References

Antiviral immunity via RIG-I-mediated recognition of RNA bearing 5’-diphosphates

Mammalian cells possess mechanisms to detect and defend themselves from invading viruses. In the cytosol, the RIG-I-like receptors (RLRs), RIG-I (retinoic acid-inducible gene 1, encoded by DDx58) and MDA5 (melanoma differentiation-associated gene 5, encoded by IfI17) sense atypical RNAs associated with virus infection. Detection triggers a signaling cascade via the adaptor MAVS that culminates in the production of type I interferons (IFN-α and β), which are key antiviral cytokines. RIG-I and MDA5 are activated by distinct viral RNA structures and much evidence indicates that RIG-I responds to RNAs bearing a triphosphate (ppp) moiety in conjunction with a blunt-ended, base-paired region at the 5’-end. Goubau et al. show that RIG-I also mediates antiviral responses to RNAs bearing 5’-diphosphates (5’pp). Genomes from mammalian reoviruses with 5’pp termini, 5’pp-RNA isolated from yeast L-A virus, and base-paired 5’pp-RNAs made by in vitro transcription or chemical synthesis, all bind to RIG-I and serve as RIG-I agonists. Furthermore, a RIG-I-dependent response to 5’pp-RNA is essential for controlling reovirus infection in cultured cells and in mice. Thus, the minimal determinant for RIG-I recognition is a base-paired RNA with 5’pp. Such RNAs are found in some viruses but not in uninfected cells, indicating that recognition of 5’pp-RNA, like that of 5’ppp-RNA, acts as a powerful means of self/non-self-discrimination by the innate immune system.

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Closing the loop on neuroprosthetic control

Patients paralyzed from a spinal cord injury may soon be able to move their legs more naturally. Current neuromodulation devices cause leg movement by electrically stimulating the spinal cord, but they require constant monitoring and adjustment. Wenger and colleagues created a closed-loop system that auto-tunes the device. The authors stimulated the spinal cords of paralyzed rats and then mapped their leg movements while they walked or climbed stairs, creating integrated feedback and feed-forward models for continuous stepping control.

Sci Transl Med 2014; 6: 255ra133
Eitan Israeli

Inflammatory caspases are innate immune receptors for intracellular LPS

The murine caspase-11 non-canonical inflammasome responds to various bacterial infections. Caspase-11 activation-induced pyroptosis, in response to cytoplasmic lipopolysaccharide (LPS), is critical for endotoxic shock in mice. The mechanism underlying cytosolic LPS sensing and the responsible pattern recognition receptor are unknown. Shi et al. show that human monocytes, epithelial cells and keratinocytes undergo necrosis upon cytoplasmic delivery of LPS. LPS-induced cytotoxicity was mediated by human caspase-4 that could functionally complement murine caspase-11. Human caspase-4 and the mouse homologue caspase-11 (caspase-4/11) and also human caspase-5, directly bound to LPS and lipid A with high specificity and affinity. LPS associated with endogenous caspase-11 in pyroptotic cells. Insect-cell purified caspase-4/11 underwent oligomerization upon LPS binding, resulting in activation of the caspases. Underacylated lipid IVA and lipopolysaccharide from Rhodobacter sphaeroides (LPS-RS) could bind to caspase-4/11 but failed to induce their oligomerization and activation. LPS binding was mediated by the CARD domain of the caspase. Binding-deficient CARD-domain point mutants did not respond to LPS with oligomerization or activation and failed to induce pyroptosis upon LPS electroporation or bacterial infections. The function of caspase-4/5/11 represents a new mode of pattern recognition in immunity and also an unprecedented means of caspase activation.

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Eitan Israeli
the philtral columns (B), width of the nasal sills (C), distance between the peak of Cupid's bow on each side to the lowest point on Cupid's bow (D), and vertical distance between the superior point of the philtral column (directly below the columna) and the inferior border of the upper lip (E).

