Capsule

Intranasal epidermal growth factor treatment rescues neonatal brain injury

There are no clinically relevant treatments available for improving function in the growing population of very preterm infants (less than 32 weeks gestation) with neonatal brain injury. Diffuse white matter injury (DWMI) is a common finding in these children and results in chronic neurodevelopmental impairments. As shown recently, failure in oligodendrocyte progenitor cell maturation contributes to DWMI. Scafidi and colleagues, who demonstrated previously that the epidermal growth factor receptor (EGFR) has an important role in oligodendrocyte development, now examine whether enhanced EGFR signaling stimulates the endogenous response of EGFR-expressing progenitor cells during a critical period after brain injury and promotes cellular and behavioral recovery in the developing brain. Using an established mouse model of very preterm brain injury, they show that selective overexpression of human EGFR in oligodendrocyte lineage cells or the administration of intranasal heparin-binding EGF immediately after injury decreases oligodendroglia death, enhances generation of new oligodendrocytes from progenitor cells, and promotes functional recovery. Furthermore, these interventions diminish ultrastructural abnormalities and alleviate behavioral deficits on white-matter-specific paradigms. Inhibition of EGFR signaling with a molecularly targeted agent used for cancer therapy demonstrates that EGFR activation is an important contributor to oligodendrocyte regeneration and functional recovery after DWMI. Thus, our study provides direct evidence that targeting EGFR in oligodendrocyte progenitor cells at a specific time after injury is clinically feasible and potentially applicable to the treatment of premature children with white matter injury.

Nature 2014; 506: 230

Eitan Israeli

Capsule

Estrogen increases hematopoietic stem cell self-renewal in females and during pregnancy

Sexually dimorphic mammalian tissues, including sexual organs and the brain, contain stem cells that are directly or indirectly regulated by sex hormones. An important question is whether stem cells also exhibit sex differences in physiological function and hormonal regulation in tissues that do not show sex-specific morphological differences. The terminal differentiation and function of some hematopoietic cells are regulated by sex hormones, but hematopoietic stem cell function is thought to be similar in both sexes. Nakada and group show that mouse hematopoietic stem cells exhibit sex differences in cell cycle regulation by estrogen. Hematopoietic stem cells in female mice divide significantly more frequently than in male mice. This difference depends on the ovaries but not the testes. Administration of estradiol, a hormone produced mainly in the ovaries, increased hematopoietic stem cell division in males and females. Estrogen levels increased during pregnancy, increasing hematopoietic stem cell division, hematopoietic stem cell frequency, cellularity, and erythropoiesis in the spleen. Hematopoietic stem cells expressed high levels of estrogen receptor-α (ERα). Conditional deletion of ERα from hematopoietic stem cells reduced hematopoietic stem cell division in female, but not male, mice and attenuated the increases in hematopoietic stem cell division, hematopoietic stem cell frequency, and erythropoiesis during pregnancy. Estrogen/ERα signaling promotes hematopoietic stem cell self-renewal, expanding splenic hematopoietic stem cells and erythropoiesis during pregnancy.

Nature 2014; 505: 555

Eitan Israeli

Capsule

Daily stressors, stress vulnerability, immune and HPA axis

Both stressors and stress vulnerability factors together with immune and hypothalamus-pituitary-adrenal (HPA) axis activity components have been suggested to contribute to disease fluctuations of chronic inflammatory diseases, such as rheumatoid arthritis (RA). Evers et al. investigate whether daily stressors and worrying as stress vulnerability factor as well as immune and HPA axis activity markers predict short-term disease activity and symptom fluctuations in patients with RA. In a prospective design, daily stressors, worrying, HPA axis (cortisol) and immune system markers (interleukin-1β, IL-6, IL-8, interferon-gamma, tumor necrosis factor-alpha), clinical and self-reported disease activity (disease activity score in 28 joints, RA disease activity index), and physical symptoms of pain and fatigue were monitored monthly during 6 months in 80 RA patients. Multilevel modeling indicated that daily stressors predicted increased fatigue in the next month and that worrying predicted increased self-reported disease activity, swollen joint count and pain in the next month. In addition, specific cytokines of IL-1β and IFNγ predicted increased fatigue 1 month later. Overall, relationships remained relatively unchanged after controlling for medication use, disease duration and demographic variables. No evidence was found for immune and HPA axis activity markers as mediators of the stress-disease relationship.

