Capsule

Candidalysin is a fungal peptide toxin critical for mucosal infection

Cytolytic proteins and peptide toxins are classical virulence factors of several bacterial pathogens which disrupt epithelial barrier function, damage cells and activate or modulate host immune responses. Such toxins have not been identified previously in human pathogenic fungi. Moyes and co-authors identify the first, to our knowledge, fungal cytolytic peptide toxin in the opportunistic pathogen *Candida albicans*. This secreted toxin directly damages epithelial membranes, triggers a danger response signaling pathway and activates epithelial immunity. Membrane permeabilization is enhanced by a positive charge at the carboxy terminus of the peptide, which triggers an inward current concomitant with calcium influx. *C. albicans* strains lacking this toxin do not activate or damage epithelial cells and are avirulent in animal models of mucosal infection. The authors propose the name 'Candidalysin' for this cytolytic peptide toxin, a newly identified, critical molecular determinant of epithelial damage and host recognition of the clinically important fungus, *C. albicans*.

Nature 2016; 532: 64

Eitan Israeli

Capsule

Oncogene control of antitumor immunity

Recent clinical success of cancer immunotherapy has intensified interest in how tumors normally evade the immune response. Whether and how oncogenes contribute to this process are not well understood. In a study of mice, Casey et al. found that the *MYC* oncogene, which is aberrantly activated in many human cancers, up-regulates the expression of genes encoding proteins that dampen the antitumor response. These include two proteins that are often overexpressed on tumor cells and that serve as immune checkpoints. One of them (PDL1) sends to the immune system a "don't find me" signal, and the other (CD47) sends a "don't eat me" signal. Thus, therapies aimed at suppressing *MYC* may help promote an immune response against tumors.

Science 2016; 352: 227

Eitan Israeli

Capsule

A repackaged cancer drug finds its way

The recent success of immunotherapy has energized the clinical oncology field, yet for many cancer types, cytotoxic drugs remain the only treatment option. One such drug, doxorubicin (Dox), is very effective but also very toxic to healthy tissues when administered at the doses needed to kill tumor cells. To target delivery of the drug, Xu et al. developed a "nanoparticle generator" (iNPG) containing a polymeric form of Dox. The design features of iNPG ensure that it selectively accumulates at the tumor and that release of Dox is slow and sustained, resulting in high drug concentrations within the tumor. In mouse models of breast cancer, iNPG induced regression of lung metastases and was less toxic than other forms of Dox.

Nat Biotechnol 2016; 10.1038/nbt.3506

Eitan Israeli

Capsule

Linking inflammation and Parkinson disease: hypochlorous acid generates parkinsonian poisons

Inflammation is a common feature of Parkinson disease and other neurodegenerative disorders. Hypochlorous acid (HOCl) is a reactive oxygen species formed by neutrophils and other myeloperoxidase-containing cells during inflammation. HOCl chlorinates the amine and catechol moieties of dopamine to produce chlorinated derivatives collectively termed chlorodopamine. Jeitalner et al. report that chlorodopamine is toxic to dopaminergic neurons both in vivo and in vitro. Intrastriatal administration of 90 nmol chlorodopamine resulted in loss of dopaminergic neurons from the substantia nigra and decreased ambulation – results that were comparable to those produced by the same dose of the parkinsonian poison, 1-methyl-4-phenylpyridinium (MPP+). Chlorodopamine was also more toxic to differentiated SH SY5Y cells than HOCl. The basis of this selective toxicity is likely mediated by chlorodopamine uptake through the dopamine transporter, since expression of this transporter in COS-7 cells conferred sensitivity to chlorodopamine toxicity. Pharmacological blockade of the dopamine transporter also mitigated the deleterious effects of chlorodopamine in vivo. The cellular actions of chlorodopamine included inactivation of the α-ketoglutarate dehydrogenase complex, as well as inhibition of mitochondrial respiration. The latter effect is consistent with inhibition of cytochrome c oxidase. Illumination at 670 nm, which stimulates cytochrome c oxidase, reversed the effects of chlorodopamine. The observed changes in mitochondrial biochemistry were also accompanied by the swelling of these organelles. Overall, these findings suggest that chlorination of dopamine by HOCl generates toxins that selectively kill dopaminergic neurons in the substantia nigra in a manner comparable to MPP+.

Toxicol Sci 2016; Mar 29. pii: kfw052. [Epub ahead of print]

Eitan Israeli

Capsule

Reversing vascular deterioration in aged mice

Stiff old arteries contribute to cardiovascular disease in the elderly, which is a leading cause of death. De Picciotto et al. report that age-related deterioration in the flexibility of the carotid artery in mice could be reversed when animals received dietary supplementation of nicotinamide mononucleotide (NMN). NMN is an intermediate in the synthesis of NAD+ (the reduced form of nicontinamide adenine dinucleotide), which improved metabolic function and stress responses in older animals. Treatment of mice with NMN for 8 weeks improved measures of elasticity in large arteries. NMN may act, at least in part, by activating sirtuin 1, an NAD+-dependent protein deacetylase. Dietary supplementation of NMN may thus provide a therapeutic strategy to reverse arterial dysfunction in the elderly.