Of the 23 patients evaluated approximately 1 year post-surgery, it was found that four of the five parameters showed minimal differences between the healthy and corrected sides (average difference of 10% or less), while one parameter failed to sustain a difference of 10% or less (namely, parameter B: the average difference of 10% or less). When comparing corrected and healthy sides for this particular parameter, the average difference between the sides was approximately 11%, which was not satisfactory given the decided-upon threshold. Furthermore, when applying the Wilcoxon signed rank test, parameter B had a P value less than 0.05 and thus reflected a statistically significant difference between the healthy and corrected sides of the philtral columns.

CONCLUSIONS
Despite the many surgical techniques available for unilateral cleft lip repair, the predominance of one method over the other is commonly due to surgical preference rather than proven superiority. This study aims to provide insight into the predominantly successful results obtained when applying the technique of Kernahan and Bauer with primary rhinoplasty. Five anatomical parameters were chosen and average differences between healthy and corrected sides for each parameter were measured. Four of the five parameters exhibited “surgical success” (difference of ≤ 10% between healthy and corrected sides), while one parameter failed to remain within this 10% range. Despite the need for a larger study group in order to achieve better statistical and conclusive results, the surgical technique described here is largely successful in achieving overall symmetry of the upper lip and nostril regions.

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Capsule
Beware of T cells that don’t know how to stop
During an infection, T cells divide extensively and secrete proteins that can severely damage tissues. But T cells know when to stop – they express proteins on their surface such as CTLA4, which put on the brakes. Kuehn et al. report genetic evidence of the importance of CTLA4 in humans. They identified six patients with mutations in one copy of CTLA4. Patients presented with symptoms of an overzealous immune response, with immune cells infiltrating their organs. The findings support the idea that CTLA4 tells the immune system when enough is enough.

Science 2014; 345: 1623
Eitan Israeli
Prospective studies are needed to make more efficient use of inflammatory markers. In the meantime, we recommend that clinicians consider the possibility of intrinsic high CRP levels when treating children with primary herpetic gingivostomatitis in whom there is no other evidence of a bacterial infection, and consider withholding antibiotic use in such cases.

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**Capsule**

**Preventing vascular scarring after surgery**

The endothelium that lines blood vessels can undergo a change called the endothelial-to-mesenchymal transition (EndMT), which can cause vessel “scarring.” Such scarring limits the success of surgical procedures that require blood vessel grafting, including, for example, heart transplantation or coronary bypass surgery. Chen et al. found that mice lacking FGFR1 in endothelial cells showed increased EndMT after blood vessel grafting. Moreover, arteries from patients who had rejected heart transplants had lower levels of FGFR1 than those from normal individuals. Thus, enhancing FGFR1 activity could limit vascular scarring in heart disease patients undergoing surgery.

*Sci Signal* 2014; 7: ra90
Eitan Israeli

**Capsule**

**The early spread and epidemic ignition of HIV-1 in human populations**

Thirty years after the discovery of HIV-1, the early transmission, dissemination and establishment of the virus in human populations remain unclear. Using statistical approaches applied to HIV-1 sequence data from central Africa, Faria et al. show that from the 1920s Kinshasa (in what is now the Democratic Republic of Congo) was the focus of early transmission and the source of pre-1960 pandemic viruses elsewhere. Location and dating estimates were validated using the earliest HIV-1 archival sample, also from Kinshasa. The epidemic histories of HIV-1 group M and non-pandemic group O were similar until ~1960, after which group M underwent an epidemiological transition and outpaced regional population growth. These results reconstruct the early dynamics of HIV-1 and emphasize the role of social changes and transport networks in the establishment of this virus in human populations. Thus, around 1960, rail links promoted the spread of the virus to mining areas in southeastern Congo and beyond. Ultimately, HIV crossed the Atlantic in Haitian teachers returning home. From those early events, a pandemic was born.

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and therefore will facilitate better medical practice concerning suspected meniscus injuries in this population.

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Capsule
Mapping human drug targets in the cell
To understand both the beneficial and the side effects of a drug, one would need to know its full binding profile to all cellular proteins. Savitski and colleagues take significant steps toward meeting this daunting challenge. They monitored the unfolding or “melting” of over 7000 human proteins and measured how small-molecule binding changes individual melting profiles. As a proof of principle, over 50 targets were identified for an inhibitor known to bind a broad spectrum of kinases. Two cancer drugs, vemurafib and alectinib, are known to have a side effect of photosensitivity. The thermal profiling approach identified drug-protein interactions responsible for these side effects.

