Capsule

How brains get the full picture

The visual system helps organisms make sense of their world. A network of brain areas called face patches helps monkeys identify other individuals and interpret their behavior. Fisher and Freiwald, wanting to determine whether these regions only interpret face information or if they integrate body information, too, scanned the brains of monkeys that were shown faces, bodies, faces on bodies, or faces on non-body objects. Posterior face patches and adjacent body patches recognized faces and bodies, respectively. However, these networks could integrate face and body information to represent whole monkeys in the anterior face patches. Thus, the brain combines visual information from distinct but related objects to help organisms understand their social world.

Proc Natl Acad Sci USA 2015; 112: 14717

Eitan Israeli

Capsule

Divergent clonal selection dominates medulloblastoma at recurrence

The development of targeted anti-cancer therapies through the study of cancer genomes is intended to increase survival rates and decrease treatment-related toxicity. Morrissy and team treated a transposon-driven, functional genomic mouse model of medulloblastoma with 'humanized' in vivo therapy (micro-neurosurgical tumor resection followed by multi-fractionated, image-guided radiotherapy). Genetic events in recurrent murine medulloblastoma exhibit a very poor overlap with those in matched murine diagnostic samples (< 5%). Whole-genome sequencing of 33 pairs of human diagnostic and post-therapy medulloblastomas demonstrated substantial genetic divergence of the dominant clone after therapy (< 12% diagnostic events were retained at recurrence). In both mice and humans, the dominant clone at recurrence arose through clonal selection of a preexisting minor clone present at diagnosis. Targeted therapy is unlikely to be effective in the absence of the target; therefore, these results offer a simple, proximal, and remediable explanation for the failure of prior clinical trials of targeted therapy.

Nature 2016; 529: 351

Eitan Israeli

Capsule

Rift Valley fever outbreaks in East Africa forecasted with El Niño

Rift Valley Fever (RVF) is mosquito-borne virus that is endemic in parts of Africa. It primarily infects animals like sheep, cattle and goats and can have an economic impact on a community due to the loss of livestock. Last month, several federal health agencies including the NOAA, USDA and the CDC released a report concerning the risk of RVF outbreaks in East Africa due to El Niño. The NOAA says the current El Niño will likely peak during the Northern Hemisphere winter 2015–16 and end up being among the strongest El Niño episodes since 1950. According to the Emerging Health Risk Notification, El Niño and Rift Valley fever (RVF) risk, East Africa, published 3 weeks ago, the several federal agencies developed a RVF outbreak forecasting model that uses satellite-derived data, drawing on the tight coupling between RVF activity and El Niño-driven flooding, said it identified areas at risk for RVF activity because of substantially elevated rainfall in Sudan, South Sudan, Ethiopia, Somalia, Kenya, and Tanzania, noting that assistance is likely needed to minimize RVF impacts in East Africa. In addition to RVF effect on animals, humans can get infected through contact with infected animal blood or organs and through mosquito bites and the bites of blood-sucking flies. The agencies offer the following recommendations concerning preparation in East Africa: animal and human surveillance and health education, animal vaccination programs and vector control.

Posted by Robert Herriman on January 7, 2016
http://outbreaknewstoday.com/rift-valley-fever-outbreaks-in-east-africa-forecasted-with-el-nino-11587/

Eitan Israeli

Capsule

Out-RANKing osteosarcoma

Osteosarcoma, the most common primary bone cancer, can be difficult to treat, especially in patients with metastatic disease. Chen et al. developed genetically engineered mouse models of osteosarcoma and used them to demonstrate that receptor activator of nuclear factor κB ligand (RANKL) signaling contributes to the progression of this disease. Furthermore, denosumab, an antibody against RANKL already used in patients with other bone diseases, inhibited osteosarcoma in mouse models and so is a viable candidate for future testing in human patients.

