Capsule

Substantial contribution of extrinsic risk factors to cancer development

Recent research has highlighted a strong correlation between tissue-specific cancer risk and the lifetime number of tissue-specific stem cell divisions. Whether such correlation implies a high unavoidable intrinsic cancer risk has become a key public health debate with the dissemination of the 'bad luck' hypothesis. Wu et al. provide evidence that intrinsic risk factors contribute only modestly (less than ~10–30% of lifetime risk) to cancer development. First, the authors demonstrated that the correlation between stem cell division and cancer risk does not distinguish between the effects of intrinsic and extrinsic factors. They then showed that intrinsic risk is better estimated by the lower bound risk controlling for total stem cell divisions. Finally, they showed that the rates of endogenous mutation accumulation by intrinsic processes are not sufficient to account for the observed cancer risks. Collectively, they conclude that cancer risk is heavily influenced by extrinsic factors. These results are important for strategizing cancer prevention, research and public health.

Nature 2016; 529: 43

Eitan Israeli

Capsule

Rationally engineered Cas9 nucleases with improved specificity

The RNA-guided endonuclease Cas9 is a versatile genome-editing tool with a broad range of applications from therapeutics to functional annotation of genes. Cas9 creates double-strand breaks (DSBs) at targeted genomic loci complementary to a short RNA guide. However, Cas9 can cleave off-target sites that are not fully complementary to the guide, which poses a major challenge for genome editing. Slaymaker et al. used structure-guided protein engineering to improve the specificity of *Streptococcus pyogenes* Cas9 (SpCas9). Using targeted deep sequencing and unbiased whole-genome off-target analysis to assess Cas9-mediated DNA cleavage in human cells, the authors demonstrated that "enhanced specificity" SpCas9 (eSpCas9) variants reduce off-target effects and maintain robust on-target cleavage. Thus, eSpCas9 could be broadly useful for genome-editing applications requiring a high level of specificity.

Science 2016; 351: 84

Eitan Israeli

Capsule

A way to modulate reward-seeking

Which brain regions are causally involved in reward-related behavior? Ferenczi et al. combined focal, cell type-specific, optogenetic manipulations with brain imaging, behavioral testing, and in vivo electrophysiology. Stimulation of midbrain dopamine neurons increased activity in a brain region called the striatum and was correlated with reward-seeking across individual animals. However, elevated excitability of an area called the medial prefrontal cortex reduced both striatal responses to the stimulation of dopamine neurons and the behavioral drive to seek the stimulation of dopamine neurons. Finally, modulating the excitability of medial prefrontal cortex pyramidal neurons drove changes in neural circuit synchrony, as well as corresponding anhedonic behavior. These observations resemble imaging and clinical phenotypes observed in human depression, addiction, and schizophrenia.

Science 2016; 351: aac9698

Eitan Israeli

Capsule

Effect of tight control of inflammation in early psoriatic arthritis (TICOPA)

Early intervention and tight control of inflammation optimize outcomes in rheumatoid arthritis but these approaches have not yet been studied in psoriatic arthritis. To assess the effect of tight control on early psoriatic arthritis using a treat-to-target approach, Coats et al. conducted an open-label multicenter randomized controlled trial in adult patients (aged ≥ 18 years) with early psoriatic arthritis (< 24 months symptom duration) who had not previously received treatment with any disease-modifying anti-rheumatic drugs. The patients, enrolled from eight secondary care rheumatology centers in the UK, were randomly assigned in a 1:1 ratio to receive either tight control (with review every 4 weeks and with escalation of treatment if minimal disease activity criteria not met) or standard care (standard therapy according to the treating clinician, with review every 12 weeks) for 48 weeks. Between 28 May 2008 and 21 March 2012, 206 eligible patients were enrolled and randomly assigned to receive tight control (n=101) or standard care (n=105). In the intention-to-treat patient population, the odds of achieving an ACR20 response at 48 weeks were higher in the tight control group than in the standard care group (odds ratio 1.91, 95%CI 1.03–3.55, $P = 0.0392$). Serious adverse events during the course of the study were reported by 20 patients (10%): 25 events in 14 patients (14%) in the tight control group and 8 events in 6 patients (6%) in the standard care group. No unexpected serious adverse events or deaths occurred. Tight control of psoriatic arthritis disease activity through a treat-to-target approach significantly improves joint outcomes for newly diagnosed patients, with no unexpected serious adverse events reported.

