Philosophically, Edith Stein initiated a new chapter in phenomenology, a new branch in intellectuality. This was empathy, where an individual identifies with the other, feeling the other's feelings rather than simply feeling sympathy or pity for the other's misfortune. The thesis, in the form of a book, comprises over 200 pages of disputation and is highly intellectual. It would be the ideal concept in the doctor-patient relationship, demanding that the physician be empathically connected with his or her patient. If translated into clinical practice, this concept would lead to an intense psychological connection, enabling the total understanding of the other's experience.

CONCLUSIONS

What is my message? None, other than commemorative. After their emancipation in the second half of the 19th century, Jews flooded the European universities – first as students and then as teachers. They brought a veritable revolution to science. For this they were sometimes honored, but often envied, persecuted, exiled and in some cases eliminated.

It is incumbent on us to preserve their memory.

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Capsule

T cells target peptide combos

One of the enduring mysteries of autoimmunity is the identity of the specific proteins targeted by autoimmune T cells. Delong et al. used mass spectrometry to elucidate the peptide targets of autoimmune T cells isolated from a mouse model of type 1 diabetes. T cells targeted hybrid peptides formed by the covalent linking of a peptide derived from pro-insulin to other peptides derived from proteins found in pancreatic beta cells. T cells isolated from the pancreatic islets of two individuals with type 1 diabetes also recognized such hybrid peptides, suggesting that they may play an important role in driving disease.

Science 2016; 351: 711

Eitan Israeli

Capsule

The real cause of cancer in Fanconi anemia

Mutations that covalently link the two strands of the DNA double helix together are highly toxic, because they block DNA replication. Failure to repair such damage results in Fanconi anemia. The Fan1 nuclease was thought to promote crosslink repair. Lachaud et al. show that the Fan1 nuclease is not involved in the repair of such crosslinks. Instead, it acts to protect stalled replication forks by restraining their progress and thereby prevents chromosomal abnormalities.

Science 2016; 351: 846

Eitan Israeli

neonatal period. This situation presents yet another important public health problem, namely the need to prevent intra-uterine underfeeding and postnatal overfeeding, as both have been proven to lead to obesity and diabetes in adolescent and adult life. The same applies to sarcopenia and osteopenia [7,16].

More recently two significant publications have appeared, so far online only, adding further information on the present topic. The first one re-affirmed the effect of starvation on bone health in survivors of the Holocaust [17] and the second found conditions in this population similar to anorexia nervosa.

The articles cited represent only part of the Israeli contribution to this extremely important new field of medicine: the metabolic programming of adult diseases [7-9] and its associated life course approach to chronic diseases [2], a contribution also acknowledged by international scientists [18,19].

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Capsule

Protection from HIV by engineered CMV

One promising approach toward an HIV-1 vaccine involves infecting people with cytomegalovirus (CMV) engineered to express proteins from HIV-1. This approach, which works by eliciting virus-killing CD8+ T cells, provides robust protection in non-human primate models. Hansen et al. discovered why this approach is so effective. Normally, peptide antigens presented by major histocompatibility complex-1a (MHC-Ia) activate CD8+ T cells. In vaccinated monkeys, however, CD8+ T cells reacted to peptide antigens presented by MHC-E molecules instead. Moreover, MHC-E could present a much wider range of peptides than MHC-Ia.

Science 2016; 351: 714
Eitan Israeli

Capsule

A T cell cause for autism?

The causes of autism spectrum disorder (ASD) are complex and not entirely clear. Alterations in the mother's immune system during pregnancy, especially during key early periods of fetal neurodevelopment, may play a role. Choi et al. provided infectious or inflammatory stimuli to pregnant mice, which resulted in offspring exhibiting behaviors reminiscent of ASD. A subset of T helper cells that make the cytokine interleukin-17a in the mothers caused cortical defects and associated ASD behaviors in offspring. Therapeutic targeting of interleukin-17a during gestation reduced ASD symptoms in offspring.

