## Capsule

### Molecular analysis of gastric cancer identifies subtypes associated with distinct clinical outcomes

Gastric cancer, a leading cause of cancer-related deaths, is a heterogeneous disease. Cristescu et al. attempted to establish clinically relevant molecular subtypes that would encompass this heterogeneity and provide useful clinical information. The authors used gene expression data to describe four molecular subtypes linked to distinct patterns of molecular alterations, disease progression and prognosis. The mesenchymal-like type includes diffuse-subtype tumors with the worst prognosis, the tendency to occur at an earlier age, and the highest recurrence frequency (63%) of the four subtypes. Microsatellite-unstable tumors are hyper-mutated intestinal-subtype tumors occurring in the antrum; these have the best overall prognosis and the lowest frequency of recurrence (22%) of the four subtypes. The tumor protein 53 (TP53)-active and TP53-inactive types include patients with intermediate prognosis and recurrence rates (with respect to the other two subtypes), with the TP53-active group showing better prognosis. They describe key molecular alterations in each of the four subtypes using targeted sequencing and genome-wide copy number microarrays and validated these subtypes in independent cohorts in order to provide a consistent and unified framework for further clinical and preclinical translational research.

*Nature Med* 2015; 21: 449

Eitan Israeli

## Capsule

### Host genetic variation in the outcome of HIV infection

In their review looking at the effect of host genetic variation on the outcome of HIV infection, McLaren and Carrington point out that apart from the considerable effect of CCR5, which is the co-receptor for viral entry, and HLA class I, which puts substantial pressure on the virus because of presentation of the viral epitopes, other genetic polymorphisms are probably context dependent. Thus, the positive effects of particular killer immunoglobulin-like receptors are functionally relevant only in the presence of their specific HLA ligands, while genetic variability in a locus that controls the amount of a microRNA that targets the gene encoding an HLA-C molecule is associated with improved control of HIV-1 only in those people with the HLA-C allele (itself polymorphic) with an intact microRNA-binding site. Thus, functional studies and increased insight into the combinatorial traits of the host genetic makeup are essential for understanding the immunological control of HIV.

http://www.nature.com/ni/focus/hiv/index.html

Eitan Israeli

Capsule

## Antibody response to HIV surface envelope antigens

Burton and Mascola discuss antibody responses to the viral surface envelope glycoprotein. Antibodies that do not bind to the native envelope trimer, and thus do not neutralize the virus, develop early during infection. Although these antibodies do not put selective pressure on the virus, they can mediate phagocytosis or sequestration of virions. Antibodies that can bind to envelope trimers appear around 3 months after infection, but they neutralize only the infecting HIV strain, and thus the virus can escape their neutralizing activity. Neutralizing antibodies with a broad spectrum of activity against multiple HIV strains take years to evolve, present a level of breadth, potency and functional features not found in most antibody responses, and have great potential for therapy.

http://www.nature.com/ni/focus/hiv/index.html

Eitan Israeli

Capsule

## HIV and innate effector mechanism

Innate effector mechanisms contribute to the control of viremia and modulate the quality of the adaptive immune response. Altfeld and Gale explore the concerted actions of signaling through pathogen-recognition receptors, activation of cells of the innate immune system, cross-talk between the innate immune system and adaptive immune system, and viral evasion strategies that direct the outcome of HIV infection. The authors discuss the biology of two newly characterized sensors of viral reverse transcription, cGAS and IFI16, and discuss how signaling from immunological sensors can induce either cell activation and an interferon-dependent antiviral state or inflammasome activation and death by pyroptosis, depending on the context of the infected cell and the interaction between the virus and host proteins.

http://www.nature.com/ni/focus/hiv/index.html

Eitan Israeli

## Capsule

### Activation of HIF-1α and LL-37 by commensal bacteria inhibits *Candida albicans* colonization

*Candida albicans* colonization is required for invasive disease. Unlike humans, adult mice with mature intact gut microbiota are resistant to *C. albicans* gastrointestinal (GI) colonization, but the factors that promote *C. albicans* colonization resistance are unknown. Fan et al. demonstrate that commensal anaerobic bacteria – specifically clostridial Firmicutes (clusters IV and XIVa) and Bacteroidetes – are critical for maintaining *C. albicans* colonization resistance in mice. Using *Bacteroides thetaiotamicron* as a model organism, the authors find that hypoxia-inducible factor-1α (HIF-1α), a transcription factor important for activating innate immune effectors, and the antimicrobial peptide LL-37 (CRAMP in mice) are key determinants of *C. albicans* colonization resistance. Although antibiotic treatment enables *C. albicans* colonization, pharmacologic activation of colonic Hif1a induces CRAMP expression and results in a significant reduction of *C. albicans* GI colonization and a 50% decrease in mortality from invasive disease. In the setting of antibiotics, Hif1a and Camp (which encodes CRAMP) are required for *B. thetaiotamicron*-induced protection against *C. albicans* colonization of the gut. Thus, modulating *C. albicans* GI colonization by activation of gut mucosal immune effectors may represent a novel therapeutic approach to prevent invasive fungal disease in humans.