Lancet 2015; 386: 248

Eitan Israeli

Capsule

BCG vaccine demonstrates long-lasting effectiveness

Recent data have shown that the Bacille Calmette-Guérin (BCG) vaccine reduced the risk for tuberculosis after 40 years of vaccination, suggesting the vaccine may be more cost-effective than previously estimated. "This finding could be relevant if countries revise their BCG vaccination policies in response to changing tuberculosis epidemiology, especially in low-incidence countries," Patrick Nguipdop-Djomo, from the Department of Infectious Disease Epidemiology at the London School of Hygiene & Tropical Medicine, and colleagues wrote. BCG is one of the most common vaccines; however, the duration of vaccine effectiveness is unclear, according to Nguipdop-Djomo and colleagues. Results from a prior study of American Indians and Alaska Natives demonstrated significant BCG effectiveness up to 40 years after vaccination; however, the findings have not been confirmed in other trials. A systematic review conducted in 2012 found that BCG was effective against TB for 10 to 15 years. The investigators concluded the vaccine was 60% (95%CI 37–74) effective for less than 5 years, 56% (95%CI 17–76) effective between 5 and less than 10 years, and 46% (95%CI 18–64) effective for up to 15 years. In addition, three observational studies observed persisting but waning patterns of BCG protection up to 20 years after vaccination. For the current retrospective study, they evaluated TB incidence in Norwegians who accepted or declined the BCG vaccine during a mass TB screening and vaccination program from 1962 to 1975. The participants were followed until 31 December 2011 or until their first TB diagnosis, emigration or death. Results were adjusted for age-specific TB risk as well as demographic and socioeconomic factors. Median follow-up was 44 years for vaccinated participants (n=297,905) and 41 years for unvaccinated participants (n=83,421). TB rates were 3.3 (95%CI 2.7–4) per 100,000 person-years in unvaccinated participants vs. 1.3 (95%CI 1.1–1.5) per 100,000 person-years in vaccinated participants. The vaccine was 49% (95%CI 26–65) effective after 40 years of vaccine receipt (adjusted HR 0.51, 95%CI 0.35–0.74); however, the findings were not significant after 20 years, the researchers wrote. They performed a sensitivity analysis to exclude participants who developed TB after 2 years of vaccination and may have been infected before receiving the vaccine. BCG was 61% (95%CI 24–80) effective up to 9 years, 58% (95%CI 27–76) effective between 10 and 19 years, 38% (95%CI -32 to 71) effective between 20 and 29 years, and 42% (95%CI -24 to 73) effective after 30 to 40 years. For pulmonary TB, the vaccine was 57% (95%CI 8–80) effective up to 9 years, 63% (95%CI 32–80) effective between 10 and 19 years, 50% (95%CI -19 to 79) effective between 20 and 29 years, and 40% (95%CI -46 to 76) effective between 30 and 40 years. "The vaccine seemed to reduce the risk of pulmonary tuberculosis, the infectious form of the disease, more than it did of all tuberculosis," Nguipdop-Djomo and colleagues wrote. "Our results are consistent with long-lived BCG-derived immunity, adding to the evidence that BCG vaccination of individuals not yet infected by (*Mycobacterium tuberculosis*) infection itself nor sensitized by environmental mycobacteria might confer some protection against tuberculosis for at least 20 years."

http://www.healio.com/infectious-disease/respiratory-infections/news/online/%7B6d0d5d67-b5ec-4834-a0de-f93539fb215c%7D/bcg-vaccine-demonstrates-long-lasting-effectiveness

Eitan Israeli

Capsule

Connected astrocytes coordinate seizures

Astrocytes are glial cells in the nervous system that are interconnected by gap junctions formed by connexins. Gap junctions form pores that enable the connected cells to function as a unit by rapidly passing cytosolic signals. By analyzing hippocampal slices from mice that were deficient in astroglial connexins, Chever et al. found that interconnected astrocytes coordinated bursts of neuronal activity over large regions, which contributed to the intensity of induced seizures. Indeed, mice with disconnected astrocytes had more frequent but less severe chemically induced seizures than did normal mice.