Science 2014; 346: 10.1126/science.1255784
Eitan Israeli

Capsule
Teaching tolerance stops the bleeding
People with hemophilia A lack a clotting factor [factor VIII (FVIII)] that stops wounds from bleeding. Regular infusions of FVIII can help, but up to 30% of patients make antibodies that attack this treatment. To prevent this, Sherman et al. developed a way to teach the immune system to tolerate FVIII, rather than make antibodies against it. For 2 months, the researchers fed mice leaves from plants engineered to produce fragments of FVIII. The fragments, safely encapsulated in plant cells, entered the area of the gut where immune cells reside and reduced the immune response to FVIII. Treated mice made fewer antibodies against FVIII, suggesting that teaching (immune) tolerance may allow FVIII to stick around and do its job.

Blood 2014; 123: 10
Eitan Israeli

Capsule
Immune cells and bugs make a sugary coat
Epithelial cells line the intestinal tract and help to keep the peace between our immune system and our trillions of gut microbes. Such peacekeeping requires glycosylated proteins (proteins with attached carbohydrate chains) present on the epithelial cell surface, but how glycosylation occurs is unclear. Goto et al. found that fucosylation (a type of glycosylation) of gut epithelial cells in mice requires gut. This process also requires innate lymphoid cells there, which produce the cytokines interleukin-22 and lymphotoxin, presumably in response to microbial signals. These cytokines signal epithelial cells to add fucose to membrane proteins, which allows the détente between microbes and immune cells to continue.

Science 2014; 345: 10.1126/science.1254009
Eitan Israeli
Capsule

**Illuminating brain stimulation therapy**

Stroke, the disruption in blood supply to the brain, affects approximately 15 million people worldwide each year. With few treatment options, strokes leave one-third of their sufferers permanently disabled. One promising therapy is magnetic stimulation of the brain but it is relatively non-specific. To determine which cell types may promote recovery Cheng and group engineered mice to express light-activated protein receptors in their neurons. They then used light to activate specific neurons and found that while stimulating neurons in the ipsilesional primary motor cortex had no effect on healthy mice, it did help mice recover after stroke. Stimulating neurons in a targeted manner may be a promising therapy for stroke patients and cause fewer side effects.

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**Interleukin-22 alleviates metabolic disorders and restores mucosal immunity in diabetes**

The connection between an altered gut microbiota and metabolic disorders such as obesity, diabetes and cardiovascular disease is well established. Defects in preserving the integrity of the mucosal barriers can result in systemic endotoxemia that contributes to chronic low grade inflammation, which further promotes the development of metabolic syndrome. Interleukin (IL)-22 exerts essential roles in eliciting antimicrobial immunity and maintaining mucosal barrier integrity within the intestine. Wang et al. investigated the connection between IL-22 and metabolic disorders. They found that the induction of IL-22 from innate lymphoid cells and CD4+ T cells is impaired in obese mice under various immune challenges, especially in the colon during infection with *Citrobacter rodentium*. While innate lymphoid cell populations are largely intact in obese mice, the upregulation of IL-23, a cytokine upstream of IL-22, is compromised during the infection. Consequently, these mice are susceptible to *C. rodentium* infection, and both exogenous IL-22 and IL-23 are able to restore the mucosal host defense. Importantly, they further unveiled unexpected functions of IL-22 in regulating metabolism. Mice deficient in IL-22 receptor and fed with a high fat diet are prone to developing metabolic disorders. Strikingly, administration of exogenous IL-22 in genetically obese leptin-receptor-deficient (db/db) mice and mice fed a high fat diet reverses many of the metabolic symptoms, including hyperglycemia and insulin resistance. IL-22 shows diverse metabolic benefits, as it improves insulin sensitivity, preserves gut mucosal barrier and endocrine functions, decreases endotoxemia and chronic inflammation, and regulates lipid metabolism in liver and adipose tissues. In summary, they identified the IL-22 pathway as a novel target for therapeutic intervention in metabolic diseases.