*Nature Med* 2015; 21: 808

Eitan Israeli

## Capsule

### HIV infection controlled in some people

Migueles and Connors use insights drawn from the study of people who control HIV infection for long periods in the absence of therapy, known as 'elite controllers' or 'long-term non-progressors', to discuss the features of a T cell response capable of potent and durable immunological control of HIV-1. The authors summarize arguments indicating that the main controllers of HIV restriction are the CD8+ T cells, that differences in the ability to recognize HIV-infected cells and escape mutations are not a barrier for an effective immune response, and that control of viral replication is due to the quantitative features of the CD8+ T cells response – that is, superior ability to produce multiple cytokines and chemokines, proliferate and kill HIV-infected cells. As these are features of an effective cellular response in many chronic infections, understanding the control mechanisms would represent a substantial advance.

http://www.nature.com/ni/focus/hiv/index.html

Eitan Israeli

## Capsule

### An interactive reference framework for modeling a dynamic immune system

Immune cells function in an interacting hierarchy that coordinates the activities of various cell types according to genetic and environmental contexts. Spitzer et al. developed graphical approaches to construct an extensible immune reference map from mass cytometry data of cells from different organs, incorporating landmark cell populations as flags on the map to compare cells from distinct samples. The maps recapitulated canonical cellular phenotypes and revealed reproducible, tissue-specific deviations. This approach revealed influences of genetic variation and circadian rhythms on immune system structure, enabled direct comparisons of murine and human blood cell phenotypes, and even enabled archival fluorescence-based flow cytometry data to be mapped onto the reference framework. This foundational reference map provides a working definition of systemic immune organization to which new data can be integrated to reveal deviations driven by genetics, environment, or pathology.

Science 2015; 349: doi: 10.1126/science.1259425

Eitan Israeli

## Capsule

### Lymphocyte expansion molecule (LEM) gets T cells the energy they need

During an infection, T cells proliferate extensively to build a sufficient army to defeat the invading pathogen. Carefully regulated changes in metabolism let T cells do this, but the specific nature of these changes is not fully understood. Using forward genetics in mice to screen for genes that regulate T cell immunity, Okoye and co-workers identified a mutation in the gene that encodes a protein they named lymphocyte expansion molecule (LEM). LEM enhanced T cell immunity, including both proliferation and memory cell generation, in response to chronic viral infection. LEM facilitated these changes through effects on mitochondrial respiration.

*Science* 2015; 348: 995

Eitan Israeli

Capsule

## Tumor cells educate the metastatic niche

Why primary tumors metastasize preferentially to particular organs is an important but still unanswered question in cancer biology. The tumor presumably communicates with the target organ, but how this long-distance molecular conversation occurs has been difficult to envisage. The answer may be exosomes, mysterious lipid vesicles that have been turning up in many diverse areas of biomedical research. Costa-Silva and colleagues show that well in advance of metastasis, primary tumor cells secrete exosomes that carry a specific molecular cargo to the target organ. This cargo helps transform the organ into a hospitable niche that supports the growth of metastatic cells. In the case of mouse pancreatic cancer, the exosomes carried a protein that induced a pro-inflammatory, tumor cell-friendly milieu in the liver.

*Nat Cell Biol* 2015; 10.1038/ncb3169

Eitan Israeli

## Capsule

### Receptor in the brain controls breathing

Control of breathing in mammals depends primarily not on sensing oxygen, but on detecting concentrations of carbon dioxide in the blood. Failure of this system can cause potentially deadly sleep apneas. Taking a hint from insects, which use a heterotrimeric guanine nucleotide-binding protein-coupled receptor (GPCR) to sense carbon dioxide, Kumar and co-authors demonstrate that the GPCR GPR4 is essential to control breathing in mice. GPR4 senses protons generated by the formation of carbonic acid in the blood and works with a pH-sensitive potassium channel called TASK-2 in a set of brain cells that control breathing.

*Science* 2015; 348: 1255

Eitan Israeli

## Capsule

### B12 boosts acne via the microbiota

Low doses of vitamin B12 supplements can help acne, but in higher doses the same supplement can cause acne flare-ups. Why? Kang et al. show that transcriptional changes in the resident microbes of the skin enhance B12-induced acne. Supplementing patients with the vitamin reduced the expression of B12-synthesis genes in *Propionibacterium acnes*. This altered the transcriptome of the skin microbiota, driving production of inflammation-inducing porphyrins.