Sci Signal 2016; 9: ra6

Eitan Israeli

Capsule

'Self-sabotage' prevents immune protection against malaria

Australian scientists have for the first time revealed how malaria parasites cause an inflammatory reaction that sabotages our body's ability to protect itself against the disease. The discovery opens up the possibility of improving new or existing malaria vaccines by boosting key immune cells needed for long-lasting immunity. This could even include vaccines that have previously been ineffective in clinical trials. Researchers from Melbourne's Walter and Eliza Hall Institute discovered that the same inflammatory molecules that drive the immune response in clinical and severe malaria also prevent the body from developing protective antibodies against the parasite. Drs. Diana Hansen, Axel Kallies and Victoria Ryg-Cornejo led a research team that examined how the immune system responded to malaria infection caused by *Plasmodium falciparum* (published in the journal *Cell Reports*). Dr. Hansen said it was the first time scientists had pinpointed why the immune system fails to develop immunity during malaria infection. "With many infections, a single exposure to the pathogen is enough to induce production of antibodies that will protect you for the rest of your life. However with malaria it can take up to 20 years for someone to build up sufficient immunity to be protected. During that time people exposed to malaria are susceptible to reinfection and become sick many times, as well as spreading the disease." Malaria has traditionally been difficult to manage because the body is not good at developing long-lasting immunity to the parasite, which has hampered vaccine development. "This was complicated by the fact that we didn't know whether it was the malaria parasite itself or the inflammatory reaction to malaria that was actually inhibiting the ability to develop protective immunity. We have now shown that it was a double-edged sword: the strong inflammatory reaction that accompanies and in fact drives severe clinical malaria is also responsible for silencing the key immune cells needed for long-term protection against the parasite." Dr. Kallies said inflammatory molecules released by the body to fight the infection were preventing protective antibodies from being made. "Long-term immunity to malaria and other pathogens requires antibody responses," he said. "Specialized immune cells called helper T cells join forces with B cells to generate these protective antibodies. However, we showed that during malaria infection critical inflammatory molecules actually arrest development of helper T cells and therefore the B cells don't get the necessary instructions to make antibodies." Dr. Hansen said the findings could lead to new avenues in the search for effective malaria vaccines. "This research opens the door to therapeutic approaches to accelerate development of protective immunity to malaria and improve efficacy of malaria vaccines. Until now, malaria vaccines have had disappointing results. We can now see a way of improving these responses, by tailoring or augmenting the vaccine to boost development of helper T cells that will enable the body to make protective antibodies that target the malaria parasites."

http://www.eurekalert.org/pub_releases/2015-12/waeh-pi122115.php#%2EVn2AedjUTQY%2Elinkedin

Eitan Israeli

Capsule

PPAR-δ is repressed in Huntington's disease, is required for normal neuronal function and can be targeted therapeutically

Huntington's disease (HD) is a progressive neurodegenerative disorder caused by a CAG trinucleotide repeat expansion in the huntingtin (*HTT*) gene, which encodes a polyglutamine tract in the HTT protein. Dickey et al. found that peroxisome proliferator-activated receptor delta (PPAR-δ) interacts with HTT and that mutant HTT represses PPAR-δ-mediated transactivation. Increased PPAR-δ transactivation ameliorated mitochondrial dysfunction and improved cell survival of neurons from mouse models of HD. Expression of dominant-negative PPAR-δ in the central nervous system of mice was sufficient to induce motor dysfunction, neurodegeneration, mitochondrial abnormalities and transcriptional alterations that recapitulated HD-like phenotypes. Expression of dominant-negative PPAR-δ specifically in the striatum of medium spiny neurons in mice yielded HD-like motor phenotypes, accompanied by striatal neuron loss. In mouse models of HD, pharmacologic activation of PPAR-δ using the agonist KD3010 improved motor function, reduced neurodegeneration and increased survival. PPAR-δ activation also reduced HTT-induced neurotoxicity in vitro and in medium spiny-like neurons generated from stem cells derived from individuals with HD, indicating that PPAR-δ activation may be beneficial in HD and related disorders.

