Capsule

The microbiota may be able to regulate sex hormones

Both genetic and environmental factors contribute to an individual's susceptibility to autoimmune disease, but the specific environmental influences are not well characterized. Markle et al. explored how microbial factors, in particular the gut microbiota, influence susceptibility to type 1 diabetes in mice. In the non-obese diabetic (NOD) mouse model of type 1 diabetes, female mice are significantly more susceptible to disease than males; however, this difference was not apparent under germ-free conditions. Transfer of cecal contents from male NOD mice to female NOD mice prior to disease onset protected against pancreatic islet inflammation, autoantibody production, and the development of diabetes and was associated with increased testosterone in female mice. Blocking androgen receptor activity abrogated protection. Thus, the microbiota may be able to regulate sex hormones and influence an individual's susceptibility to autoimmunity.

Science 2013; 339: 1084

Eitan Israeli

Capsule

Ovarian surface epithelium at the junction area contains a cancer-prone stem cell niche

Epithelial ovarian cancer (EOC) is the fifth leading cause of cancer deaths among women in the United States, but its pathogenesis is poorly understood. Some epithelial cancers are known to occur in transitional zones between two types of epithelium, whereas others have been shown to originate in epithelial tissue stem cells. The stem cell niche of the ovarian surface epithelium (OSE), which is ruptured and regenerates during ovulation, has not yet been defined unequivocally. Flesken-Nikitin et al. identified the hilum region of the mouse ovary, the transitional (or junction) area between the OSE, mesothelium and tubal (oviductal) epithelium, as a previously unrecognized stem cell niche of the OSE. They found that cells of the hilum OSE cycle slowly and express stem and/or progenitor cell markers ALDH1, LGR5, LEF1, CD133 and CK6B. These cells display long-term stem cell properties ex vivo and in vivo, as shown by serial sphere generation and long-term lineage-tracing assays. Importantly, the hilum cells show increased transformation potential after inactivation of tumor suppressor genes *Trp53* and *Rb1*, whose pathways are altered frequently in the most aggressive and common type of human EOC, high grade serous adenocarcinoma. This study supports experimentally the idea that susceptibility of transitional zones to malignant transformation may be explained by the presence of stem cell niches in those areas. Identification of a stem cell niche for the OSE may have important implications for understanding EOC pathogenesis.

Nature 2013; 495: 241

Eitan Israeli

Capsule

Spreading depression triggers headache by activating neuronal Panx1 channels

The initial phase in the development of a migraine is still poorly understood. Karatas and fellow researchers describe a previously unknown signaling pathway between stressed neurons and trigeminal afferents during cortical spreading depression (CSD), the putative cause of migraine aura and headache. CSD caused neuronal Pannexin1 (Panx1) megachannel opening and caspase-1 activation followed by high mobility group box 1 (HMGB1) release from neurons and nuclear factor κB activation in astrocytes. Suppression of this cascade abolished CSD-induced trigeminovascular activation, dural mast cell degranulation, and headache. CSD-induced neuronal megachannel opening may promote sustained activation of trigeminal afferents via parenchymal inflammatory cascades reaching glia limitans. This pathway may function to alarm an organism with headache when neurons are stressed.

Science 2013; 339:1092

Eitan Israeli

Capsule

Macrophage replenishment in tumors by the spleen

Solid tumors contain not only malignant cells but also a wide array of host-derived cells that can have dramatic effects on tumor behavior. These include macrophages, immune cells that enhance tumor progression in part by promoting inflammation and whose presence in tumors correlates with reduced patient survival times. Macrophages must be continually replenished as the tumor grows, but little is known about this replenishment process. Studying mice bearing lung cancers produced by activation of the RAS oncogene, Cortez-Retamozo et al. found that tumor-associated macrophages are supplied by the spleen, through amplification of hematopoietic stem cells and macrophage progenitor cells. This cell amplification process was stimulated by angiotensin II, a peptide hormone better known for its role in the renin-angiotensin system, which regulates blood pressure. Notably, mice treated with the blood pressure medication enalapril, which inhibits angiotensin II production, had fewer tumor-associated macrophages and fewer lung tumor nodules than control mice. Whether these results can be extrapolated to human lung cancer remains to be determined.

Immunity 2013; 38: 296

Eitan Israeli

Capsule

A role for IFNε

Type I interferons (IFNs) are critical cytokines involved in host defense against pathogens, particularly viruses. IFNε is an IFN-like gene encoded within the type I IFN locus in mice and humans whose function has not been characterized. Fung and co-authors created mice with a genetic deletion in *Ifnε* and found that, like other type I IFNs, IFNε signals through the IFNα receptors 1 and 2. However, unlike these other cytokines, which are primarily expressed by immune cells and are induced upon immune cell triggering, IFNε was expressed exclusively by epithelial cells of the female reproductive tract in both mice and humans and its expression was hormonally regulated. IFNε-deficient mice were more susceptible to infection with herpes simplex virus 2 and *Chlamydia muridarum*, two common sexually transmitted pathogens.