Ann Rheum Dis 2013 Jul 9. doi: 10.1136/annrheumdis-2012-203143

Eitan Israeli

Capsule

Genetics of rheumatoid arthritis contributes to biology and drug discovery

A major challenge in human genetics is to devise a systematic strategy to integrate disease-associated variants with diverse genomic and biological data sets to provide insight into disease pathogenesis and guide drug discovery for complex traits such as rheumatoid arthritis (RA). Okada et al. performed a genome-wide association study meta-analysis in a total of › 100,000 subjects of European and Asian ancestries (29,880 RA cases and 73,758 controls), by evaluating ~10 million single-nucleotide polymorphisms. The authors discovered 42 novel RA risk loci at a genome-wide level of significance, bringing the total to 101. They devised an *in silico* pipeline using established bioinformatics methods based on functional annotation, *cis*-acting expression quantitative trait loci and pathway analyses – as well as novel methods based on genetic overlap with human primary immunodeficiency, hematological cancer somatic mutations and knockout mouse phenotypes – to identify 98 biological candidate genes at these 101 risk loci. They demonstrate that these genes are the targets of approved therapies for RA, and further suggest that drugs approved for other indications may be repurposed for the treatment of RA. Together, this comprehensive genetic study sheds light on fundamental genes, pathways and cell types that contribute to RA pathogenesis, and provides empirical evidence that the genetics of RA can provide important information for drug discovery.

Nature 2014; 506: 376

Eitan Israeli

Capsule

Broadly neutralizing hemagglutinin stalk-specific antibodies require FcγR interactions for protection against influenza virus in vivo

Neutralizing antibodies against influenza viruses have traditionally been thought to provide protection exclusively through their variable region; the contributions of mechanisms conferred by the Fc domain remain controversial. DiLillo et al. investigated the in vivo contributions of Fc interactions with their cognate receptors for a collection of neutralizing anti-influenza antibodies. Whereas five broadly neutralizing monoclonal antibodies (bNAbs) targeting the conserved stalk region of hemagglutinin (HA) required interactions between the antibody Fc and Fc receptors for IgG (FcγRs) to confer protection from lethal H1N1 challenge, three strain-specific monoclonal Abs (mAbs) against the variable head domain of HA were equally protective in the presence or absence of FcγR interactions. Although all antibodies blocked infection, only anti-stalk bNAbs were capable of mediating cytotoxicity of infected cells, which accounts for their FcγR dependence. Immune complexes generated with anti-HA stalk mAb efficiently interacted with FcγRs, but anti-HA head immune complexes did not. These results suggest that FcγR binding capacity by anti-HA antibodies was dependent on the interaction of the cognate Fab with antigen. The researchers exploited these disparate mechanisms of mAb-mediated protection to reengineer an anti-stalk bNAb to selectively enhance FcγR engagement to augment its protective activity. These findings reveal a previously uncharacterized property of bNAbs and guide an approach toward enhancing mAb-mediated antiviral therapeutics.

Nature Med 2014; 20: 143

Eitan Israeli

Capsule

Stimulus-triggered fate conversion of somatic cells into pluripotency

Obokata et al. from Japan report a unique cellular reprogramming phenomenon, called stimulus-triggered acquisition of pluripotency (STAP), which requires neither nuclear transfer nor the introduction of transcription factors. In STAP, strong external stimuli such as a transient low-pH stressor reprogrammed mammalian somatic cells, resulting in the generation of pluripotent cells. Through real-time imaging of STAP cells derived from purified lymphocytes, as well as gene rearrangement analysis, the authors found that committed somatic cells give rise to STAP cells by reprogramming rather than selection. STAP cells showed a substantial decrease in DNA methylation in the regulatory regions of pluripotency marker genes. Blastocyst injection showed that STAP cells efficiently contribute to chimeric embryos and to offspring via germline transmission. They also demonstrate the derivation of robustly expandable pluripotent cell lines from STAP cells. These findings indicate that epigenetic fate determination of mammalian cells can be markedly converted in a context-dependent manner by strong environmental cues.