Science 2016; 351: 933
Eitan Israeli

Appendix 1. Study trip plan

Seven-hour visit to Auschwitz-Birkenau		
Auschwitz	**Places**	**Readings**
	Main entrance	Testimony of Jacques Stroumsa [4], violinist in the inmates' orchestra
	Visit to the exhibitions: Block 4. *Extermination* Block 5. *Evidence of crimes* Block 6-7. *The life of prisoners* Block 7. *Living and sanitary conditions* Block 11. *The Death Block*	
	Block 10. *Medical experiments*	Testimony of Tadeusz Kopyta [5], víctim of typhus experiments
	Block 21. *Hospital*	Testimony of Dr. Ella Lingens [6]: selection of patients for the gas chambers
	Block 27. *Jewish Holocaust* Block 13. *Genocide of Roma people (gypsies)* Gas chamber I. Crematorium	
Birkenau	Block 30. *Sterilization experiments*	Testimony of Mrs. Mazaltov Behar Mordoh [7], victim of sterilization experiments
	Twins experiment block	Testimony of Mrs. Eva Mozes Kor [8], victim of experiments with twins
	Dwarfs experiment block	Testimony of Mrs. Perla Ovitz [9], victim of experiments with dwarfs
	Block at the women's camp	Testimony of Dr. Gisella Perl [10]: ethical dilemmas of imprisoned doctors
	The unloading ramp *(Judenrampe)*	Testimony of Mrs. Violeta Friedman [11]: selection at the platform for forced labor
	Memorial at the Gypsy Families camp	Testimony of Dr. Lucie Adelsberger [12]: the life at Gypsy Families camp
	Gas chamber II. Crematorium	Testimony of Dr. Miklos Nyszli [13], Dr. Mengele´s assistant
	Central camp sauna building. Family photographic exhibition	
	International monument to victims	Poems *Remember (Yizkor)* by Abba Kovner [14], and *Auschwitz* by Charlotte Delbo [15]
Six-hour visit to Krakow		
Krakow	**Places**	**Readings**
In the morning	Visit to the Museum at Oskar Schindler's Factory	
	Visit to the old Jewish District (Kazimiercz)	
	Visit to the old hospitals at Krakow Ghetto	Testimony of Dr. Avraham Veinreb [16]: ethical dilemmas of Jewish doctors in the ghettos
	Heroes of the Ghetto Square (Old Jewish Ghetto)	Jewish doctors in the Warsaw Ghetto: The underground medical school [17], Hunger disease research [18]
	"Under the Eagle" pharmacy in the Krakow Ghetto	Poem dedicated to Tadeusz Pankiewicz [19]: the Righteous Among the Nations
	Plazsow Camp	Poem: *If This is a Man* by Primo Levi [20]
In the afternoon	Jagiellonian University	Sonderaktion Krakau: The story of Polish professors taken to Sachsenhausen concentration camp (Berlin).
	Krakow Old City	
	Wavel Castle	

Capsule

Unleashing natural killer cells

The cytokine transforming growth factor-beta (TGFβ) can resolve inflammation and prevent autoimmunity, but it can also inhibit anti-tumor immune responses. Viel and group found that TGFβ signaling suppressed the activity of a metabolism-regulating kinase in mouse and human natural killer (NK) cells, rendering them less cytotoxic towards tumor cells. NK cells deficient in a TGFβ receptor subunit decreased metastasis in mice, suggesting that enhancing metabolism in NK cells may provide a therapeutic strategy to kill cancer cells.

Sci Signal 2016; 9: ra19

Eitan Israeli

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Capsule

Powering down yields a healthier heart

In hypertrophic cardiomyopathy (HCM), the heart muscle enlarges and becomes progressively less efficient at pumping blood. HCM can be caused by mutations in components of the sarcomere (the heart's contractile unit), most notably myosin. Hypercontractility is among the earliest heart disturbances seen in mice carrying these myosin mutations, implying that the mutations inflict their damage by increasing myosin's power production. Green et al. identified a small molecule that binds to myosin and inhibits its activity. When orally administered to young mice, the molecule prevented the development of several hallmark features of HCM without adversely affecting skeletal muscle.

Science 2016; 351; 617

Eitan Israeli

Capsule

Potassium loss stresses out kidney cells

African-Americans are five times more likely than Caucasians to develop advanced kidney disease. Two sequence variants in a gene called *APOL1* confer most of this elevated risk. Scientists think that the prevalence of these sequence variants in people of African descent probably arose because they also confer protection against parasite infection. The *APOL1* gene encodes the protein apolipoprotein L1, which forms ion pores in the kidney cell membrane, but how the risk variants cause kidney disease remains a mystery. Studying cultured kidney cells, Olabisi et al. found that the *APOL1* risk variants cause excessive loss of potassium from the cells. This in turn activates stress-activated enzymes called kinases, which ultimately leads to kidney cell death.