Aging Cell 2016; 10.1111/acel.12461

Eitan Israeli

Capsule

Single-cell expression profiles of melanoma

Tumors harbor multiple cell types that are thought to play a role in the development of resistance to drug treatments. Tirosh et al. used single-cell sequencing to investigate the distribution of these differing genetic profiles within melanomas. Many cells harbored heterogeneous genetic programs that reflected two different states of genetic expression, one of which was linked to resistance development. Following drug treatment, the resistance-linked expression state was found at a much higher level. Furthermore, the environment of the melanoma cells affected their gene expression programs.

Science 2016; 352: 189

Eitan Israeli

Capsule

Macrophages block tumors' spread

Tumors constantly communicate with their surrounding tissue and the immune system. One way tumors likely do this is by secreting extracellular vesicles (tEVs), which can carry bits of the tumor to distant sites in the body. Pucci et al. tracked tEVs in tumor-bearing mice and people and studied how they affect cancer progression. They found that tEVs disseminate through lymph to nearby lymph nodes, where a specialized population of macrophages largely block any further travel. This barrier breaks down, however, as cancer progresses and also in the face of certain therapies. The tEVs can then penetrate lymph nodes, where they interact with B cells that promote further tumor growth.

Science 2016; 352: 242

Eitan Israeli

Capsule

Chloroquine protects against Zika in vitro

A team of researchers at the Federal University of Rio de Janeiro tested the effects of chloroquine in different Zika virus-infected cell types, observing each culture for 5 days. Flow cytometry and immunofluorescence staining revealed that chloroquine at 25 and 50 µM reduced the number of Zika-infected Vero cells by 65% and 95%, respectively. When tested in human brain microvascular endothelial cells (hBMEC), which are often used to model the blood-brain barrier, chloroquine protected 80% of the cells examined from Zika-induced death. Although chloroquine-mediated inhibition of viral infection can occur in both early and late stages of the viral replication cycle, the team observed that adding chloroquine at 30 minutes to 12 hours after infection reduced release of Zika virus (9 to 20 times compared with untreated cells). The drug did not reduce viral production when administered 24 hours after infection. This indicated that chloroquine is most effective in the early phase of Zika infection, when the virus enters the cell. Dosing remains a hurdle, however. The half maximal effective concentration of chloroquine that protected 50% of cells from Zika-induced death was between 9.82 and 14.2 µM, depending on the cell type. (Chloroquine is sometimes administered in high concentrations – 250 and 500 mg – to pregnant women who have lupus or rheumatoid arthritis.)

bioRxiv 2016; doi:10.1101/051268

Eitan Israeli

Capsule

Unwinding DNA and unleasing inflammation

Fighting infections often comes with collateral damage, which sometimes can be deadly. For instance, in septic shock, the overwhelming release of inflammatory mediators drives multi-organ failure. Rialdi and team report a potential new therapeutic target for controlling excessive inflammation: the DNA unwinding enzyme topoisomerase I (Top1). Upon infection, Top1 specifically localizes to the promoters of pathogen-induced genes and promotes their transcription by helping to recruit RNA polymerase II. Pharmacological inhibition of Top1 in a therapeutic setting increased survival in several mouse models of severe microbially induced inflammation.

Science 2016; 352: 10.1126/science.aad7993

Eitan Israeli

Capsule

Major histocompatibility complex class I molecules protect motor neurons from astrocyte-induced toxicity in amyotrophic lateral sclerosis

Astrocytes isolated from individuals with amyotrophic lateral sclerosis (ALS) are toxic to motor neurons (MNs) and play a non-cell autonomous role in disease pathogenesis. The mechanisms underlying the susceptibility of MNs to cell death remain unclear. Song and team report that astrocytes derived from either mice bearing mutations in genes associated with ALS or human subjects with ALS reduce the expression of major histocompatibility complex class I (MHCI) molecules on MNs; reduced MHCI expression makes these MNs susceptible to astrocyte-induced cell death. Increasing MHCI expression on MNs increases survival and motor performance in a mouse model of ALS and protects MNs against astrocyte toxicity. Overexpression of a single MHCI molecule, HLA-F, protects human MNs from ALS astrocyte-mediated toxicity, whereas knockdown of its receptor, the killer cell immunoglobulin-like receptor KIR3DL2, on human astrocytes results in enhanced MN death. Thus, in ALS, loss of MHCI expression on MNs renders them more vulnerable to astrocyte-mediated toxicity.

