Capsule

A Crohn's disease variant in *ATG16L1* enhances its degradation by caspase 3

Crohn's disease is a debilitating inflammatory bowel disease (IBD) that can involve the entire digestive tract. A single-nucleotide polymorphism (SNP) encoding a missense variant in the autophagy gene *ATG16L1* (rs2241880, Thr300Ala) is strongly associated with the incidence of Crohn's disease. Numerous studies have demonstrated the effect of *ATG16L1* deletion or deficiency; however, the molecular consequences of the Thr300Ala (T300A) variant remains unknown. Murthy et al. show that amino acids 296–299 constitute a caspase cleavage motif in ATG16L1 and that the T300A variant (T316A in mice) significantly increases ATG16L1 sensitization to caspase-3-mediated processing. The authors observed that death-receptor activation or starvation-induced metabolic stress in human and murine macrophages increased degradation of the T300A or T316A variants of ATG16L1, respectively, resulting in diminished autophagy. Knock-in mice harboring the T316A variant showed defective clearance of the ileal pathogen *Yersinia enterocolitica* and an elevated inflammatory cytokine response. In turn, deletion of the caspase-3-encoding gene, *Casp3*, or elimination of the caspase cleavage site by site-directed mutagenesis rescued starvation-induced autophagy and pathogen clearance, respectively. These findings demonstrate that caspase 3 activation in the presence of a common risk allele leads to accelerated degradation of ATG16L1, placing cellular stress, apoptotic stimuli and impaired autophagy in a unified pathway that predisposes to Crohn's disease.

Nature 2014; 506: 456

Eitan Israeli

Capsule

Vitamin D and multiple health outcomes: umbrella review

Theodoratou et al. evaluated the breadth, validity, and presence of biases of the associations of vitamin D with diverse outcomes. The authors performed an umbrella review of the evidence across systematic reviews and meta-analyses of observational studies of plasma 25-hydroxyvitamin D or 1,25-dihydroxyvitamin D concentrations and randomized controlled trials of vitamin D supplementation. The identified 107 systematic literature reviews and 74 meta-analyses of observational studies of plasma vitamin D concentrations and 87 meta-analyses of randomized controlled trials of vitamin D supplementation. The relation between vitamin D and 137 outcomes was explored, covering a wide range of skeletal, malignant, cardiovascular, autoimmune, infectious, metabolic, and other diseases. Ten outcomes were examined by both meta-analyses of observational studies and meta-analyses of randomized controlled trials, but the direction of the effect and level of statistical significance was concordant only for birth weight (maternal vitamin D status or supplementation). On the basis of the available evidence, an association between vitamin D concentrations and birth weight, dental caries in children, maternal vitamin D concentrations at term, and parathyroid hormone concentrations in patients with chronic kidney disease requiring dialysis is probable, but further studies and better designed trials are needed to draw firmer conclusions. In contrast to previous reports, evidence does not support the argument that vitamin D-only supplementation increases bone mineral density or reduces the risk of fractures or falls in older people. The authors conclude that despite a few hundred systematic reviews and meta-analyses, highly convincing evidence of a clear role of vitamin D does not exist for any outcome, but associations with a selection of outcomes are probable.

BMJ 2014; 348: g2035

Eitan Israeli

Capsule

A new transcriptional role for matrix metalloproteinase-12 in antiviral immunity

Interferon-alpha (IFNα) is essential for antiviral immunity, but in the absence of matrix metalloproteinase-12 (MMP-12) or IκBα (encoded by NFKBIA) Marchant et al. show that IFNα is retained in the cytosol of virus-infected cells and is not secreted. These findings suggest that activated IκBα mediates the export of IFNα from virus-infected cells and that the inability of cells in Mmp12–/– but not wild-type mice to express IκBα and thus export IFNα makes coxsackievirus type B3 infection lethal and renders respiratory syncytial virus more pathogenic. The authors show that after macrophage secretion, MMP-12 is transported into virus-infected cells. In HeLa cells MMP-12 is also translocated to the nucleus, where it binds to the NFKBIA promoter, driving transcription. They also identified dual-regulated substrates that are repressed both by MMP-12 binding to the substrate's gene exons and by MMP-12-mediated cleavage of the substrate protein itself. Whereas intracellular MMP-12 mediates NFKBIA transcription, leading to IFNα secretion and host protection, extracellular MMP-12 cleaves off the IFNα receptor 2 binding site of systemic IFNα, preventing an unchecked immune response. Consistent with an unexpected role for MMP-12 in clearing systemic IFNα, treatment of coxsackievirus type B3-infected wild-type mice with a membrane-impermeable MMP-12 inhibitor elevates systemic IFNα levels and reduces viral replication in pancreas while sparing intracellular MMP-12. These findings suggest that inhibiting extracellular MMP-12 could be a new avenue for the development of antiviral treatments.

Nature Med 2014; 20: 493

Eitan Israeli

Capsule

Aggregated neutrophil extracellular traps limit inflammation by degrading cytokines and chemokines

Gout is characterized by an acute inflammatory reaction and the accumulation of neutrophils in response to monosodium urate (MSU) crystals. Inflammation resolves spontaneously within a few days, although MSU crystals can still be detected in the synovial fluid and affected tissues. Schauer and co-workers report that neutrophils recruited to sites of inflammation undergo oxidative burst and form neutrophil extracellular traps (NETs). Under high neutrophil densities, these NETs aggregate and degrade cytokines and chemokines via serine proteases. Tophi, the pathognomonic structures of chronic gout, share characteristics with aggregated NETs, and MSU crystals can induce NETosis and aggregation of NETs. In individuals with impaired NETosis, MSU crystals induce uncontrolled production of inflammatory mediators from neutrophils and persistent inflammation. Furthermore, in models of neutrophilic inflammation, NETosis-deficient mice develop exacerbated and chronic disease that can be reduced by adoptive transfer of aggregated NETs. These findings suggest that aggregated NETs promote the resolution of neutrophilic inflammation by degrading cytokines and chemokines and disrupting neutrophil recruitment and activation.