Science 2013; 339: 108

Eitan Israeli

Capsule

Immunomodulation in adult epilepsy: the role of IVIG

Much of the research on intravenous immunoglobulin (IVIG) use in epilepsy has focused on childhood epilepsies and the results have been inconclusive. With the accumulation of evidence for inflammation in epilepsy and epileptogenesis, IVIG might have a role to play in adult epilepsy. In a literature review Sharp and Javidan focus on the purported mechanisms of IVIG, the link between inflammation and the various causes of adult epilepsy, and the different steps of epileptogenesis at which inflammation might play a role. They also review the current clinical evidence supporting IVIG as a treatment for epilepsy in the adult population. Though there is interesting theoretical potential for treatment of refractory epilepsy in adults with IVIG, there is insufficient evidence to support its standard use. The question remains if IVIG should still be considered as an end-of-the-line option for patients with epilepsy poorly responsive to all other treatments.

Can J Neurol Sci 2012; 39 (5): 584

Elias Toubi

Capsule

Phosphorylation of FOXP3 controls regulatory T cell function and is inhibited by TNFα in rheumatoid arthritis

Regulatory T (Treg) cells suppress autoimmune disease, and impaired Treg cell function is associated with rheumatoid arthritis. Nie and team demonstrate that forkhead box P3 (FOXP3) transcriptional activity and, consequently, Treg cell suppressive function are regulated by phosphorylation at Ser418 in the C-terminal DNA-binding domain. In rheumatoid arthritis-derived Treg cells, the Ser418 site was specifically dephosphorylated by protein phosphatase 1 (PP1), whose expression and enzymatic activity were induced in the inflamed synovium by tumor necrosis factor-alpha (TNFα), leading to impaired Treg cell function. Moreover, TNFα-induced Treg cell dysfunction correlated with increased numbers of interleukin-17 (IL17)+ and interferon-γ (IFNγ)+CD4+ T cells within the inflamed synovium in rheumatoid arthritis. Treatment with a TNFα-specific antibody restored Treg cell function in subjects with rheumatoid arthritis, which was associated with decreased PP1 expression and increased FOXP3 phosphorylation in Treg cells. Thus, TNFα controls the balance between Treg cells and pathogenic TH17 and TH1 cells in the synovium of individuals with rheumatoid arthritis through FOXP3 dephosphorylation.

Nature Med 2013; 19: 322

Eitan Israeli

Capsule

Aggregates as a mechanistic insight into the pathogenesis of FTLD/ALS

Several recent papers have revealed the unexpected genetic and pathological overlap between frontotemporal lobar degeneration (FTLD) and amyotrophic lateral sclerosis (ALS). The most common genetic cause is the GGGGCC hexanucleotide repeat expansion upstream of the *C9orf72* coding region affecting about 10% of all patients. It is currently unknown how repeat expansion might lead to neurodegeneration. *C9orf72* patients show two distinct types of ubiquitinated inclusions in the central nervous system, one of which was identified as phosphorylated TDP-43 protein. However, all inclusions in the cerebellum and most inclusions in the hippocampus and neocortex lack TDP-43, and the actual disease protein is unknown. Mori et al. discovered that most of these characteristic inclusions contain poly-(Gly-Ala) and, to a lesser extent, poly-(Gly-Pro) and poly-(Gly-Arg) dipeptide-repeat proteins that are generated by non-ATG–initiated translation from the expanded GGGGCC repeats in three reading frames. The findings yield mechanistic insight into the pathogenesis of FTLD/ALS with *C9orf72* repeat expansions and directly link this common mutation to the characteristic pathology.

Science 2013; 339: 1335

Eitan Israeli

Capsule

Lowered serum amyloid-β1-42 autoantibodies in individuals with lifetime depression

Reduced levels of naturally occurring autoantibodies against amyloid-β (Aβ) have been described in Alzheimer's disease (AD). Lifetime depression doubles the risk of AD, thus these autoantibodies may also be reduced in this group. Maetzler and colleagues measured serum immunoglobulin G autoantibody titers against Aβ1-42, S100b and α-synuclein in 214 individuals with depression and 419 controls. Titers against Aβ1-42 were lower in individuals with lifetime depression (5544.6 ± 389.3) compared to controls (7208.7 ± 482.4, $P = 0.048$). Titers against S100b and α-synuclein were comparable between the cohorts. These data suggest an AD-like impairment of the humoral immune response in a relevant proportion of individuals with depression.