Sci Transl Med 2015; 7: 317ra197

Eitan Israeli

Capsule

Complementarity and redundancy of IL-22-producing innate lymphoid cells

Intestinal T cells and group 3 innate lymphoid cells (ILC3 cells) control the composition of the microbiota and gut immune responses. Within the gut, ILC3 subsets coexist that either express or lack the natural cytoxicity receptor (NCR) NKp46. Rankin et al. identified the transcriptional signature associated with the transcription factor T-bet-dependent differentiation of NCR– ILC3 cells into NCR+ ILC3 cells. Contrary to the prevailing view, the authors found by conditional deletion of the key ILC3 genes *Stat3*, *Il22*, *Tbx21* and Mcl1 that NCR+ ILC3 cells were redundant for the control of mouse colonic infection with *Citrobacter rodentium* in the presence of T cells. However, NCR+ ILC3 cells were essential for cecal homeostasis. These data show that interplay between intestinal ILC3 cells and adaptive lymphocytes results in robust complementary failsafe mechanisms that ensure gut homeostasis.

Nature Immunol 2016; 17: 179

Eitan Israeli

Capsule

A double-drug approach for chronic pain

Chronic pain is a major reason why people visit a doctor. Unfortunately, the underlying causes of chronic pain are still poorly understood. To gain more insight, Ren et al. studied a mouse model of neuropathic pain. Nerve injury resulted in a rewiring of neuronal circuits in a region of the brain called the nucleus accumbens, which regulates emotions and addictive behavior. The excitability of some neurons increased, but their number of excitatory synapses fell. Nerve injury also led to reduced extracellular dopamine concentrations in the nucleus accumbens. Combined treatment of mice with dopamine receptor antagonists and a non-steroidal anti-inflammatory drug blunted neuropathic pain, suggesting potential new drug combinations for treating chronic pain.

Nat Neurosci 2015; 10.1038/nn.4199

Eitan Israeli

Capsule

Severe malaria infections impair germinal center responses by inhibiting T follicular helper cell differentiation

Naturally acquired immunity to malaria develops only after years of repeated exposure to *Plasmodium* parasites. Despite the key role antibodies play in protection, the cellular processes underlying the slow acquisition of immunity remain unknown. Using mouse models, Ryg-Cornejo and fellow researchers show that severe malaria infection inhibits the establishment of germinal centers (GCs) in the spleen. The authors demonstrated that infection induces high frequencies of T follicular helper (Tfh) cell precursors but results in impaired Tfh cell differentiation. Despite high expression of Bcl-6 and IL-21, precursor Tfh cells induced during infection displayed low levels of PD-1 and CXCR5 and co-expressed Th1-associated molecules such as T-bet and CXCR3. Blockade of the inflammatory cytokines TNF and IFNγ or T-bet deletion restored Tfh cell differentiation and GC responses to infection. Thus, this study demonstrates that the same pro-inflammatory mediators that drive severe malaria pathology have detrimental effects on the induction of protective B cell responses.

http://www.sciencedirect.com/science/journal/aip/22111247

Eitan Israeli

Capsule

KIR haplotypes are associated with late-onset type 1 diabetes in European-American families

Classical human leukocyte antigen (HLA) genes confer the strongest, but not the only, genetic susceptibility to type 1 diabetes. Killer cell immunoglobulin-like receptors (KIR), on natural killer (NK) cells, bind ligands including class I HLA. Traherne et al. examined the presence or absence, with copy number, of *KIR* loci in 1698 individuals, from 339 multiplex type 1 diabetes families, from the Human Biological Data Interchange, previously genotyped for HLA. Combining family data with *KIR* copy number information allowed assignment of haplotypes using identity by descent. This is the first disease study to use KIR copy number typing and unambiguously define haplotypes by gene transmission. *KIR* A1 haplotypes were positively associated with T1D in the subset of patients without the high T1D risk HLA genotype, DR3/DR4 (odds ratio 1.29, $P = 0.0096$). The data point to a role for KIR in type 1 diabetes risk in late-onset patients. In the top quartile (age of onset › 14), *KIR* A2 haplotype was overtransmitted (63.4%, odds ratio 1.73, $P = 0.024$) and *KIR* B haplotypes were undertransmitted (41.1%, odds ratio 0.70, $P = 0.0052$) to patients. The data suggest that inhibitory 'A' haplotypes are predisposing and stimulatory 'B' haplotypes confer protection in both DR3/DR4-negative and late-onset patient groups.