Nature Med 2016; 22: 397

Eitan Israeli

Capsule

A view of pathogenic fibrils

The protein α-synuclein (α-syn) accumulates in the brains of people with Parkinson's disease (PD), forming fibrils that are a hallmark of the disease. Tuttle et al. used sophisticated solid-state nuclear magnetic resonance techniques to determine a high resolution three-dimensional structure of α-syn fibrils which they validated by electron microscopy and X-ray fiber diffraction. The structure exhibits many of the features that stabilize typical amyloid fibrils (like those seen in Alzheimer's disease), including a stacked α-sheet structure with a tightly packed core, but in this case the strands in each α sheet follow a serpentine, Greek key-like pattern. The structure may facilitate the development of diagnostic agents for PD.

Nat Struct Mol Biol 2016; 10.1038/nsmb.3194

Eitan Israeli

Capsule

IL-1β, IL-4 and IL-12 control the fate of group 2 innate lymphoid cells in human airway inflammation in the lungs

Group 2 innate lymphoid cells (ILC2s) secrete type 2 cytokines, which protect against parasites but can also contribute to a variety of inflammatory airway diseases. Bal et al. report that interleukin 1β (IL-1β) directly activated human ILC2s and that IL-12 induced the conversion of these activated ILC2s into interferon-γ (IFNγ)-producing ILC1s, which was reversed by IL-4. The plasticity of ILCs was manifested in diseased tissues of patients with severe chronic obstructive pulmonary disease (COPD) or chronic rhinosinusitis with nasal polyps (CRSwNP), which displayed IL-12 or IL-4 signatures and the accumulation of ILC1s or ILC2s, respectively. Eosinophils were a major cellular source of IL-4, which revealed cross-talk between IL-5-producing ILC2s and IL-4-producing eosinophils. The authors propose that IL-12 and IL-4 govern ILC2 functional identity and that their imbalance results in the perpetuation of type 1 or type 2 inflammation.

Nature Immunol 2016; 17: 636

Eitan Israeli

Capsule

Dissolving away cholesterol

Atherosclerosis-driven cardiovascular disease is one of the most common causes of death worldwide. Existing therapies do not treat all patients effectively. Cyclodextrin, a common FDA-approved substance, is already used as a solubilizing agent to improve drug delivery. Zimmer and colleagues found that cyclodextrin solubilizes cholesterol, removes it from plaques, dissolves cholesterol crystals, and successfully treated atherosclerosis in a mouse model. Because cyclodextrin is already known to be safe in humans, this drug is now a candidate for testing in patients with atherosclerosis.

Sci Trans Med 2016; 8: 333ra50

Eitan Israeli

Capsule

Pfizer puts stopper in lethal injections

Pfizer is taking steps to block governments from using its drugs in executions, the *New York Times* reported. The company announced that it will make wholesalers certify that they will not resell the drugs to corrections departments, and the company will closely monitor these distributors in order to prevent their products from being used in lethal injections, according to the article. More than 20 other companies have already adopted such measures, and with Pfizer being among the largest, the impact will likely be measurable. Indeed, now all companies regulated by FDA that make drugs used in lethal injection have imposed a ban on their use in execution – so governments that allow capital punishment will be challenged to find other ways to procure drugs for this use. Such restrictions on drugs have already led to problems with executions, as states have improvised with various cocktails of medications that, in some cases, have failed to work, leaving inmates struggling and writhing. For instance, in 2014, it took the state of Arizona 2 hours to kill convicted murderer Joseph R. Wood III with a cocktail of an opioid and a benzodiazepine. States do not have to reveal the identity of the sources from which they obtain the drugs. In some cases, they have been turning to compounding pharmacies, which do not have to adhere to the same rigorous testing standards that drugs produced by pharmaceutical companies do. Last year, Pfizer acquired Hospira, which has long been opposed to the use of their drugs that have been sought for executions, including barbiturates and sedatives. The *Times* reported that Hospira has long tried to prevent diversion of its products to prisons, but has not succeeded. The death penalty is legal in 32 states in the U.S.

http://www.medpagetoday.com/PublicHealthPolicy/HealthPolicy/57914?isalert=1&uun=g1017600d5028R8415526u&xid=NL_breakingnews_2016-05-13

Eitan Israeli

Capsule

Early short-term treatment with neutralizing human monoclonal antibodies halts SHIV infection in infant macaques

Prevention of mother-to-child transmission (MTCT) of HIV remains a major objective where antenatal care is not readily accessible. Hessel et al. tested HIV-1-specific human neutralizing monoclonal antibodies (NmAbs) as a post-exposure therapy in an infant macaque model for intrapartum MTCT. Rhesus macaques aged 1 month were inoculated orally with the simian-human immunodeficiency virus SHIVSF162P3. On days 1, 4, 7 and 10 after virus exposure, the authors injected animals subcutaneously with NmAbs and quantified systemic distribution of NmAbs in multiple tissues within 24 hours after antibody administration. Replicating virus was found in multiple tissues by day 1 in animals that were not treated. All NmAb-treated macaques were free of virus in blood and tissues at 6 months after exposure. They detected no anti-SHIV T cell responses in blood or tissues at necropsy, and no virus emerged after CD8+ T cell depletion. These results suggest that early passive immunotherapy can eliminate early viral foci and thereby prevent the establishment of viral reservoirs.