Proc Natl Acad Sci USA 2016; 113: 830

Eitan Israeli

Capsule

Translating stem cell quiescence

Many tissues harbor a reservoir of stem cells that remain quiescent but can be activated as needed for growth and repair. How cells enter, maintain, and then exit quiescence is incompletely defined. Studying skeletal muscle stem cells in mice, Zismanov et al. reveal a role for translational repression. Stem cell quiescence requires phosphorylation (a post-translational protein modification) of the translation initiation factor eIF2α at a particular amino acid residue; dephosphorylation (removal of the phorphoryl group) or blocking phorphorylation causes muscle stem cells to exit quiescence and differentiate. Moreover, inhibiting dephosphorylation leads muscle stem cells to self-renew and regenerate. Manipulating eIF2α phosphorylation may represent a method to regulate the regenerative capacity of stem cells for clinical use.

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Eitan Israeli

Gastric Polyp Growth during Endoscopic Surveillance for Esophageal Varices or Barrett's Esophagus

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ABSTRACT: **Background:** We recently observed patients with chronic liver disease (CLD) or chronic reflux symptoms (CRS) who developed gastric polyps (GPs) while undergoing surveillance gastroscopies for the detection of esophageal varices or Barrett's esophagus, respectively.

Objectives: To identify risk factors for GP growth and estimate its growth rate.

Methods: GP growth rate was defined as the number of days since the first gastroscopy (without polyps) in the surveillance program, until the gastroscopy when a GP was discovered.

Results: Gastric polyp growth rates in CLD and CRS patients were similar. However, hyperplastic gastric polyps (HGPs) were detected more often (87.5% vs. 60.5%, $P = 0.051$) and at a higher number (2.57 ± 1.33 vs. 1.65 ± 0.93, $P = 0.021$) in the CLD patients. Subgroup analysis revealed the following findings only in CLD patients with HGPs: (i) a positive correlation between the GP growth rate and the patient's age; the older the patient, the higher the GP growth rate ($r = 0.7$, $P = 0.004$). (ii) A negative correlation between the patient's age and the Ki-67 proliferation index value; the older the patient, the lower the Ki-67 value ($r = -0.64$, $P = 0.02$). No correlation was detected between Ki-67 values of HGPs in CLD patients and the presence of portal hypertension, infection with *Helicobacter pylori*, or proton pump inhibitor use.

Conclusions: In comparison with CRS patients, CLD patients developed HGPs more often and at a greater number. Young CLD patients may have a tendency to develop HGPs at a faster rate than elderly CLD patients.

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KEY WORDS: hyperplastic gastric polyp (HGP), fundic gland polyp (FGP), *Helicobacter pylori*, proton pump inhibitor (PPI), Ki-67, chronic liver disease (CLD)

Gastric polyps (GPs) are lesions that originate from the gastric epithelium and protrude into the gastric lumen. They are usually asymptomatic and in most patients are incidentally discovered during an esophagogastroduodenoscopy (EGD). With expanding indications for EGD, GPs are being encountered with increasing frequency [1,2]. Histologically, although there is a wide variety of GP types, the most prevalent are hyperplastic gastric polyp (HGP) and fundic gland polyp (FGP) [1-4]. The pathogenesis of HGPs and FGPs is poorly understood; however, it is believed to be a multifactorial process that includes chronic gastric mucosal injury from various etiologies, including infection with *Helicobacter pylori* and hypergastrinemia [5-10]. Infection with *H. pylori* is associated with mucosal injury and inflammation, as well as epithelial healing with an increase in epithelial cell turnover, regeneration and development of hyperplastic tissue that may persist and progress to the development of HGP [5,6]. Secondary hypergastrinemia caused by chronic *H. pylori* infection and/or chronic proton pump inhibitor (PPI) use has trophic effects on the gastric mucosa and may facilitate the growth of HGPs [5,6].

Following the widespread use of PPIs, a rise in the prevalence of FGPs has been documented [8-10]. It had been estimated that chronic PPI treatment (over 48 months) leads to a fivefold increase in the development of FGPs [7,8,11].