Genes Immunity 2016; 17: 8

Eitan Israeli

Capsule

Zika virus spreads to new areas – the Americas, May 2015 to January 2016

It is already known that Zika virus is a mosquito-borne flavivirus transmitted primarily by *Aedes aegypti* mosquitoes. Most infections are asymptomatic, and symptomatic disease is generally mild. In May 2015, the first local transmission of Zika virus in the region of the Americas was reported in Brazil. Following the spread of Zika virus in Brazil, there has been a marked reported increase in the number of infants born with microcephaly; it is not known how many of these cases are associated with Zika virus infection. By mid-January 2016, local Zika virus transmission had been reported to the Pan American Health Organization from 20 countries or territories in the region of the Americas; spread to other countries in the region is likely. Although local transmission of Zika virus has not been documented in the continental United States, infections have been reported among travelers visiting or returning to the U.S., and these will likely increase. Imported cases might result in local transmission in limited areas of the continental USA. With regard to public health practice, the best way to prevent Zika virus infection is to avoid mosquito bites by avoiding exposure and eliminating mosquito breeding areas. Until more is known, pregnant women should consider postponing travel to any area with ongoing Zika virus transmission. Health care providers should contact their state or local health department about testing patients with symptoms of Zika virus infection and a compatible travel history.

MMWR 2016; 65: 55

Eitan Israeli

Capsule

Zika virus infection in pregnant women in Rio de Janeiro

Zika virus (ZIKV) has been linked to neonatal microcephaly. To characterize the spectrum of ZIKV disease in pregnancy, Patricia Brasil et al. followed patients in Rio de Janeiro to describe clinical manifestations in mothers and repercussions of acute ZIKV infection in fetuses. Of 88 women enrolled from September 2015 through February 2016, 72 (82%) tested positive for ZIKV in blood, urine, or both. The timing of acute ZIKV infection ranged from 5 to 38 weeks of gestation. Predominant clinical features included pruritic descending macular or maculopapular rash, arthralgias, conjunctival injection, and headache; 28% had fever (short-term and low-grade). Women who were positive for ZIKV were more likely than those who were ZIKV-negative to have maculopapular rash (44% vs. 12%, $P = 0.02$), conjunctival involvement (58% vs. 13%, $P = 0.002$), and lymphadenopathy (40% vs. 7%, $P = 0.02$). Fetal ultrasonography was performed in 42 ZIKV-positive women (58%) and in all ZIKV-negative women. Fetal abnormalities were detected by Doppler ultrasonography in 12 of the 42 ZIKV-positive women (29%) and in none of the 16 ZIKV-negative women. Adverse findings included fetal deaths at 36 and 38 weeks of gestation (2 fetuses), in utero growth restriction with or without microcephaly (5 fetuses), ventricular calcifications or other central nervous system (CNS) lesions (7 fetuses), and abnormal amniotic fluid volume or cerebral or umbilical artery flow (7 fetuses). To date, 8 of the 42 women in whom fetal ultrasonography was performed have delivered their babies, and the ultrasonographic findings have been confirmed. The authors conclude that despite mild clinical symptoms, ZIKV infection during pregnancy appears to be associated with grave outcomes, including fetal death, placental insufficiency, fetal growth restriction, and central nervous system injury.

N Engl J Med 201 doiOI: http://dx.doi.org/10.1056/NEJMoa1602412

Eitan Israeli

Capsule

Group 3 innate lymphoid cells continuously require the transcription factor GATA-3 after commitment

The transcription factor GATA-3 is indispensable for the development of all innate lymphoid cells (ILCs) that express the interleukin 7 receptor α-chain (IL-7Rα). However, the function of low GATA-3 expression in committed group 3 ILCs (ILC3 cells) has not been identified. Zhong et al. found that GATA-3 regulated the homeostasis of ILC3 cells by controlling IL-7Rα expression. In addition, GATA-3 served a critical function in the development of the NKp46+ ILC3 subset by regulating the balance between the transcription factors T-bet and RORγt. Among NKp46+ ILC3 cells, although GATA-3 positively regulated genes specific to the NKp46+ ILC3 subset, it negatively regulated genes specific to lymphoid tissue inducer (LTi) or LTi-like ILC3 cells. Furthermore, GATA-3 was required for IL-22 production in both ILC3 subsets. Thus, despite its low expression, GATA-3 was critical for the homeostasis, development and function of ILC3 subsets.