*Sci Transl Med* 2015; 7: 293ra103

Eitan Israeli

Capsule

## Tissue regeneration by a molecule that promotes recovery of the hematopoietic system

Tissue damage can be caused by injury, disease, and even certain medical treatments. There is great interest in identifying drugs that accelerate tissue regeneration and recovery, especially drugs that might benefit multiple organ systems. Zhang et al. describe a compound with this desired activity, at least in mice. SW033291 promotes recovery of the hematopoietic system after bone marrow transplantation, prevents the development of ulcerative colitis in the intestine, and accelerates liver regeneration after hepatic surgery. It acts by inhibiting an enzyme that degrades prostaglandins, lipid-signaling molecules that have been implicated in tissue stem cell maintenance.

*Science* 2015; 348: 10.1126/science.aaa2340

Eitan Israeli

Capsule

## (Mis)matching tumors to immunotherapy

Despite the amazing success stories seen in some patients receiving cancer immunotherapy, the sobering reality is that not all patients or cancer types respond. For instance, colorectal cancer does not respond in the dramatic way that melanomas and other cancers do to the so-called immune checkpoint inhibitors. A subset of colorectal cancers cannot repair mismatched bases in DNA and therefore harbor high levels of somatic mutations. In a small clinical trial, Le et al. found that patients with mismatch repair-deficient colorectal tumors responded more favorably to an immune checkpoint inhibitor than those with mismatch repair-proficient tumors. The greater response observed in the former group is probably due to a higher abundance of mutation-associated neoantigens that boost antitumor immunity.

*N Engl J Med* 2015; 372: 2509

Eitan Israeli

## Capsule

### HIV and restriction factors

Landau and colleagues show how research into accessory proteins expressed by HIV has revealed the ingenious biology of specific host antiviral proteins known as 'restriction factors'. Their review presents fascinating details of the continuous arms race between viral proteins and their restriction factors, by exploring the interaction among three such pairs, Vif-APOBEC3, Vpx-SAMHD1 and Vpu-tetherin, and offers insight into the mechanisms that dictate, restrict or drive viral evolution during the course of adaptation to new hosts.

http://www.nature.com/ni/focus/hiv/index.html

Eitan Israeli

Capsule

## Finding better immunosuppressants

The immunosuppressant cyclosporin A (CsA) prevents organ rejection in transplant patients. CsA inhibits the phosphatase calcineurin and prevents the activation of the NFAT transcription factors, both of which are required for T cell proliferation. However, CsA also prevents calcineurin from binding to other targets, leading to many side effects. Matsoukas and team identified compounds that displaced NFAT from calcineurin-NFAT complexes without inhibiting the activity of the phosphatase. Four of these compounds blocked the expression of NFAT target genes and inhibited the proliferation of human CD4+ T cells, and may be good leads for further testing as immunosuppressants.

*Sci Signal* 2015; 8: ra63

Eitan Israeli

Capsule

## How bladder cells kick out unwelcome intruders

The bladder epithelium acts as the front line of the urinary defense system against microbial infection. Miao and co-authors examined urine samples from humans and mice and the extracellular medium of cultured bladder epithelial cells after infection by uropathogenic *Escherichia coli*. Remarkably, they found numerous viable bacteria encased in host-derived membrane-bound vesicles. Intracellular bacteria were initially taken up by autophagosomes and targeted to lysosomes. The bacteria raised the normally low lysosomal pH, which might be expected to protect them from lysosomal degradation. However, the bladder cells sensed the neutralized lysosomes and exocytosed them, expelling the membrane-encased bacteria. The bacteria were thus incapable of reinfection, and the bladder cells defended against their unwelcome visitors.

*Cell* 2015; 161: 1306

Eitan Israeli

Capsule

## Calming the cytokine storm

The innate immune response is poised to act quickly in the face of pathogenic invaders. However, this priming can incite a cytokine storm: excessive production of inflammatory cytokines that harm the host. Coon et al. report that HECTD2, a ubiquitin E3 ligase, can degrade the anti-inflammatory protein PIAS1, enhancing this inflammatory effect. People with a polymorphism in the *HECTD2* gene exhibit lower inflammation and are protected from acute respiratory distress syndrome. Moreover, a small-molecule inhibitor of HECTD2 reduced lung inflammation in mice. These observations pinpoint HECTD2 as a therapeutic target for inflammation-induced lung injury.

*Sci Transl Med* 2015; 7: 295ra

Eitan Israeli