J Alzheimers Dis 2012; 32 (1): 95

Elias Toubi

Capsule

Epidermal growth factor regulates hematopoietic regeneration after radiation injury

The mechanisms that regulate hematopoietic stem cell (HSC) regeneration after myelosuppressive injury are not well understood. Doan et al. identified epidermal growth factor (EGF) to be highly enriched in the bone marrow serum of mice bearing deletion of *Bak* and *Bax* in TIE2-expressing cells in *Tie*2Cre; *Bak1*$^{-/-}$; *Bax*flox/$^{-}$ mice. These mice showed radioprotection of the HSC pool and 100% survival after a lethal dose of total-body irradiation (TBI). Bone marrow HSCs from wild-type mice expressed functional EGF receptor (EGFR), and systemic administration of EGF promoted the recovery of the HSC pool in vivo and improved the survival of mice after TBI. Conversely, administration of erlotinib, an EGFR antagonist, decreased both HSC regeneration and the survival of mice after TBI. Mice with EGFR deficiency in VAV-expressing hematopoietic cells also had delayed recovery of bone marrow stem and progenitor cells after TBI. Mechanistically, EGF reduced radiation-induced apoptosis of HSCs and mediated this effect through repression of the proapoptotic protein PUMA. These findings show that EGFR signaling regulates HSC regeneration after myelosuppressive injury.

Nature Med 2013; 19: 295

Eitan Israeli

Capsule

Interaction with activated monocytes enhances cytokine expression and suppressive activity of human CD4+CD45ro+CD25+CD127(low) regulatory T cells

Despite the high frequency of CD4+ T cells with a regulatory phenotype (CD25+CD127(low) FoxP3+) in the joints of patients with rheumatoid arthritis (RA), inflammation persists. One possible explanation is that human Treg cells are converted into pro-inflammatory interleukin-17 (IL-17)-producing cells by inflammatory mediators and thereby lose their suppressive function. Walter et al. set out to investigate whether activated monocytes, which are potent producers of inflammatory cytokines and are abundantly present in the rheumatic joint, induce pro-inflammatory cytokine expression in human Treg cells and impair their regulatory function. The presence and phenotype of CD4+CD45RO+CD25+CD127(low) T cells (memory Treg cells) and CD14+ monocytes in the peripheral blood (PB) and synovial fluid (SF) of patients with RA were investigated by flow cytometry. Memory Treg cells obtained from healthy control subjects underwent fluorescence-activated cell sorting and were then co-cultured with autologous activated monocytes and stimulated with anti-CD3 monoclonal antibodies. Intracellular cytokine expression, phenotype, and function of cells were determined by flow cytometry, enzyme-linked immunosorbent assay, and proliferation assays. In patients with RA, the frequencies of CD4+CD45RO+CD25+CD127(low) Treg cells and activated CD14+ monocytes were higher in SF compared with PB. In vitro-activated monocytes induced an increase in the percentage of IL-17-positive, interferon-gamma (IFNγ)-positive, and tumor necrosis factor-alpha (TNFα)-positive Treg cells as well as IL-10-positive Treg cells. The observed increase in IL-17-positive and IFNγ-positive Treg cells was driven by monocyte-derived interleukin (IL)-1β, IL-6, and TNFα and was mediated by both CD14+CD16- and CD14+CD16+ monocyte subsets. Despite enhanced cytokine expression, cells maintained their CD25+FoxP3+CD39+ Treg cell phenotype and showed an enhanced capacity to suppress T cell proliferation and IL-17 production. Treg cells exposed to a pro-inflammatory environment showed increased cytokine expression as well as enhanced suppressive activity.

Arthritis Rheum 2013; 65 (3): 627

Elias Toubi

Capsule

Cytokine levels and histopathology in chronic HBV and HCV

The changes in balance of cytokine profile may result in either recovery or persistence of hepatitis B virus (HBV) and hepatitis C virus (HCV) infections. Akcam and co-scientists aimed to reveal a possible correlation between cytokine levels, i.e., tumor necrosis factor-alpha (TNFα), interferon-gamma (IFNγ), interleukin (IL)-10, IL-18, and transforming growth factor-beta (TGFβ); and Ishak score or fibrosis in patients with chronic hepatitis B (CHB) or chronic hepatitis C (CHC). Fifty patients with CHB (n=25), CHC (n=25), and the control group of subjects with negative hepatitis B and C serology (n=30) were included in the study. Patients who did not agree to participate in the study were excluded. Serum cytokine levels were measured by ELISA. Liver biopsies from the patients were also taken for pathological analyses by the same pathologist. The serum levels of TNFα, IL-10 and IL-18 in the hepatitis C group were significantly high compared with those of the control group ($P = 0.017$, $P = 0.001$, and $P = 0.004$ respectively), but only IL-10 levels in the hepatitis B group were significantly high ($P = 0.001$). These groups did not show any significant difference with respect to IFNγ or TGFβ levels. In patients with CHB or CHC, there was a significant correlation ($P = 0.000$) between TNFα and Ishak score or fibrosis, but no such correlation was found with IFNγ, IL-10, IL-18, or TGFβ. Results showed that cytokine activities were important indicators of clinical severity and progression of HBV and HCV infections. Further investigation on possible effects of cytokines on hepatocellular damage and fibrosis should be undertaken with new immunopathological approaches to viral hepatitis.