Nature Immunol 2016; 17: 169

Eitan Israeli

Capsule

Breast implants linked to chronic pulmonary silicone embolism

Chronic pulmonary silicone embolism related to saline breast implants has been detailed in a letter to the editor published in the January issue of the *Annals of the American Thoracic Society*. Ayush Arora, from the Cleveland Clinic, and colleagues describe the first case of pulmonary silicone embolism related to saline breast implants in a 45 year old woman. The patient had been repeatedly hospitalized over the course of 14 months with a clinical presentation that included acute dyspnea on exertion and fever, and bilateral lung infiltrates on chest radiograph. The patient had undergone bilateral breast augmentation with saline implants 18 years earlier. The researchers note that on examination the implants were found to be in place, although there was marked asymmetry, the right implant being considerably smaller. There was slight but notable distortion of the right implant, with a potion seemingly embedded in the chest wall. Review of pathology slides showed the presence of multiple clear vacuoles surrounded by histiocytes and/or multinucleated giant cells. The morphology was consistent with silicone emboli. The patient was diagnosed with chronic pulmonary silicone emboli and referred for implant removal. The authors conclude: "In summary, silicone microemboli derived from breast implants can potentially embolize to the lung, causing a chronic form of lung disease mimicking interstitial lung disease."

Ann Am Thorac Soc 2016; 13: 139

Eitan Israeli

Capsule

Autophagy maintains stemness by preventing senescence

During aging, muscle stem-cell regenerative function declines. At advanced geriatric age, this decline is maximal owing to transition from a normal quiescence into an irreversible senescence state. How satellite cells maintain quiescence and avoid senescence until advanced age remains unknown. Garcia-Prat et al. report that basal autophagy is essential to maintain the stem-cell quiescent state in mice. Failure of autophagy in physiologically aged satellite cells or genetic impairment of autophagy in young cells causes entry into senescence by loss of proteostasis, increased mitochondrial dysfunction and oxidative stress, resulting in a decline in the function and number of satellite cells. Re-establishment of autophagy reverses senescence and restores regenerative functions in geriatric satellite cells. Since autophagy also declines in human geriatric satellite cells, our findings reveal autophagy to be a decisive stem-cell-fate regulator, with implications for fostering muscle regeneration in sarcopenia.

Nature 2016; 529: 37

Eitan Israeli

Capsule

French drug trial details murky but should not influence future cannabinoid research

Contrary to initial reports, the drug tested on paid volunteers in a French study, which resulted in one death and five hospitalizations, did not contain cannabis or cannabinoids. The drug, an FAAH inhibitor manufactured by the Portuguese company Bial, was instead designed to act on the human endocannabinoid system as a potential painkiller and treatment for anxiety. Beyond that, very little information is publicly known and as such, no conclusions can be drawn about the safety or efficacy related to future cannabis and cannabinoid research. "Without adequate information it is impossible to advance any realistic theory about causes of toxicity," said Daniele Piomelli, PhD, Louise Turner Arnold Chair in Neurosciences and Professor, Anatomy & Neurobiology, University of California-Irvine, School of Medicine, and Editor-in-Chief of *Cannabis and Cannabinoid Research*. "Several structurally different FAAH inhibitors have been previously tested for human safety in rigorous phase 1 clinical trials. These include compounds from Sanofi, Pfizer, Merck, Johnson and Johnson, and others. All these FAAH inhibitors were shown to be safe in humans. The human safety of multiple FAAH inhibitors suggests that toxicity of the Bial compound is unlikely to be a 'class effect' – in other words, it is unlikely to be due to the interaction of the Bial compound with FAAH. It is more probable that the Bial compound interacts with another, as yet unknown protein that is responsible for the observed toxicity, or that a toxic impurity was present in the test drug. Of course, while we can tentatively exclude a class effect at this point, we cannot pin-point which other target might be responsible for the toxicity of the Bial compound."