Nature Med 2016; 22: 37

Eitan Israeli

Capsule

Parkinson's disease-associated mutant *VPS35* causes mitochondrial dysfunction by recycling DLP1 complexes

Mitochondrial dysfunction represents a critical step during the pathogenesis of Parkinson's disease (PD), and increasing evidence suggests abnormal mitochondrial dynamics and quality control as important underlying mechanisms. The *VPS35* gene, which encodes a key component of the membrane protein-recycling retromer complex, is the third autosomal-dominant gene associated with PD. However, how *VPS35* mutations lead to neurodegeneration remains unclear. Wang et al. demonstrate that PD-associated *VPS35* mutations caused mitochondrial fragmentation and cell death in cultured neurons in vitro, in mouse substantia nigra neurons in vivo, and in human fibroblasts from an individual with PD who has the VPS35D620N mutation. *VPS35*-induced mitochondrial deficits and neuronal dysfunction could be prevented by inhibition of mitochondrial fission. *VPS35* mutants showed increased interaction with dynamin-like protein (DLP) 1, which enhanced turnover of the mitochondrial DLP1 complexes via the mitochondria-derived vesicle-dependent trafficking of the complexes to lysosomes for degradation. Notably, oxidative stress increased the *VPS35*-DLP1 interaction, which was also found to be increased in the brains of sporadic PD cases. These results revealed a novel cellular mechanism for the involvement of *VPS35* in mitochondrial fission, dysregulation of which is probably involved in the pathogenesis of familial, and possibly sporadic, PD.

Nature Med 2016; 22: 54

Eitan Israeli

Capsule

An innate antiviral pathway acting before interferons at epithelial surfaces

Mucosal surfaces are exposed to environmental substances and represent a major portal of entry for microorganisms. The innate immune system is responsible for early defense against infections and it is believed that the interferons (IFNs) constitute the first line of defense against viruses. Iversen et al. have identified an innate antiviral pathway that works at epithelial surfaces before the IFNs. The pathway is activated independently of known innate sensors of viral infections through a mechanism dependent on viral O-linked glycans, which induce CXCR3 chemokines and stimulate antiviral activity in a manner dependent on neutrophils. This study therefore identifies a previously unknown layer of antiviral defense that exerts its action on epithelial surfaces before the classical IFN response is operative.

Nature Immunol 2016; 17: 150

Eitan Israeli

Capsule

The genetic associations of acute anterior uveitis and their overlap with the genetics of ankylosing spondylitis

Acute anterior uveitis (AAU) involves inflammation of the iris and ciliary body of the eye. It occurs both in isolation and as a complication of ankylosing spondylitis (AS). It is strongly associated with *HLA-B*27*, but previous studies have suggested that further genetic factors may confer additional risk. Robinson et al. sought to investigate this using the Illumina Exomechip microarray, to compare 1504 cases with AS and AAU, 1805 with AS but no AAU and 21,133 healthy controls. The authors also used a heterogeneity test to test the differences in effect size between AS with AAU and AS without AAU. In the analysis comparing AS+AAU+ cases versus controls, *HLA-B*27* and *HLA-A*02:01* were significantly associated with the presence of AAU ($P < 10^{-300}$ and $P = 6 \times 10^{-8}$, respectively). Secondary independent association with *PSORS1C3* ($P = 4.7 \times 10^{-5}$) and TAP2 ($P = 1.1 \times 10^{-5}$) were observed in the major histocompatibility complex. There was a new suggestive association with a low frequency variant at zinc-finger protein 154 in the AS without AAU versus control analysis (zinc-finger protein 154 (*ZNF154*), $P = 2.2 \times 10^{-6}$). Heterogeneity testing showed that rs30187 in ERAP1 has a larger effect on AAU compared with that in AS alone. These findings also suggest that variants in ERAP1 have a differential impact on the risk of AAU when compared with AS, and hence the genetic risk for AAU differs from AS.

