis-induced bone destruction, upregulated NADPH oxidase 4 (Nox4), resulting in elevated oxidization of skeletal muscle proteins, including the ryanodine receptor and calcium (Ca^{2+}) release channel (RyR1). The oxidized RyR1 channels leaked Ca^{2+}, resulting in lower intracellular signaling, which is required for proper muscle contraction. They found that inhibiting RyR1 leakage, TGFβ signaling, TGFβ release from bone or Nox4 activity improved muscle function in mice with MDA-MB-231 bone metastases. Humans with breast or lung cancer-associated bone metastases also had oxidized skeletal muscle RyR1 that is not seen in normal muscle. Similarly, skeletal muscle weakness, increased Nox4 binding to RyR1 and oxidation of RyR1 were present in a mouse model of Camurati-Engelmann disease, a non-malignant metabolic bone disorder associated with increased TGFβ activity. Thus, pathological TGFβ release from bone contributes to muscle weakness by decreasing Ca^{2+}-induced muscle force production.

Nature Med 2015; 21; 1262

Eitan Israeli

Capsule

Everolimus-eluting bioresorbable scaffolds for coronary artery disease

In patients with coronary artery disease who receive metallic drug-eluting coronary stents, adverse events such as late target lesion failure may be related in part to the persistent presence of the metallic stent frame in the coronary vessel wall. In an attempt to improve long-term outcomes Ellis et al. developed bioresorbable vascular scaffolds. In a large multicenter randomized trial, 2008 patients with stable or unstable angina were randomly assigned in a 2:1 ratio to receive an everolimus-eluting bioresorbable vascular (Absorb) scaffold (1322 patients) or an everolimus-eluting cobalt-chromium (Xience) stent (686 patients). The primary endpoint, which was tested for both non-inferiority (margin 4.5 percentage points for the risk difference) and superiority, was target lesion failure (cardiac death, target vessel myocardial infarction, or ischemia-driven target lesion revascularization) at 1 year. Target lesion failure at 1 year occurred in 7.8% of patients in the Absorb group and in 6.1% of patients in the Xience group (difference 1.7 percentage points, 95% confidence interval 0.5–3.9, $P = 0.007$ for non-inferiority and $P = 0.16$ for superiority). There was no significant difference between the Absorb group and the Xience group in rates of cardiac death (0.6% and 0.1% respectively, $P = 0.29$), target vessel myocardial infarction (6.0% and 4.6% respectively, $P = 0.18$), or ischemia-driven target lesion revascularization (3.0% and 2.5% respectively, $P = 0.50$). Device thrombosis within 1 year occurred in 1.5% of patients in the Absorb group and in 0.7% of patients in the Xience group ($P = 0.13$).

N Engl J Med 2015; 373: 1905

Eitan Israeli

Capsule

A better vaccine against RSV

Respiratory syncytial virus (RSV) infection can cause a severe respiratory illness in young children. Researchers are working to fashion a live attenuated vaccine, which would mimic the natural course of infection, but blocking viral replication also stems the immune response. Now Karron et al. report on a version of RSV that induced a protective immune response with decreased viral shedding in humans. Children who received the vaccine produced antibodies to RSV without symptoms in the subsequent RSV season.

Sci Transl Med 2015; 7: 312ra175

Eitan Israeli

Capsule

Genome-wide identification of microRNAs regulating cholesterol and triglyceride homeostasis

Genome-wide association studies (GWASs) have linked genes to various pathological traits. However, the potential contribution of regulatory non-coding RNAs, such as microRNAs (miRNAs), to a genetic predisposition to pathological conditions has remained unclear. Wagschal et al. leveraged GWAS meta-analysis data from › 188,000 individuals to identify 69 miRNAs in physical proximity to single-nucleotide polymorphisms (SNPs) associated with abnormal levels of circulating lipids. Several of these miRNAs (miR-128-1, miR-148a, miR-130b, miR-301b) control the expression of key proteins involved in cholesterol-lipoprotein trafficking, such as the low density lipoprotein (LDL) receptor (LDLR) and the ATP-binding cassette A1 (ABCA1) cholesterol transporter. Consistent with human liver expression data and genetic links to abnormal blood lipid levels, overexpression and antisense targeting of miR-128-1 or miR-148a in high fat diet-fed C57BL/6J and *Apoe*-null mice resulted in altered hepatic expression of proteins involved in lipid trafficking and metabolism, and in modulated levels of circulating lipoprotein-cholesterol and triglycerides. Taken together, these findings support the notion that altered expression of miRNAs may contribute to abnormal blood lipid levels, predisposing individuals to human cardiometabolic disorders.

Nature Med 2015; 21: 1290

Eitan Israeli

Capsule

Pharmacological chaperone for α-crystallin partially restores transparency in cataract models

Cataracts reduce vision in 50% of individuals over 70 years of age and are a common form of blindness worldwide. Cataracts are caused when damage to the major lens crystallin proteins causes their misfolding and aggregation into insoluble amyloids. Using a thermal stability assay, Makley et al. identified a class of molecules that bind α-crystallins (cryAA and cryAB) and reversed their aggregation in vitro. The most promising compound improved lens transparency in the R49C cryAA and R120G cryAB mouse models of hereditary cataract. It also partially restored protein solubility in the lenses of aged mice in vivo and in human lenses ex vivo. These findings suggest an approach to treating cataracts by stabilizing α-crystallins.