Press release from Mary Ann Liebert, Inc., Publishers, 19 January 2016

Eitan Israeli

Capsule

Self-renewing resident arterial macrophages arise from embryonic CX3CR1+ precursors and circulating monocytes immediately after birth

Resident macrophages densely populate the normal arterial wall, yet their origins and the mechanisms that sustain them are poorly understood. Ensan et al. use gene-expression profiling to show that arterial macrophages constitute a distinct population among macrophages. Using multiple fate-mapping approaches, the authors show that arterial macrophages arise embryonically from CX3CR1+ precursors and postnatally from bone marrow-derived monocytes that colonize the tissue immediately after birth. In adulthood, proliferation (rather than monocyte recruitment) sustains arterial macrophages in the steady state and after severe depletion following sepsis. After infection, arterial macrophages return rapidly to functional homeostasis. Finally, survival of resident arterial macrophages depends on a CX3CR1-CX3CL1 axis within the vascular niche.

Nature Immunol 2016; 17: 159

Eitan Israeli

Capsule

Antisense oligonucleotide to lowers low density lipoprotein

Mipomersen is a U.S. Food and Drug Administration-approved antisense oligonucleotide that lowers low density lipoprotein (LDL) in patients with high cholesterol by targeting apolipoprotein B (apoB) synthesis. It is unclear exactly how mipomersen works in humans. Reyes-Soffer et al. found that in healthy volunteers the drug reduced levels of LDL and its precursor, very low density lipoprotein (VLDL), by increasing clearance of both of these vessel-clogging agents rather than reducing their secretion by the liver. Direct clearance of VLDL led to reduced production of LDL. Studies in mice and cell lines revealed how the liver compensates for reduced apoB synthesis to potentially avoid fatty liver disease.

Sci Transl Med 2016; 8: 323ra12

Eitan Israeli

Capsule

Interactome analysis of gene expression profile reveals potential novel key transcriptional regulators of skin pathology in vitiligo

Selective destruction of epidermal melanocytes is central to vitiligo (VL), a common acquired autoimmune depigmentory disorder of the skin. Like other autoimmune diseases, the pathogenesis of VL is obscure and both multifactorial and polygenic. The prevailing theory is that VL may be part of an autoimmune diathesis. To evaluate mechanisms underlying disease development and progression, Dey-Rao and co-researchers studied genome-wide gene expression from lesional and non-lesional skin of patients with non-segmental VL. Unbiased clustering and principal components analyses reveals a 'lesional pathology'-based signature. Pathway-based analyses of the differentially expressed genes underscore processes such as melanocyte development and cell cycle as central drivers of the disease state. Interactome analysis identifies several key transcriptional regulators potentially affecting disease pathogenesis both within and 'hidden' from the data set. Finally, two genes within six identified transcriptional 'hot spots' coincide with previous VL-associated genetic elements. The remaining genes in the 'hot spots' offer an additional set of potential disease-linked loci that may help to guide future studies aimed at identifying disease risk genes.

Genes Immunity 2016; 17: 30

Eitan Israeli

Capsule

Most microbe-specific naïve CD4+ T cells produce memory cells during infection

One of the hallmarks of adaptive immunity is that T and B lymphocytes 'remember' previous infections, protecting the host from subsequent infections. When T cells respond to a pathogen, they proliferate, and a fraction of their progeny goes on to form long-lived memory cells. It is not clear whether all of the T cell clones that respond to the initial infection have the potential to form memory T cells. Tubo and colleagues used a single-cell adoptive transfer model in mice to answer this question. Nearly all T cell clones produced memory cells, which suggests that breadth is probably an important component of immunological memory. Infection elicits CD4+ memory T lymphocytes that participate in protective immunity. Although memory cells are the progeny of naïve T cells, it is unclear whether all naïve cells from a polyclonal repertoire have memory cell potential. Using a single-cell adoptive transfer and spleen biopsy method, the authors found that in mice, essentially all microbe-specific naïve cells produced memory cells during infection. Different clonal memory cell populations had different B cell or macrophage helper compositions that matched effector cell populations generated much earlier in the response. Thus, each microbe-specific naïve CD4+ T cell produces a distinctive ratio of effector cell types early in the immune response that is maintained as some cells in the clonal population become memory cells.