In a survey of 50,071 EGDs that were performed in our institution from 1994 to 2009, an increase in the GP prevalence was detected [12]. In patients with either chronic liver disease (CLD) or chronic reflux symptoms (CRS) who were undergoing surveillance EGD for the presence of either esophageal varices or Barrett's esophagus respectively, GP development was noticed during the study period. Based on these findings it was hypothesized that it would be possible to estimate the growth rate of GPs in CRS and CLD patients and to identify risk factors for GP growth.

PATIENTS AND METHODS

In our previous work [12] we retrospectively analyzed all pathologic material extracted from 50,071 EGDs that were performed at the Hadassah Medical Center in Jerusalem between January 1994 and December 2009. A database of demographic, clinical and pathologic data of 727 individuals found to have GPs was generated [12]. In the present work, we searched this database for patients with CLD or CRS who were discovered to have a GP while undergoing surveillance EGDs for the presence of either esophageal varices or Barrett's esophagus, respectively. Individuals who were found to have a GP during the surveillance program and had at least one previous EGD without a GP were selected for this study. The decision to perform the surveil-

DISCUSSION

This male predominated extreme water sport is potentially dangerous, with musculoskeletal injuries – ranging from minor injuries such as ankle sprain to major fractures such as femur and acetabulum – being most common among the athletes. Most musculoskeletal injuries are injuries to the lower limbs, which is supported by previous studies. A re-injury rate of 25% could not be overlooked, but as noted above most are isolated injuries rather than polytrauma.

Our results reveal only a tip of the iceberg, since most injuries are not recorded properly in the emergency department's electronic records or in the database of the National Center for Trauma and Emergency Medicine Research. Furthermore, our internet appeal was not met with much enthusiasm.

In our opinion, the main reason for under-reporting of such injuries in the hospitals' digital records is the lack of specific codes for kite surfing injuries in the ICD-9 injuries list, resulting in an underestimated prevalence of kite surfing injuries. This is true for many other athletic activities. Additionally, cases reported to the National Center for Trauma and Emergency Medicine Research are only of injuries requiring hospitalization. This contributes to lack of accurate reporting.

CONCLUSIONS

Based on our findings, we advise the following precautions:

- Head helmets: Severe head trauma reported here highlights the need to wear helmets as a standard safety precaution. Commercially made helmets are now available at low cost; they are easy to wear and do not narrow the surfer's visual field.
- Impact and life vests: Chest injuries, including rib fractures, stress the importance of wearing these life-saving items, which in addition to preventing direct chest injury keep the surfer afloat. A surfer afloat may also capture the attention of fellow surfers.
- Wetsuits: The importance of wetsuits cannot be overemphasized especially between seasons when athletes tend to dismiss their use as unnecessary. Wetsuits can save lives when an injured surfer is waiting for rescue while immersed in water for a long time.
- Other precautions: Although most injuries are of the musculoskeletal system, there are no specific precautions that can be taken. Hence, adjustment of the surfer's skill level to the current weather conditions, using a fast-release system to detach from the kite, and safety hook knives to cut the strings, are all necessary to prevent or lower injury rates.
- If needed, gloves, foot protection, and of course sunscreen, should be used.

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Capsule

Keeping immune cells quiet on a diet

Over thousands of years, our immune system has evolved to distinguish self from foreign, perpetrating attacks on microbes but not ourselves. Given this, why do we fail to mount an immune response against most of the food we eat? Kim et al. compared normal mice, mice lacking microbes, and mice lacking microbes that were fed an elemental diet devoid of dietary antigens. Dietary antigens normally induced a population of suppressive immune cells called regulatory T cells in the small intestine. The cells were distinct from regulatory T cells induced by microbial antigens and prevented strong reactions against food.

Science 2016; 351: 858

Eitan Israeli

"You can only protect your liberties in this world by protecting the other man's freedom. You can only be free if I am free"

Clarence Darrow (1857-1938), American lawyer and leading member of the American Civil Liberties Union

activity in PsA. Although our study is limited by its retrospective observational design, all our patients were evaluated for CRP level at the first clinic visit, at the time of diagnosis of PsA and prior to administration of a DMARD, and all were prescribed DMARD and/or TNFα inhibitor therapy to achieve disease control based on the clinical judgment of the attending rheumatologist. Therefore, we can draw reliable conclusions regarding the predictive ability of CRP level at diagnosis, before the onset of any treatment, to identify patients at high risk for failure of conventional therapy who are potential candidates for early initiation of TNFα inhibitor treatment. The decision of switch treatment with conventional DMARDs to a TNFα inhibitor was based on the attending rheumatologist's clinical assessment, thus it reflects a real-life situation.