Nature Med 2016; 22: 362

Eitan Israeli

Capsule

Genes and microbes converge in colitis

Both host genetics and intestinal microbes probably contribute to a person's overall susceptibility to inflammatory bowel disease (IBD). The human gut microbe *Bacteroides fragilis* produces immunomodulatory molecules that it releases via outer membrane vesicles (OMVs). These molecules can protect mice from experimentally induced colitis. Chu et al. found that OMV-mediated protection from colitis requires Atg16l1 and Nod2 genes whose human orthologs are associated with an increased risk for developing IBD. OMVs trigger an *ATG16L1* and *NOD2*-dependent non-canonical autophagy pathway in dendritic cells (DCs). OMV-primed DCs, in turn, induce regulatory T cells in the intestine that protect against colitis.

Science 2016; 352: 1116

Eitan Israeli

Capsule

Mycobacterium tuberculosis induces the miR-33 locus to reprogram autophagy and host lipid metabolism

Mycobacterium tuberculosis (Mtb) survives in macrophages by evading delivery to the lysosome and promoting the accumulation of lipid bodies, which serve as a bacterial source of nutrients. Quimet et al. found that by inducing the microRNA (miRNA) miR-33 and its passenger strand miR-33*, Mtb inhibited integrated pathways involved in autophagy, lysosomal function and fatty acid oxidation to support bacterial replication. Silencing of miR-33 and miR-33* by genetic or pharmacological means promoted autophagy flux through derepression of key autophagy effectors (such as ATG5, ATG12, LC3B and LAMP1) and AMPK-dependent activation of the transcription factors FOXO3 and TFEB, which enhanced lipid catabolism and Mtb xenophagy. These data define a mammalian miRNA circuit used by Mtb to coordinately inhibit autophagy and reprogram host lipid metabolism to enable intracellular survival and persistence in the host.

Nature Immunol 2016; 17: 677

Eitan Israeli

Capsule

Seven subgroups in lupus

For some diseases such as cancer, doctors routinely use molecular profiling to match patients to the most effective drugs, leading to improved patient care. With this goal in mind, Banchereau et al. explored the molecular heterogeneity of systemic lupus erythematosus, an autoimmune disease in which patients produce autoantibodies to nucleic acids. Through longitudinal profiling of blood samples from 158 children with lupus, they found a transcriptional signature in plasmablasts (a type of antibody-secreting cell) that strongly correlates with disease activity. Notably, a rise in neutrophil transcripts marked the onset of kidney inflammation. Overall, this approach revealed that lupus patients fall into seven subgroups who conceivably would show different responses to treatment.

Cell 2016; 165: 551

Eitan Israeli

Capsule

A secret weapon for food poisoning

Trillions of microbes reside in our gut, producing essential nutrients and defending gut integrity. So how do a few incoming pathogens compete against these masses to establish an infection? Some strains of the bacteria *Listeria monocytogenes* cause gastroenteritis, which can be fatal in the immunocompromised and in pregnant women. Studying mice, Quereda et al. found that a virulent strain of L. monocytogenes produces a toxin called listeriolysin S, but only when it is in the gut. The toxin led to changes in the abundance of acetate- and butyrate-producing gut resident microbes in *L. monocytogenes*-infected mice. These short-chain fatty acids can inhibit *L. monocytogenes* growth, implying that L. monocytogenes expresses the toxin to overwhelm resident microbial competition.

Proc Natl Acad Sci USA 2016; 10.1073/pnas.1523899113

Eitan Israeli

Capsule

Zika virus tested in human brain organoids

The pernicious and resilient *Aedes* mosquito is rapidly spreading Zika virus (ZIKV) through the Americas. ZIKV infection mostly causes mild disease, but in some patients, nervous system involvement is indicated. A particular worry is an observed correlation between infection of mothers in the first trimester of pregnancy and microcephaly in newborns. Garcez and collaborators tested the effects of ZIKV compared with dengue virus infection on human neural stem cells grown as organoids. ZIKV targeted the human brain cells, reduced their size and viability in vitro, and caused programmed cell death responses.

Science 2016; 352: 816

Eitan Israeli