J Interferon Cytokine Res 2012; 32 (12): 570

Elias Toubi

Capsule

Vitamin D deficiency and risk for rheumatic diseases

The role of vitamin D in situations other than calcium homeostasis and bone health has become topical. It is apparent that vitamin D has significant effects on the immune system and as such may contribute to the pathogenesis of autoimmune disease. Gatenby examines the evidence to date that vitamin D has a role in immune-mediated rheumatic disorders. Low vitamin D status is reported in many inflammatory rheumatic conditions. In some this extends to an association with disease activity. Vitamin D acts on a number of cells involved in both innate and acquired immunity, biasing the adaptive immune system away from Th17 and Th1 towards Th2 and Tregs. Deficiency, accordingly, could encourage autoimmunity. Direct evidence for this plausible mechanism in specific diseases remains to be demonstrated. To date, there is a dearth of controlled trials of vitamin D in prophylaxis or therapy. Vitamin D deficiency may well be an important factor in autoimmune rheumatic disease, including initial disease development and worsening the disease once present. This is testable and there is a pressing need for therapeutic studies.

Curr Opin Rheumatol 2013; 2 (2): 184

Elias Toubi

Capsule

In vitro assessment of mesenchymal stem cells immunosuppressive potential in multiple sclerosis patients

Mesenchymal stem cells (MSC) are promising for multiple sclerosis (MS) treatment. However, clinical results remain controversial, and no criteria are available for predicting the efficiency of MSC therapy. Using an in vitro model of lymphocytes and MSC co-cultivation, Zafranskaya et al. revealed that the Index of MSC Suppression of myelin-induced memory T cells proliferation was stronger than that of PHA-stimulated proliferation and inversely correlated with patients' EDSS score. In vitro expression of CD119 (IFNGR1) in mitogen/myelin-stimulated T cells increased in the presence of MSC, being inversely correlated with T lymphocyte proliferation. The Index of MSC Suppression and CD119 expression in T lymphocytes may be useful when assessing MSC immunosuppressive potential in MS patients.

Immunol Lett 2013; 149 (1-2): 9

Elias Toubi

Capsule

Cerebrospinal fluid CD19(+) B cell expansion in N-methyl-D-aspartate receptor encephalitis

There is increasing interest in the role of autoantibodies in acquired autoimmune central nervous system disorders. N-methyl-D-aspartate receptor (NMDAR) encephalitis is an autoimmune encephalitis defined by the presence of autoantibodies that bind to the NMDAR. Although there is evidence of NMDAR antibody pathogenicity, it is unclear which treatment results in the best outcome. Dale et al. measured the proportion of B cells in the cerebrospinal fluid of two children with NMDAR encephalitis (a 6 year old male and a 4 year old female), one in the acute phase and one in the relapsing phase. The proportion of CD19(+) B cells in both children was greater than 10%, significantly higher than seen in non-inflammatory neurological disorders (< 1%). This finding supports the use of drugs, such as rituximab, that deplete B cells in severe or refractory cases of NMDAR encephalitis, and lends further support to the humoral autoimmune hypothesis in NMDAR encephalitis.

Dev Med Child Neurol 2013; 55 (2): 191

Elias Toubi

Capsule

Anti-IFN-α/β receptor antibody treatment ameliorates disease in lupus-predisposed mice

The demonstration in humans and mice that nucleic acid-sensing TLRs and type 1 interferons are essential disease mediators is a milestone in delineating the mechanisms of lupus pathogenesis. Baccala et al. show that *Ifnb* gene deletion does not modify disease progression in NZB mice, thereby strongly implicating IFNα subtypes as the principal pathogenic effectors. They further document that long-term treatment of male BXSB mice with an anti-IFNα/β receptor Ab of mouse origin reduced serologic, cellular and histologic disease manifestations and extended survival, suggesting that disease acceleration by the *Tlr7* gene duplication in this model is mediated by type 1 IFN signaling. The efficacy of this treatment in BXSB mice was clearly evident when applied early in the disease process, but only partial reductions in some disease characteristics were observed when treatment was initiated at later stages. A transient therapeutic effect was also noted in the MRL-Fas(lpr) model, although overall mortality was unaffected. The combined findings suggest that IFNα/β receptor blockade, particularly when started at early disease stages, may be a useful treatment approach for human systemic lupus erythematosus and other autoimmune syndromes.

J Immunol 2012; 189 (12): 5976

Elias Toubi