Another limitation of the study is the lack of information about the patients' weight. Since obesity is a prevalent cause of elevated CRP, the average weight of patients with elevated CRP could not be compared with that of patients with normal CRP.

Our study findings have important clinical implications, suggesting that patients whose serum CRP level at disease onset is ≥ 0.9 mg/dl have a greater probability of their disease not completely responding to conventional DMARDs and will require treatment with biologics such as TNF inhibitors.

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Capsule

Non-coding recurrent mutations in chronic lymphocytic leukemia

Chronic lymphocytic leukemia (CLL) is a frequent disease in which the genetic alterations determining the clinicobiological behavior are not fully understood. Puente et al. describe a comprehensive evaluation of the genomic landscape of 452 CLL cases and 54 patients with monoclonal B lymphocytosis, a precursor disorder. The authors extended the number of CLL driver alterations, including changes in *ZNF292*, *ZMYM3*, *ARID1A* and *PTPN11*. They also identified novel recurrent mutations in non-coding regions, including the 3' region of *NOTCH1*, which cause aberrant splicing events, increase NOTCH1 activity and result in a more aggressive disease. In addition, mutations in an enhancer located on chromosome 9p13 resulted in reduced expression of the B cell-specific transcription factor PAX5. The accumulative number of driver alterations (0 to ≥ 4) discriminated between patients with differences in clinical behavior. This study provides an integrated portrait of the CLL genomic landscape, identifies new recurrent driver mutations of the disease, and suggests clinical interventions that may improve the management of this neoplasia.

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Eitan Israeli

The ability to detect changes during a longitudinal study [16], such as qualitative measurements, has been shown in long-term follow-up of gluteal fat grafting [17], vocal cord fat grafting [18] and facial fat grafting [19], emphasizing the potential important role of MRI in long-term breast volume assessments after fat grafting.

Although not statistically significant, our study yielded important findings regarding tumor growth rate. In summarizing the MRI measurements, we noticed a substantial difference in the weekly average tumor growth rate among the AdMSC-enriched fat and non-enriched fat groups as compared to the control group.

The ability to quantify the tumor growth rate after enriched and non-enriched fat grafting by using MRI scans in SCID mice allowed us to assess each group individually and then compare the rate with the other groups. In other words, we were able to assess the influence of enriched and non-enriched fat grafting on the volume and growth rate of breast tumors.

LIMITATIONS

The lack of statistical significance may be due to our small sample size. A larger study might reveal significant outcomes. However, since we did not aim to assess the influence of fat grafting, but rather the validity of the model, this does not detract from the importance of our findings.

IMPLICATIONS AND FUTURE RESEARCH

An MRI modal study with a significant number of mice is needed to examine the influence of grafted fat or grafted fat enriched with mesenchymal progenitor cells on breast cancer recurrence.

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Capsule

Bringing atopic dermatitis up to scratch

Targeted therapies are transforming medicine, but complex diseases such as atopic dermatitis are difficult to target. Jarrett et al. report a mechanism that links two contributors to atopic dermatitis pathogenesis: cutaneous inflammation and barrier dysfunction. They found that the dust mite allergen phospholipase (PLA2) induces neolipid antigens in human skin. These antigens can then be presented by the non-classical MHC family member CD1a to CD1a-restricted T cells, which contribute to inflammation. The skin barrier protein filaggrin inhibits PLA2 and decreases inflammation. Indeed, individuals with filaggrin mutations experience severe atopic dermatitis. Thus, barrier dysfunction and inflammation may be linked, and PLA2 may provide a target for treating atopic dermatitis.

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Eitan Israeli

incomplete data for several parameters (HPV was measured in only a minority of the women, and data on smoking history and sexual history were frequently missing). However, our data do show that vulvar and vaginal malignant and premalignant diseases in our medical center were similar to the epidemiologic findings of studies from around the world.

Since almost half the women with vaginal cancer, VAIN3 and VIN3 had a history of warts or cervical carcinoma or CIN 3, it is imperative to follow those women meticulously and to explain to them as well as to the medical community the importance of frequent observation and examination even years after the original diagnosis of their cervical malignant or premalignant lesion. The effect of the vaccine against HPV on the incidence of vulvar and vaginal neoplasia will have to be evaluated in the future.