Science 2016; 351: 511

Eitan Israeli

Capsule

Neuroendocrine cells as air sensors

Liters of air pass through the lung every minute. Signals in the atmospheric environment are processed into physiological outputs, including the immune response. Branchfield and colleagues show that rare airway cells called pulmonary neuroendocrine cells (PNECs) sense and respond to airborne cues. Inactivating *Roundabout* genes in mouse PNECs prevent normal PNEC clustering and cause an increase in the production of neuropeptides, which in turn trigger a heightened immune response. Thus PNECs, despite their rarity, are sensitive and effective rheostats on the airway wall that receive, interpret, and respond to environmental stimuli.

Science 2016; 351: 707

Eitan Israeli

Capsule

Unusual antibodies target malaria

B cells make antibodies through a process of somatic recombination. This gives rise to a diverse repertoire of antibodies able to target many pathogens, such as the malaria-causing parasite *Plasmodium falciparum*. Tan and collaborators screened the plasma of *P. falciparum* – in infected individuals to look for antibodies that kill infected red blood cells (RBCs). They isolated several monoclonal antibodies from multiple individuals that showed broad reactivity for infected RBCs. To their surprise, these antibodies all contained a genomic insertion that encoded a collagen-binding protein called LAIR1, and it was this insert, rather than the antibody-encoding gene segments themselves, which recognized the infected RBCs. Whether such insertions exist in other antibodies remains to be determined.

Nature 2016; 529: 105

Eitan Israeli

Capsule

Airway infections put to an acid test

Cystic fibrosis (CF) is caused by mutations in the gene that encodes the cystic fibrosis transmembrane conductance regulator (CFTR) anion channel. In humans and pigs, the loss of CFTR impairs respiratory host defenses, causing airway infection. But CF mice are spared. Shah et al. found that in all three species, CFTR secreted bicarbonate into airway surface liquid. In humans and pigs lacking CFTR, unchecked H^+ secretion by the non-gastric H^+/K^+adenosine triphosphatase (ATP12A) acidified airway surface liquid, which impaired airway host defenses. In contrast, mouse airways expressed little ATP12A and secreted minimal H^+; consequently, airway surface liquid in CF and non-CF mice had similar pH. Inhibiting ATP12A reversed host defense abnormalities in human and pig airways. Conversely, expressing ATP12A in CF mouse airways acidified airway surface liquid, impaired defenses, and increased airway bacteria. These findings help explain why CF mice are protected from infection and nominate ATP12A as a potential therapeutic target for CF.

Science 2016; 351: 503

Eitan Israeli

Capsule

Microbiota and infant development

Malnutrition in children is a persistent challenge that is not always remedied by improvements in nutrition. This is because a characteristic community of gut microbes seems to mediate some of the pathology. Human gut microbes can be transplanted effectively into germ-free mice to recapitulate their associated phenotypes. Using this model, Blanton et al. (*Science* 2016; 351: 10.1126/science.aad3311) found that the microbiota of healthy children relieved the harmful effects on growth caused by the microbiota of malnourished children. In infant mammals, chronic undernutrition results in growth hormone resistance and stunting. In mice, Schwarzer et al. (*Science* 2016; 351: 854) showed that strains of *Lactobacillus plantarum* in the gut microbiota sustained growth hormone activity via signaling pathways in the liver, thus overcoming growth hormone resistance. Together these studies reveal that specific beneficial microbes could potentially be exploited to resolve undernutrition syndromes.

Eitan Israeli

Capsule

Treating Alzheimer's from the start

The formation of beta-amyloid plaques, known as Aβ aggregates, is implicated as a driving force of Alzheimer's disease. Vendruscolo et al. applied chemical kinetic approaches to identify bexarotene, an anticancer drug that selectively activates retinoid X receptor, as a molecule that can alter Aβ aggregation in vitro and in a *C. elegans* model. The inhibition of Aβ aggregate nucleation by bexarotene may therefore reduce the risk of development and progression of Alzheimer's disease and other similar neurodegenerative disorders.