*Nature* 2014; 514: 237

Eitan Israeli


**Capsule**

**Progranulin protects against amyloid β deposition and toxicity in Alzheimer’s disease mouse models**

Haploinsufficiency of the progranulin (PGRN) gene (GRN) causes familial frontotemporal lobar degeneration (FTLD) and modulates an innate immune response in humans and in mouse models. GRN polymorphism may be linked to late-onset Alzheimer’s disease (AD). However, the role of PGRN in AD pathogenesis is unknown. Minami et al. show that PGRN inhibits amyloid β (Aβ) deposition. Selectively reducing microglial expression of PGRN in AD mouse models impaired phagocytosis, increased plaque load threefold and exacerbated cognitive deficits. Lentivirus-mediated PGRN overexpression lowered plaque load in AD mice with aggressive amyloid plaque pathology. Aβ plaque load correlated negatively with levels of hippocampal PGRN, showing the dose-dependent inhibitory effects of PGRN on plaque deposition. PGRN also protected against Aβ toxicity. Lentivirus-mediated PGRN overexpression prevented spatial memory deficits and hippocampal neuronal loss in AD mice. The protective effects of PGRN against Aβ deposition and toxicity have important therapeutic implications. The authors propose enhancing PGRN as a potential treatment for PGRN-deficient FTLD and AD.

*Nature Med* 2014; 20: 1157

Eitan Israel

**Capsule**

**Regulation of astrocyte activation by glycolipids drives chronic CNS inflammation**

Astrocytes have complex roles in health and disease, thus it is important to study the pathways that regulate their function. Mayo and co-researchers report that lactosylceramide (LacCer) synthesized by β1,4-galactosyltransferase 6 (B4GALT6) is upregulated in the central nervous system (CNS) of mice during chronic experimental autoimmune encephalomyelitis (EAE), a model of multiple sclerosis (MS). LacCer acts in an autocrine manner to control astrocyte transcriptional programs that promote neurodegeneration. In addition, LacCer in astrocytes controls the recruitment and activation of microglia and CNS-infiltrating monocytes in a non-cell autonomous manner by regulating production of the chemokine CCL2 and granulocyte-macrophage colony-stimulating factor (GM-CSF), respectively. The authors also detected high B4GALT6 gene expression and LacCer concentrations in CNS MS lesions. Inhibition of LacCer synthesis in mice suppressed local CNS innate immunity and neurodegeneration in EAE and interfered with the activation of human astrocytes in vitro. Thus, B4GALT6 regulates astrocyte activation and is a potential therapeutic target for MS and other neuroinflammatory disorders.

*Nature Med* 2014; 20: 1147

Eitan Israel

“Those who do not want to imitate anything, produce nothing”

Salvador Dali (1904-1989), Spanish Catalan surrealist painter. Dali was highly imaginative. He enjoyed indulging in unusual and grandiose behavior, such that his eccentric manner and attention-grabbing public actions sometimes drew more attention than his artwork.
sequencing for a single gene disorder is that it reduces the risk of missing an uncommon but severe mutation. In the future one might recommend whole exome sequencing (i.e., of the protein-coding genes), although admittedly this might engender more information than requisite for an informed decision (informed consent is indeed required) regarding family planning. Clearly this is a challenge that will confront clinicians in the near future as the sum total of informatics derived from sequencing multiplies exponentially.