Nature 2014; 505: 641

Eitan Israeli

Capsule

Gut microbiota metabolism of dietary fiber influences allergic airway disease and hematopoiesis

Metabolites from intestinal microbiota are key determinants of host-microbe mutualism and, consequently, the health or disease of the intestinal tract. However, whether such host-microbe cross-talk influences inflammation in peripheral tissues, such as the lung, is poorly understood. Trompette et al. found that dietary fermentable fiber content changed the composition of the gut and lung microbiota, in particular by altering the ratio of firmicutes to bacteroidetes. The gut microbiota metabolized the fiber, consequently increasing the concentration of circulating short-chain fatty acids (SCFAs). Mice fed a high fiber diet had increased circulating levels of SCFAs and were protected against allergic inflammation in the lung, whereas a low fiber diet decreased levels of SCFAs and increased allergic airway disease. Treatment of mice with the SCFA propionate led to alterations in bone marrow hematopoiesis that were characterized by enhanced generation of macrophage and dendritic cell (DC) precursors and subsequent seeding of the lungs by DCs with high phagocytic capacity but an impaired ability to promote T helper type 2 (T_H2) cell effector function. The effects of propionate on allergic inflammation were dependent on G protein-coupled receptor 41 (GPR41, also called free fatty acid receptor 3 or FFAR3), but not GPR43 (also called free fatty acid receptor 2 or FFAR2). Our results show that dietary fermentable fiber and SCFAs can shape the immunological environment in the lung and influence the severity of allergic inflammation.

Nature Med 2014; 20: 159

Eitan Israeli

Capsule

In vivo discovery of immunotherapy targets in the tumor microenvironment

Recent clinical trials showed that targeting of inhibitory receptors on T cells induces durable responses in a subset of cancer patients, despite advanced disease. However, the regulatory switches controlling T cell function in immunosuppressive tumors are not well understood. Zhou et al. show that such inhibitory mechanisms can be systematically discovered in the tumor microenvironment. The authors devised an in vivo pooled short hairpin RNA (shRNA) screen in which shRNAs targeting negative regulators became highly enriched in murine tumors by releasing a block on T cell proliferation upon tumor antigen recognition. Such shRNAs were identified by deep sequencing of the shRNA cassette from T cells infiltrating tumor or control tissues. One of the target genes was *Ppp2r2d*, a regulatory subunit of the PP2A phosphatase family. In tumors, *Ppp2r2d* knockdown inhibited T cell apoptosis and enhanced T cell proliferation as well as cytokine production. Key regulators of immune function can therefore be discovered in relevant tissue microenvironments.

Nature 2014; 506: 52

Eitan Israeli

Capsule

RNA viruses can hijack vertebrate microRNAs to suppress innate immunity

Currently, there is little evidence for a notable role of the vertebrate microRNA (miRNA) system in the pathogenesis of RNA viruses. This is primarily attributed to the ease with which these viruses mutate to disrupt recognition and growth suppression by host miRNAs. Trobaugh et al. report that the hematopoietic cell-specific miRNA miR-142-3p potently restricts the replication of the mosquito-borne North American eastern equine encephalitis virus in myeloid-lineage cells by binding to sites in the 3' non-translated region of its RNA genome. However, by limiting myeloid cell tropism and consequent innate immunity induction, this restriction directly promotes neurologic disease manifestations characteristic of eastern equine encephalitis virus infection in humans. Furthermore, the region containing the miR-142-3p binding sites is essential for efficient virus infection of mosquito vectors. We propose that RNA viruses can adapt to use antiviral properties of vertebrate miRNAs to limit replication in particular cell types and that this restriction can lead to exacerbation of disease severity.