Sci Adv 2016; 2: 10.1126.sciadv.01244

Eitan Israeli

Capsule

Helping cancer cells exit blood vessels

Metastasizing cancer cells must migrate into the bloodstream to colonize secondary sites. Locard-Paulet et al. cocultured breast cancer cells with endothelial cells, a system that mimics the early events associated with exit from the bloodstream. The receptor EPHA2 can mediate repulsion between cells. Activation of EPHA2 in breast cancer cells by an endothelial cell ligand was associated with decreased lung colonization in vivo. EPHA2 activation was decreased in a metastatic breast cancer cell line that targets the lung, which in vitro had greater migration rates through endothelial cell monolayers.

Sci Signal 2016; 9: ra15

Eitan Israeli

Capsule

Neutrophil extracellular traps enriched in oxidized mitochondrial DNA are interferogenic and contribute to lupus-like disease

Neutrophil extracellular traps (NETs) are implicated in autoimmunity, but how they are generated and what their roles are in sterile inflammation remain unclear. Ribonucleoprotein immune complexes (RNP ICs), inducers of NETosis, require mitochondrial reactive oxygen species (ROS) for maximal NET stimulation. After RNP IC stimulation of neutrophils, mitochondria become hypopolarized and translocate to the cell surface. Extracellular release of oxidized mitochondrial DNA is pro-inflammatory in vitro, and when this DNA is injected into mice, it stimulates type I interferon (IFN) signaling through a pathway dependent on the DNA sensor STING. Mitochondrial ROS are also necessary for spontaneous NETosis of low density granulocytes from individuals with systemic lupus erythematosus. This was also observed in individuals with chronic granulomatous disease, who lack NADPH oxidase activity but still develop autoimmunity and type I IFN signatures. Mitochondrial ROS inhibition in vivo reduces disease severity and type I IFN responses in a mouse model of lupus. Together, these findings highlight a role for mitochondria in the generation not only of NETs but also of pro-inflammatory oxidized mitochondrial DNA in autoimmune diseases.

Nature Med 2016; 22: 146

Eitan Israeli

Capsule

Managing metastasis

Because of the poor prognosis of metastatic cancer, it is critical to determine exactly how various factors contribute to cancer spread. Mlecnik et al. examined the impact of tumor-intrinsic, microenvironmental, and immunological factors on tumor metastasis in colorectoral cancer patients. A decrease in the presence of lymphatic vessels and a reduction in immune cytotoxicity was associated more strongly with the metastatic process than were tumor-intrinsic factors such as chromosomal instability or cancer-associated mutations. Testing this so-called Immunoscore could be used as a biomarker to predict metastasis and guide therapy.

Sci Transl Med 2016; 8: 327ra26

Eitan Israeli

Capsule

Visualizing the beginnings of melanoma

The 'cancerized field' concept posits that cells in a given tissue sharing an oncogenic mutation are cancer-prone, yet only discreet clones within the field initiate tumors. Studying the process of cancer initiation has remained challenging because of (i) the rarity of these events, (ii) the difficulty of visualizing initiating clones in living organisms, and (iii) the transient nature of a newly transformed clone emerging before it expands to form an early tumor. A more complete understanding of the molecular processes that regulate cancer initiation could provide important prognostic information about which precancerous lesions are most prone to becoming cancer and also implicate druggable molecular pathways that, when inhibited, may prevent the cancer from ever starting. Kaufman and group developed a *crestin:EGFP* reporter that recapitulates the embryonic neural crest expression pattern of *crestin* and its expression in melanoma tumors. The authors show through live imaging of transgenic zebrafish *crestin* reporters that within a cancerized field (*BRAF*^{V600E}-mutant, *p*53-deficient), a single melanocyte reactivates the NCP state, establishing that a fate change occurs at melanoma initiation in this model. Early *crestin*$^{+}$ patches of cells expand and are transplantable in a manner consistent with their possessing tumorigenic activity, and they exhibit a gene expression pattern consistent with the NCP identity readout by the *crestin* reporter. The *crestin* element is regulated by NCP transcription factors, including *sox*10. Forced *sox*10 overexpression in melanocytes accelerated melanoma formation, whereas CRISPR/Cas9 targeting of *sox*10 delayed melanoma onset. They also show activation of super-enhancers at NCP genes in both zebrafish and human melanomas, identifying an epigenetic mechanism for control of this NCP signature leading to melanoma.

Science 2016; 351: 10.1126/*science*.aad3867

Eitan Israeli