Vulvar and vaginal malignancy and neoplasia are rare pathologies in women's health, and larger prospective studies are needed to better understand their etiology and natural history, as well as prevention and optimal treatment of those diseases.

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Capsule

Killing cancer with a soft touch

Bleomycin is an effective chemotherapy drug that is used against multiple types of cancer. Unfortunately, it often causes lung fibrosis (or stiffening of the lungs), the severity of which correlates with the extent of exposure to the drug. To overcome this problem, Burgy and co-authors produced deglyco-bleomycin. This modified version of the drug was just as effective against several different models of cancer but did not cause any detectable fibrosis in mouse lungs. If these findings are confirmed in clinical testing, deglyco-bleomycin could be a valuable addition to the therapeutic regimens for treating a variety of human cancers.

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Eitan Israeli

"He who does not bellow the truth when he knows the truth makes himself the accomplice of liars and forgers"

Charles Peguy (1873-1914), French poet, essayist and editor. His two main philosophies were socialism and nationalism, but by 1908, after years of uneasy agnosticism, he had become a believing but non-practicing Roman Catholic

Capsule

Over-expression of proteasomal activator PA28α serves as a prognostic factor in oral squamous cell carcinoma

Despite recent advances in the diagnosis and therapy of oral squamous cell carcinoma (OSCC), disease recurrence remains common and is strongly associated with mortality. In an attempt to identify new targets for both treatment and diagnostic purposes, Feng et al. explored the role of PA28α, a proteasomal activator in OSCC. The expression of PA28α was examined in a panel of OSCC cell lines and tissues, associated with oncomine analysis. In a large OSCC patient cohort, the prognostic value of PA28α expression was evaluated. Primary clinical end-points were recurrence-free and overall survival rate. Functional involvement of PA28α in OSCC was examined in both in vitro and in vivo models upon specific siRNA knockdown. PA28α was found to be overexpressed in OSCC cell lines and tumor tissues. High expression of PA28α was significantly associated with recurrence and poorer overall survival. Specific knockdown of PA28α inhibited OSCC cell proliferation, migration, and invasion in vitro and reduced the growth of OSCC xenografts in vivo. Multivariate Cox regression analyses revealed PA28α as independent prognostic predictors. These results suggest that PA28α is involved in OSCC oncogenesis and may serve as a potential prognostic factor.

J Exp Clin Cancer 2016; 35: 35

Eitan Israeli

Capsule

Sumoylation coordinates the repression of inflammatory and antiviral gene-expression programs during innate sensing

Innate sensing of pathogens initiates inflammatory cytokine responses that need to be tightly controlled. Decque and team found that after engagement of Toll-like receptors (TLRs) in myeloid cells, deficient sumoylation caused increased secretion of transcription factor NF-κB-dependent inflammatory cytokines and a massive type I interferon signature. In mice, diminished sumoylation conferred susceptibility to endotoxin shock and resistance to viral infection. Overproduction of several NF-κB-dependent inflammatory cytokines required expression of the type I interferon receptor, which identified type I interferon as a central sumoylation-controlled hub for inflammation. Mechanistically, the small ubiquitin-like modifier SUMO operated from a distal enhancer of the gene encoding interferon-β (*Ifnb*1) to silence both basal and stimulus-induced activity of the *Ifnb*1 promoter. Therefore, sumoylation restrained inflammation by silencing *Ifnb*1 expression and by strictly suppressing an unanticipated priming by type I interferons of the TLR-induced production of inflammatory cytokines.

Nature Immunol 2016; 17: 140

Eitan Israeli

Capsule

Tuning down an overactive thyroid

Overproduction of thyroid hormone is the hallmark of Graves' disease. Therapy is limited to suppression of thyroid hormone (which shows a high relapse rate) or destruction/removal of the thyroid gland. Saxena et al. have created a synthetic gene network that can sense and respond to abnormally high thyroid hormone levels. The circuit contained a thyroid hormone-sensing receptor fused to the DNA binding domain of yeast Gal4 and reversibly induced expression of a thyroid hormone receptor antagonist. This antagonist competed with thyroid-stimulating hormone and autoantibodies that cause abnormal activity. When cells transgenic for the circuit were injected into a mouse model of Graves' disease, the regulation of thyroid hormone was improved.