Nature 2014; 506: 245

Eitan Israeli

Capsule

Elevated serum pesticide levels and risk for Alzheimer disease

Richardson and co-authors evaluated the association between serum levels of DDE and Alzheimer disease (AD) and whether the apolipoprotein E (*APOE*) genotype modifies the association. The authors performed a case-control study consisting of existing samples from patients with AD and control. Serum levels of DDE were measured in 79 control and 86 AD cases. The results showed that levels of DDE were 3.8-fold higher in the serum of those with AD (mean [SEM], 2.64 [0.35] ng/mg cholesterol) when compared with control participants (mean [SEM], 0.69 [0.1] ng/mg cholesterol, $P < 0.001$). The highest tertile of DDE levels was associated with an odds ratio of 4.18 for increased risk for and lower Mini-Mental State Examination scores (-1.605). The Mini-Mental State Examination scores in the highest tertile of DDE were -1.753 points lower in the subpopulation carrying an *APOE* ε4 allele compared with those carrying an *APOE* ε3 allele (P interaction = 0.04). Serum levels of DDE were highly correlated with brain levels of DDE ($P = 0.95$). Exposure of human neuroblastoma cells to DDT or DDE increased levels of amyloid precursor protein. The authors conclude that elevated serum DDE levels are associated with an increased risk for AD and carriers of an *APOE*4 ε4 allele may be more susceptible to the effects of DDE. Both DDT and DDE increase amyloid precursor protein levels, providing mechanistic plausibility for the association of DDE exposure with AD. Identifying people who have elevated levels of DDE and carry an *APOE* ε4 allele may lead to early identification of some cases of AD.

JAMA Neurol 2014; Doi:10.1001/jamaneurol.2013.60300

Eitan Israeli

Capsule

Spectinamides: a new class of semisynthetic antituberculosis agents that overcome native drug efflux

Although the classical antibiotic spectinomycin is a potent bacterial protein synthesis inhibitor, poor antimycobacterial activity limits its clinical application for treating tuberculosis. Using structure-based design, Lee et al. generated a new semisynthetic series of spectinomycin analogs with selective ribosomal inhibition and excellent narrow-spectrum antitubercular activity. In multiple murine infection models, these spectinamides were well tolerated, significantly reduced lung mycobacterial burden, and increased survival. In vitro studies demonstrated a lack of cross-resistance with existing tuberculosis therapeutics, activity against multidrug-resistant (MDR) and extensively drug-resistant tuberculosis, and an excellent pharmacological profile. Key to their potent antitubercular properties was their structural modification to evade the Rv1258c efflux pump, which is upregulated in MDR strains and is implicated in macrophage-induced drug tolerance. The antitubercular efficacy of spectinamides demonstrates that synthetic modifications to classical antibiotics can overcome the challenge of intrinsic efflux pump-mediated resistance and expands opportunities for target-based tuberculosis drug discovery.

Nature Med 2014; 20: 152

Eitan Israeli

Capsule

In situ identification of bipotent stem cells in the mammary gland

The mammary epithelium undergoes profound morphogenetic changes during development. Architecturally, it comprises two primary lineages, the inner luminal and outer myoepithelial cell layers. Two opposing concepts on the nature of mammary stem cells (MaSCs) in the postnatal gland have emerged. One model, based on classical transplantation assays, postulates that bipotent MaSCs have a key role in coordinating ductal epithelial expansion and maintenance in the adult gland, whereas the second model proposes that only unipotent MaSCs identified by lineage tracing contribute to these processes. Through clonal cell-fate mapping studies using a stochastic multicolor *cre* reporter combined with a new three-dimensional imaging strategy, Rios et al. provide evidence for the existence of bipotent MaSCs as well as distinct long-lived progenitor cells. The cellular dynamics at different developmental stages support a model in which both stem and progenitor cells drive morphogenesis during puberty, whereas bipotent MaSCs coordinate ductal homeostasis and remodeling of the mouse adult gland.