Genes Immunity 2016; 17: 4

Eitan Israeli

Elephants infected seven Oregon zoo workers with tuberculosis

Seven employees of an Oregon zoo contracted tuberculosis from three elephants in their care in 2013, the U.S. Centers for Disease Control and Prevention said on Friday. The staff members at the Oregon Zoo in Portland were infected with a latent form of the respiratory illness and therefore displayed no symptoms and were not contagious, a report published by the CDC said. The report was issued two days after a U.S. judge ordered the CDC to release documents on TB in elephants to the animal-rights group "People for the Ethical Treatment of Animals." Oregon health officials said the timing of the report was unrelated to the lawsuit. PETA sued the U.S. Department of Health and Human Services, parent of the CDC, last year. It sought release of data because of what it said was a serious risk that elephants could spread the potentially deadly disease to other elephants or to humans. The CDC report on the outbreak pointed to a lack of research about TB in elephants. It also called for improved screening to detect the disease because the present method of detection – taking cultures – may miss some cases or result in false positives. Jennifer Vines, deputy health officer for Multnomah County, whose office worked with the CDC on its report, said the investigation did not conclude that tuberculosis is highly transmissible between elephants and people. About 5% of captive Asian elephants in North America, like those in Portland, are believed to have TB, the CDC said. Human-to-elephant transmission was first identified in 1996 and there have been a handful of cases in recent years in Tennessee and elsewhere. The outbreak prompted the Portland zoo to say it would conduct more frequent tuberculosis tests of both animals and staff through at least June 2016. The outbreak was identified in May 2013 when a routine annual check of elephants found that a 20 year old bull named Rama was infected. Rama's father, 51 year old Packy, also tested positive as did Tusko, a 44 year old former circus performer. Public health officials do not know the cause of the outbreak. The CDC said it was possible that a zoo volunteer diagnosed with TB in 2012 may have spread the disease to the elephants. The zoo's other elephants were not infected, nor were another roughly 100 people who were near the three sickened bull elephants.

Reuters/Health | Sat Jan 9, 2016 8:08pm EST http://www.reuters.com/article/us-oregon-elephants-idUSKBN0UM2HA20160110

Eitan Israeli

Capsule

In vivo imaging of inflammasome activation reveals a subcapsular macrophage burst response that mobilizes innate and adaptive immunity

The inflammasome is activated in response to a variety of pathogens and has an important role in shaping adaptive immunity, yet the spatiotemporal orchestration of inflammasome activation in vivo and the mechanisms by which it promotes an effective immune response are not fully understood. Using an in vivo reporter to visualize inflammasome assembly, Sagoo and co-workers established the distribution, kinetics and propagation of the inflammasome response to a local viral infection. They show that modified vaccinia Ankara virus induces inflammasome activation in subcapsular sinus (SCS) macrophages, which is immediately followed by cell death and release of extracellular ASC specks. This transient inflammasome signaling in the lymph node generates a robust influx of inflammatory cells and mobilizes T cells from the circulation to increase the magnitude of T cell responses. The authors propose that after infection, SCS macrophages deliver a burst response of inflammasome activity and cell death that translates into the broadening of T cell responses, identifying an important aspect of inflammasome-driven vaccination strategies.

Nature Med 2016; 22: 64

Eitan Israeli

Capsule

Self-reactive IgE exacerbates interferon responses associated with autoimmunity

Canonically, immunoglobulin E (IgE) mediates allergic immune responses by triggering mast cells and basophils to release histamine and type 2 helper cytokines. Henault and co-authors found that in human systemic lupus erythematosus (SLE), IgE antibodies specific for double-stranded DNA (dsDNA) activated plasmacytoid dendritic cells (pDCs), a type of cell of the immune system linked to viral defense, which led to the secretion of substantial amounts of interferon-α (IFN-α). The concentration of dsDNA-specific IgE found in patient serum correlated with disease severity and greatly potentiated pDC function by triggering phagocytosis via the high-affinity FcεRI receptor for IgE, followed by Toll-like receptor 9 (TLR9)-mediated sensing of DNA in phagosomes. These findings expand the known pathogenic mechanisms of IgE-mediated inflammation beyond those found in allergy and demonstrate that IgE can trigger interferon responses capable of exacerbating self-destructive autoimmune responses.

Nature Immunol 2016; 17: 196

Eitan Israeli