Proc Natl Acad Sci USA 2016; 10.1073pnas.1514383113

Eitan Israeli

Capsule

NLRP3 activation and mitosis are mutually exclusive events coordinated by NEK7, a new inflammasome component

The NLRP3 inflammasome responds to microbes and danger signals by processing and activating pro-inflammatory cytokines, including interleukin 1β (IL-1β) and IL-18. Shi et al. found that activation of the NLRP3 inflammasome was restricted to interphase of the cell cycle by NEK7, a serine-threonine kinase previously linked to mitosis. Activation of the NLRP3 inflammasome required NEK7, which bound to the leucine-rich repeat domain of NLRP3 in a kinase-independent manner downstream of the induction of mitochondrial reactive oxygen species (ROS). This interaction was necessary for the formation of a complex containing NLRP3 and the adaptor ASC, oligomerization of ASC and activation of caspase-1. NEK7 promoted the NLRP3-dependent cellular inflammatory response to intraperitoneal challenge with monosodium urate and the development of experimental autoimmune encephalitis in mice. These findings suggest that NEK7 serves as a cellular switch that enforces mutual exclusivity of the inflammasome response and cell division.

Nature Immunol 2016; 17: 250

Eitan Israeli

Capsule

Quiescent and aging hair follicle stem cells

Stem cells enable normal cell homeostasis, but they also exist in a quiescent state, ready to proliferate and differentiate after tissue damage. Now, two studies reveal features of stem cells in the hair follicle, an epithelial mini-organ of the skin that is responsible for hair growth and recycling. Wang et al. found that the Foxc1 transcription factor is induced in activated hair follicle stem cells, which in turn promote Nfatc1 and BMP signaling, to reinforce quiescence. Matsumura et al. analyzed hair follicle stem cells during aging. They identified type XVII collagen (COL17A1) as key to hair thinning. DNA damage-induced depletion of COL17A1 triggered cell differentiation resulting in the shedding of epidermal keratinocytes from the skin surface. These changes then caused hair follicle shrinkage and hair loss.

Science 2016; 351: 559

Eitan Israeli

Capsule

Polyclonal antibodies are better for cancer treatment than monoclonal

Monoclonal antibodies against the epidermal growth factor receptor (EGFR), which drives tumor growth, are frequently used to treat colorectal cancer. Unfortunately, the cancers commonly develop drug-resistant mutations, and the monoclonal antibodies become ineffective. To overcome this problem, Arena and fellow researchers used a polyclonal antibody called MM-151, which binds multiple parts of the EGFR molecule at once, so that the cancer cannot develop resistance by mutating one site at a time. The approach was effective in both preclinical models and patients who were resistant to other anti-EGFR therapies, paving the way for further clinical development of MM-151.

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Eitan Israeli

Capsule

Schizophrenia risk from complex variation of complement component 4

Schizophrenia is a heritable brain illness with unknown pathogenic mechanisms. Schizophrenia's strongest genetic association at a population level involves variation in the major histocompatibility complex (MHC) locus, but the genes and molecular mechanisms accounting for this have been challenging to identify. Sekar et al. show that this association arises in part from many structurally diverse alleles of the complement component 4 (*C4*) genes. The authors found that these alleles generated widely varying levels of *C4A* and *C4B* expression in the brain, with each common *C4* allele associating with schizophrenia in proportion to its tendency to generate greater expression of *C4A*. Human *C4* protein localized to neuronal synapses, dendrites, axons and cell bodies. In mice, *C4* mediated synapse elimination during postnatal development. These results implicate excessive complement activity in the development of schizophrenia and may help explain the reduced numbers of synapses in the brains of individuals with schizophrenia.

Nature 2016; 530: 177

Eitan Israeli

Capsule

Metastatic breast tumors break down bone

Most breast cancer cells activate the breakdown of bone to promote metastases. Wang et al. found that the ABL kinases enhanced the ability of breast cancer cells to invade and break down bone in mice. In breast cancer cells, the ABL kinases activated pathways that triggered the transcription of genes encoding factors that activate osteoclasts (cells that break down bone) and those that enhanced the survival of breast cancer cells in the bone microenvironment. An ABL-specific inhibitor decreased bone metastasis in mice.

Sci Signal 2016; 9: ra12

Eitan Israeli