Nature 2014; 506: 322

Eitan Israeli

Capsule

The immune system suffers in space at least in flies

A concern regarding manned long-term space missions is that changes in gravitational force compromise the human immune system, but the underlying cellular and molecular reasons have not been clear. Taylor et al. studied innate immunity in *Drosophila melanogaster* that traveled aboard Space Shuttle Discovery in 2006. Flies reared in space were compared to flies that underwent development on Earth. Upon the return of the space-reared flies to Earth, both groups of flies were subjected to bacterial (*Escherichia coli*) or fungal (*Beauveria bassiana*) infections, and their gene expression profiles were examined. Genes associated with Toll receptor-mediated immune responses to fungal infection were activated only in the Earth flies. The expression of specific antimicrobial peptides also failed in the space flies. Other mechanisms, such as the Imd signaling pathway response to bacterial infection, were not affected in space flies. The space flies exhibited increased expression of heat shock response genes, a subset of stress response genes that are activated to manage aberrant protein folding. The authors suggest that microgravity may alter the folding and stability of proteins, which triggers the deployment of heat shock proteins that, in turn, may interfere with the Toll receptor signaling pathway.

PLOS One 2014; 9: e86485

Eitan Israeli

Capsule

Fas ligand-mediated immune surveillance by T cells is essential for the control of spontaneous B cell lymphomas

Loss of function of the tumor suppressor gene *PRDM1* (also known as *BLIMP1*) or deregulated expression of the oncogene *BCL6* occurs in a large proportion of diffuse large B cell lymphoma (DLBCL) cases. However, targeted mutation of either gene in mice leads to only slow and infrequent development of malignant lymphoma, and despite frequent mutation of *BCL6* in activated B cells of healthy individuals, lymphoma development is rare. Afshar-Sterle and collaborators show that T cells prevent the development of overt lymphoma in mice caused by Blimp1 deficiency or overexpression of Bcl6 in the B cell lineage. Impairment of T cell control results in rapid development of DLBCL-like disease, which can be eradicated by polyclonal $CD8^+$ T cells in a T cell receptor-, CD28- and Fas ligand-dependent manner. Thus, malignant transformation of mature B cells requires mutations that impair intrinsic differentiation processes and permit escape from T cell-mediated tumor surveillance.

Nature Med 2014; 20: 283

Eitan Israeli

Capsule

Specific and non-hepatotoxic degradation of nuclear hepatitis B virus cccDNA

Current antiviral agents can control but not eliminate hepatitis B virus (HBV), because HBV establishes a stable nuclear covalently closed circular DNA (cccDNA). Interferon-α treatment can clear HBV but is limited by systemic side effects. Lucifora et al. describe how interferon-α can induce specific degradation of the nuclear viral DNA without hepatotoxicity and propose lymphotoxin-β receptor activation as a therapeutic alternative. Interferon-α and lymphotoxin-β receptor activation up-regulated APOBEC3A and APOBEC3B cytidine deaminases, respectively, in HBV-infected cells, primary hepatocytes, and human liver needle biopsies. HBV core protein mediated the interaction with nuclear cccDNA, resulting in cytidine deamination, apurinic/apyrimidinic site formation, and finally cccDNA degradation that prevented HBV reactivation. Genomic DNA was not affected. Thus, inducing nuclear deaminases – for example, by lymphotoxin-β receptor activation – allows the development of new therapeutics that, in combination with existing antivirals, may cure hepatitis B.

Science 2014; 343: 1221

Eitan Israeli

Capsule

Voice-sensitive regions in the dog and human brain are revealed by comparative fMRI

During the approximately 18–32 thousand years of domestication, dogs and humans have shared a similar social environment. Dog and human vocalizations are thus familiar and relevant to both species, although they belong to evolutionarily distant taxa, as their lineages split approximately 90–100 million years ago. In this first comparative neuroimaging study of a non-primate and a primate species, Andics and team made use of this special combination of shared environment and evolutionary distance. The authors presented dogs and humans with the same set of vocal and non-vocal stimuli to search for functionally analogous voice-sensitive cortical regions. They demonstrate that voice areas exist in dogs and that they show a similar pattern to anterior temporal voice areas in humans. These findings also reveal that sensitivity to vocal emotional valence cues engages similarly located non-primary auditory regions in dogs and humans. Although parallel evolution cannot be excluded, their findings suggest that voice areas may have a more ancient evolutionary origin than previously known.