Science 2015; 350: 674

Eitan Israeli

Capsule

The genetic evolution of melanoma from precursor lesions

The pathogenic mutations in melanoma have been largely catalogued; however, the order of their occurrence is not known. Shain and co-authors sequenced 293 cancer-relevant genes in 150 areas of 37 primary melanomas and their adjacent precursor lesions. The histopathologic spectrum of these areas included unequivocally benign lesions, intermediate lesions, and intraepidermal or invasive melanomas. Precursor lesions were initiated by mutations of genes known to activate the mitogen-activated protein kinase pathway. Unequivocally benign lesions harbored *BRAF* V600E mutations exclusively, whereas those categorized as intermediate were enriched for *NRAS* mutations and additional driver mutations. A total of 77% of areas of intermediate lesions and melanomas in situ harbored *TERT*promoter mutations, a finding that indicates that these mutations are selected at an unexpectedly early stage of the neoplastic progression. Biallelic inactivation of *CDKN2A* emerged exclusively in invasive melanomas. *PTEN* and *TP53* mutations were found only in advanced primary melanomas. The point-mutation burden increased from benign through intermediate lesions to melanoma, with a strong signature of the effects of ultraviolet radiation detectable at all evolutionary stages. Copy-number alterations became prevalent only in invasive melanomas. Tumor heterogeneity became apparent in the form of genetically distinct subpopulations as melanomas progressed.

N Engl J Med 2015; 373: 1926

Eitan Israeli

Capsule

Oxidative stress inhibits distant metastasis by human melanoma cells

Solid cancer cells commonly enter the blood and disseminate systemically, but are highly inefficient at forming distant metastases for poorly understood reasons. Piskounova et al. studied human melanomas that differed in their metastasis histories in patients and in their capacity to metastasize in NOD-SCID-*Il2rg*$^{-/-}$ (NSG) mice. The authors show that melanomas had high frequencies of cells that formed subcutaneous tumors, but much lower percentages of cells that formed tumors after intravenous or intrasplenic transplantation, particularly among inefficiently metastasizing melanomas. Melanoma cells in the blood and visceral organs experienced oxidative stress not observed in established subcutaneous tumors. Successfully metastasizing melanomas underwent reversible metabolic changes during metastasis that increased their capacity to withstand oxidative stress, including increased dependence on NADPH-generating enzymes in the folate pathway. Antioxidants promoted distant metastasis in NSG mice. Folate pathway inhibition using low dose methotrexate, ALDH1L2 knockdown, or MTHFD1 knockdown inhibited distant metastasis without significantly affecting the growth of subcutaneous tumors in the same mice. Oxidative stress thus limits distant metastasis by melanoma cells in vivo.

Nature 2015; 527: 186

Eitan Israeli

Capsule

The perils of anitoxidants in metastatic cancer

In today's health-conscious world, it is not unusual for a food item to achieve "superfood" status simply because it contains high levels of "cancer-fighting" antioxidants. This view may be simplistic, because cancer develops and progresses in multiple steps that potentially respond differently to antioxidants. Two new studies converge on the theme that, in the setting of metastasis, antioxidants help the cancer cell and hurt the host. Piskounova and fellow-researchers show that melanoma cells which successfully metastasized in mice were those that had undergone certain metabolic changes which allowed them to withstand oxidative stress. In the other study Le Gal et al. show that the administration of antioxidants to mice that were predisposed to melanoma had no effect on primary tumor development but enhanced lymph node metastases.

Nature 2015; 10.1038/*nature*15726, *Sci Transl Med* 2015; 7: 308re8

Eitan Israeli

Capsule

High throughput screening using patient-derived tumor xenografts to predict clinical trial drug response

Profiling candidate therapeutics with limited cancer models during preclinical development hinders predictions of clinical efficacy and identifying factors that underlie heterogeneous patient responses for patient-selection strategies. Gao et al. established ~1000 patient-derived tumor xenograft models (PDXs) with a diverse set of driver mutations. With these PDXs, the authors performed in vivo compound screens using a 1 x 1 x 1 experimental design (PDX clinical trial or PCT) to assess the population responses to 62 treatments across six indications. They demonstrated both the reproducibility and the clinical translatability of this approach by identifying associations between a genotype and drug response, and established mechanisms of resistance. In addition, these results suggest that PCTs may represent a more accurate approach than cell line models for assessing the clinical potential of some therapeutic modalities. The authors propose that this experimental paradigm could potentially improve preclinical evaluation of treatment modalities and enhance our ability to predict clinical trial responses.

Nature Med 2015; 21: 1318

Eitan Israeli

Capsule

Early signs of dementia

There is currently no cure for Alzheimer's disease. One of the reasons could be that interventions start too late, when there is already irreversible damage to the brain. Developing a biomarker that would help to effectively start therapy at very early stages of the disease is thus of high interest. Kunz et al. studied neural correlates of spatial navigation in the entorhinal cortex in control study participants and individuals at risk of developing Alzheimer's. The at-risk group showed a different brain signal many decades before the onset of the disease, and they navigated differently in a virtual environment.

Science 2015; 350: 430

Eitan Israeli

Capsule

Diet shapes host and gut microbe fitness

The human gut microbiota is hugely diverse, with many strain variants having a multiplicity of effects on host metabolism and immunity. To define some of these functions, Wu and team made libraries of mutants of *Bacteroides* species known for their capacity to process otherwise intractable dietary fiber. Germ-free mice colonized with defined gut microbiota communities containing the mutants were fed specific diets containing different ratios of fat and fiber. Genes, strains and species were identified that were associated with specific metabolic pathways. The community responses to dietary shifts were manipulated in an attempt to characterize species for their probiotic or therapeutic potential.

Science 2015; 350: 10.1126/science.aac5992

Eitan Israeli