But, finally, this is no longer the entire story that can be attached to identification of mutations causing Gaucher disease. In the past decade or so, the medical community in general has become aware of the added risk for Parkinson disease not only among patients with Gaucher disease [13] but also among carriers with a single mutation in the β-glucocerebrosidase gene [14]. The presence of a “severe” mutation such as 84GG or L444P in a single copy is associated with a greater risk for an early-onset form of Parkinson disease than the risk associated with “milder” mutations [15]. Thus, the “mild” N370S mutation that had heretofore been considered “neuroprotective” (by definition making the presence of the N370S mutation synonymous with type 1 Gaucher disease), because it has never been identified in patients who suffer from neurological signs (i.e., types 2 and 3 Gaucher disease), is now also recognized as conferring a 2.2-fold increased risk of Parkinson disease [15] among patients and among carriers but the risk is greater for “severe” mutations. This unexpected association between a rare genetic disease and a common neurodegenerative disorder [16] introduces further complexities in the approach of genetic counseling to family planning [17]. While the challenges are clear, the means to address them are not intuitive. Our classic thinking about the clinical ramifications of carrying a single mutation for an autosomal recessive disorder is itself being challenged. The implications of being a carrier of Gaucher disease today may have more devastating implications (i.e., risk for Parkinson disease) than Gaucher disease itself, and this issue is making genetic counseling for Gaucher disease all the more complex.

It is to be hoped that the technology that provides us with pellucid information about our individual genetic codes will also support its clinical explication and application.

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References

Capsule

Mutant protein in tumors hits the DEK

Cancer genome sequencing projects have uncovered a multitude of mutations in human tumors. Understanding whether and how these mutations contribute to tumor development and progression could ultimately lead to new therapies. Theurillat et al. studied the protein product of a gene that is recurrently mutated in prostate cancer. Normally this protein helps attach a biochemical tag to cellular proteins that marks them for degradation. The new work shows that the tumor-associated mutant protein loses this tagging ability, which results in the stabilization of a handful of cellular proteins that would otherwise be degraded. One of the most intriguing of these proteins was DEK, which helps prostate cancer cells invade into surrounding tissue. Science 2014; 345: 85

Eitan Israeli
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Capsule
Continuous requirement for the TCR in regulatory T cell function
Forko3+ regulatory T cells (Treg cells) maintain immunological tolerance, and their deficiency results in fatal multi-organ autoimmunity. Although heightened signaling via the T cell antigen receptor (TCR) is critical for the differentiation of Treg cells, the role of TCR signaling in Treg cell function remains largely unknown. Levine et al. demonstrated that inducible ablation of the TCR resulted in Treg cell dysfunction that could not be attributed to impaired expression of the transcription factor Foxp3, decreased expression of Treg cell signature genes or altered ability to sense and consume interleukin 2 (IL-2). Instead, TCR signaling was required for maintaining the expression of a limited subset of genes comprising 25% of the activated Treg cell transcriptional signature. These results reveal a critical role for the TCR in the suppressor capacity of Treg cells. Nature Immunol 2014; 15: 1070

Eitan Israeli

Capsule
Induction of the nuclear receptor PPAR-γ by the cytokine GM-CSF is critical for the differentiation of fetal monocytes into alveolar macrophages
Tissue-resident macrophages constitute heterogeneous populations with unique functions and distinct gene-expression signatures. While it has been established that they originate mostly from embryonic progenitor cells, the signals that induce a characteristic tissue-specific differentiation program remain unknown. Schneider and team found that the nuclear receptor PPAR-γ determined the perinatal differentiation and identity of alveolar macrophages (AMs). In contrast, PPAR-γ was dispensable for the development of macrophages located in the peritoneum, liver, brain, heart, kidneys, intestines and fat. Transcriptome analysis of the precursors of AMs from newborn mice showed that PPAR-γ conferred a unique signature, including several transcription factors and genes associated with the differentiation and function of AMs. Expression of PPAR-γ in fetal lung monocytes was dependent on the cytokine GM-CSF. Therefore, GM-CSF has a lung-specific role in the perinatal development of AMs through the induction of PPAR-γ in fetal monocytes. Nature Immunol 2014; 15: 1026

Eitan Israeli
Artificial sweeteners induce glucose intolerance by altering the gut microbiota

Non-caloric artificial sweeteners (NAS) are among the most widely used food additives worldwide, regularly consumed by lean and obese individuals alike. NAS consumption is considered safe and beneficial owing to their low caloric content, yet supporting scientific data remain sparse and controversial. Suez et al. from the Weizmann Institute of Science demonstrated that consumption of commonly used NAS formulations drives the development of glucose intolerance through induction of compositional and functional alterations to the intestinal microbiota. These NAS-mediated deleterious metabolic effects are abrogated by antibiotic treatment and are fully transferable to germ-free mice upon fecal transplantation of microbiota configurations from NAS-consuming mice, or of microbiota anerobically incubated in the presence of NAS. The authors identified NAS-altered microbial metabolic pathways that are linked to host susceptibility to metabolic disease and demonstrated similar NAS-induced dysbiosis and glucose intolerance in healthy human subjects. These results link NAS consumption, dysbiosis and metabolic abnormalities, thereby calling for a reassessment of massive NAS usage.