Curr Biol 20 February 2014,10.1016/j.cub.2014.01.058

Eitan Israeli

Capsule

FoxA1 directs the lineage and immunosuppressive properties of a novel regulatory T cell population in EAE and MS

The defective generation or function of regulatory T (T_{reg}) cells in autoimmune disease contributes to chronic inflammation and tissue injury. Liu and co-authors report the identification of FoxA1 as a transcription factor in T cells that, after ectopic expression, confers suppressive properties in a newly identified T_{reg} cell population, herein called FoxA1$^+$ T_{reg} cells. FoxA1 bound to the *Pdl1* promoter, inducing programmed cell death ligand 1 (Pd-l1) expression, which was essential for the FoxA1$^+$ T_{reg} cells to kill activated T cells. FoxA1$^+$ T_{reg} cells develop primarily in the central nervous system in response to autoimmune inflammation, have a distinct transcriptional profile and are CD4$^+$FoxA1$^+$CD47$^+$CD69$^+$PD-L1^{hi}FoxP3$^-$. Adoptive transfer of stable FoxA1$^+$ T_{reg} cells inhibited experimental autoimmune encephalomyelitis in a FoxA1- and Pd-l1- dependent manner. The development of FoxA1$^+$ T_{reg} cells is induced by interferon-β (IFN-β) and requires T cell-intrinsic IFN-α/β receptor (Ifnar) signaling, as the frequency of FoxA1$^+$ T_{reg} cells was reduced in *Ifnb*$^{-/-}$ and *Ifnar*$^{-/-}$ mice. In individuals with relapsing-remitting multiple sclerosis, clinical response to treatment with IFN-β was associated with an increased frequency of suppressive FoxA1$^+$ T_{reg} cells in the blood. These findings suggest that FoxA1 is a lineage-specification factor that is induced by IFN-β and supports the differentiation and suppressive function of FoxA1$^+$ T_{reg} cells.

Nature Med 2014; 20: 272

Eitan Israeli

Capsule

Ultraviolet radiation-induced inflammation promotes angiotropism and metastasis in melanoma

Intermittent intense ultraviolet (UV) exposure represents an important etiological factor in the development of malignant melanoma. The ability of UV radiation to cause tumor-initiating DNA mutations in melanocytes is now firmly established, but how the microenvironmental effects of UV radiation influence melanoma pathogenesis is not fully understood. Bald et al. report that repetitive UV exposure of primary cutaneous melanomas in a genetically engineered mouse model promotes metastatic progression, independent of its tumor-initiating effects. UV irradiation enhanced the expansion of tumor cells along abluminal blood vessel surfaces and increased the number of lung metastases. This effect depended on the recruitment and activation of neutrophils, initiated by the release of high mobility group box 1 (HMGB1) from UV-damaged epidermal keratinocytes and driven by Toll-like receptor 4 (TLR4). The UV-induced neutrophilic inflammatory response stimulated angiogenesis and promoted the ability of melanoma cells to migrate towards endothelial cells and use selective motility cues on their surfaces. These results not only reveal how UV irradiation of epidermal keratinocytes is sensed by the innate immune system, but also show that the resulting inflammatory response catalyses reciprocal melanoma-endothelial cell interactions leading to perivascular invasion, a phenomenon originally described as angiotropism in human melanomas by histopathologists. Angiotropism represents a hitherto underappreciated mechanism of metastasis that also increases the likelihood of intravasation and hematogenous dissemination. Consistent with these findings, ulcerated primary human melanomas with abundant neutrophils and reactive angiogenesis frequently show angiotropism and a high risk for metastases. This study indicates that targeting the inflammation-induced phenotypic plasticity of melanoma cells and their association with endothelial cells represents rational strategies to specifically interfere with metastatic progression.

Nature 2014; 507: 109

Eitan Israeli