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Eitan Israeli
submucosa, rupturing the epithelium. The submucosal layer was markedly expanded by an increase in the number of smooth muscle cells, where islands of smooth muscle cells were present in a disorganized fashion. There was no sign of malignancy. On the grounds of MCTD, pneumonitis appeared which progressed to mild pulmonary fibrosis. After 21 years of MCTD diagnosis the patient developed AIH.

**COMMENT**

Generally, liver enzyme abnormalities are relatively common among patients with systemic autoimmune diseases, where hepatic injury from hepatotoxic drugs, coincidental viral hepatitis, is a common etiologic factor. Previously, AIH associated with MCTD, showing HLA-DR4 association, was only described in a few cases in the literature.

AIH can be associated with diffuse interstitial pneumonitis, mediated by anti-smooth muscle antibodies (aSMA) or an immunocomplex-mediated mechanism. The increase in smooth muscle thickness is due primarily to the presence of the aSMA, which can provoke local inflammation, leading to subsequent reactive proliferation. [4]. In our patient, azathioprine, administered for AIH, also effectively ameliorated the symptoms of ILD. In chronic fibrotic lung disorders, the proliferation of smooth muscle cells has been shown, probably derived from myofibroblasts in the interstitium, which produce collagen and other matrix proteins, proteases, growth factors and cytokines, affecting alveolar epithelial structures [4,5]. Thus they are able to perpetuate fibrotic processes [5].

Patients with MCTD associated with AIH usually respond well to steroid therapy in combination with azathioprine. In our patient, serum transaminase levels began to decline after 2 weeks of steroid and azathioprine therapy and normalized in 5 months.

In MCTD, the presence of aSMA, indicating AIH, may induce myomatosous lesions and smooth muscle hypertrophy in the lungs, which may eventually lead to pulmonary fibrosis. The proper and early diagnosis and assessment of solid organ involvement is pivotal to initiate appropriate and effective therapy in MCTD patients and decelerate pathogenetic processes and organ damage.

**References**


**Capsule**

**Chaperone-mediated autophagy regulates T cell responses through targeted degradation of negative regulators of T cell activation**

Chaperone-mediated autophagy (CMA) targets soluble proteins for lysosomal degradation. Valdor et al. found that CMA was activated in T cells in response to engagement of the T cell antigen receptor (TCR), which induced expression of the CMA-related lysosomal receptor LAMP-2A. In activated T cells, CMA targeted the ubiquitin ligase Itch and the calcineurin inhibitor RCAN1 for degradation to maintain activation-induced responses. Consequently, deletion of the gene encoding LAMP-2A in T cells caused deficient in vivo responses to immunization or infection with *Listeria monocytogenes*. Impaired CMA activity also occurred in T cells with age, which negatively affected their function. Restoration of LAMP-2A in T cells from old mice resulted in enhancement of activation-induced responses. These findings define a role for CMA in regulating T cell activation through the targeted degradation of negative regulators of T cell activation.

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**“The whole purpose of education is to turn mirrors into windows”**

Sydney J. Harris (1917-1986), American journalist for the *Chicago Daily News* and later the *Chicago Sun-Times*. His weekday column “Strictly Personal” was syndicated in many newspapers throughout the United States and Canada

**“I have always found that mercy bears richer fruits than strict justice”**

Abraham Lincoln (1809-1865), 16th U.S. President, who served from March 1861 until his assassination in April 1865. Lincoln led the United States through its Civil War — its bloodiest war and its greatest moral, constitutional and political crisis. In doing so, he preserved the Union, abolished slavery, strengthened the federal government, and modernized the economy