Nature Med 2014; 20: 511

Eitan Israeli

Capsule

Protection against filovirus diseases by a novel broad-spectrum nucleoside analogue BCX4430

Filoviruses are emerging pathogens and causative agents of viral hemorrhagic fever. Case-fatality rates of filovirus disease outbreaks are among the highest reported for any human pathogen, exceeding 90%. Licensed therapeutic or vaccine products are not available to treat filovirus diseases. Candidate therapeutics previously shown to be efficacious in non-human primate disease models are based on virus-specific designs and have limited broad-spectrum antiviral potential. Warren et al. show that BCX4430, a novel synthetic adenosine analogue, inhibits infection of distinct filoviruses in human cells. Biochemical, reporter-based and primer-extension assays indicate that BCX4430 inhibits viral RNA polymerase function, acting as a non-obligate RNA chain terminator. Post-exposure intramuscular administration of BCX4430 protects against Ebola virus and Marburg virus disease in rodent models. Most importantly, BCX4430 completely protects cynomolgus macaques from Marburg virus infection when administered as late as 48 hours after infection. In addition, BCX4430 exhibits broad-spectrum antiviral activity against numerous viruses, including bunyaviruses, arenaviruses, paramyxoviruses, coronaviruses and flaviviruses. This is the first report of non-human primate protection from filovirus disease by a synthetic drug-like small molecule. The authors provide additional pharmacological characterizations supporting the potential development of BCX4430 as a counter-measure against human filovirus diseases and other viral diseases representing major public health threats.

Nature 2014; 508: 402

Eitan Israeli

Capsule

Variability in the CIITA gene interacts with HLA in multiple sclerosis

The human leukocyte antigen (HLA) is the main genetic determinant of multiple sclerosis (MS) risk. Within the HLA, the class II HLA-DRB1*15:01 allele exerts a disease-promoting effect, whereas the class I HLA-A*02 allele is protective. The CIITA gene is crucial for expression of class II HLA molecules and has previously been found to associate with several autoimmune diseases, including MS and type 1 diabetes. Gyllenberg et al. performed association analyses with CIITA in 2000 MS cases and up to 6900 controls as well as interaction analysis with HLA. The authors found that the previously investigated single-nucleotide polymorphism rs4774 is associated with MS risk in cases carrying the HLA-DRB1*15 allele ($P = 0.01$, odds ratio OR 1.21, 95% confidence interval 1.04–1.40) or the HLA-A*02 allele ($P = 0.01$, OR 1.33, 95%CI 1.07–1.64) and that these associations are independent of the adjacent confirmed MS susceptibility gene CLEC16A. They also confirm interaction between rs4774 and HLA-DRB1*15:01 such that individuals carrying the risk allele for rs4774 and HLA-DRB1*15:01 have a higher than expected risk for MS. In conclusion, these findings support previous data that variability in the CIITA gene affects MS risk, but also that the effect is modulated by MS-associated HLA haplotypes. These findings further underscore the biological importance of HLA for MS risk.

Genes Immun 2014; 15: 162

Eitan Israeli

Capsule

Dynamics and associations of microbial community types across the human body

A primary goal of the Human Microbiome Project (HMP) was to provide a reference collection of 16S ribosomal RNA gene sequences collected from sites across the human body that would allow microbiologists to better associate changes in the microbiome with changes in health. The HMP Consortium has reported the structure and function of the human microbiome in 300 healthy adults at 18 body sites from a single time point. Using additional data collected over the course of 12–18 months, Ding and fellow-researchers used Dirichlet multinomial mixture models to partition the data into community types for each body site and made three important observations. First, there were strong associations between whether individuals had been breastfed as an infant, their gender, and their level of education on the one hand, and their community types at several body sites on the other. Second, although the specific taxonomic compositions of the oral and gut microbiomes were different, the community types observed at these sites were predictive of each other. Finally, over the course of the sampling period, the community types from sites within the oral cavity were the least stable, whereas those in the vagina and gut were the most stable. These results demonstrate that even with the considerable intra- and interpersonal variation in the human microbiome, this variation can be partitioned into community types that are predictive of each other and are probably the result of life-history characteristics. Understanding the diversity of community types and the mechanisms that result in an individual having a particular type or changing types will allow us to use their community types to assess disease risk and to personalize therapies.

Nature 2014; 509: 357

Eitan Israeli

Capsule

Tadalafil for prevention of erectile dysfunction after radiotherapy for prostate cancer

Tadalafil is used to treat erectile dysfunction after prostate cancer treatment, but its role as a preventive agent is undefined. Pisansky et al. tried to determine primarily whether tadalafil preserved erectile function in men treated with radiotherapy for prostate cancer, and secondarily to determine whether participant- or partner-reported overall sexual function and sexual and marital satisfaction were affected. Among 221 evaluable participants, 80 (79%, 95%CI 70–88%) assigned to receive tadalafil retained erectile function between weeks 28 and 30 compared with 61 (74%, 95%CI 63–85%) assigned to receive placebo (P = 0.49), an absolute difference of 5% (95% CI, –9% to 19%). A significant difference was also not observed at 1 year (72%, 95%CI 60–84% vs. 71%, 95%CI 59–84%; P=0.93). Tadalafil was not associated with significantly improved overall sexual function or satisfaction; a significant difference was not observed in any domain subscale. Partners of men assigned tadalafil noted no significant effect on sexual satisfaction, and marital adjustment was not significantly improved in participants or partners.

JAMA 2014; 311: 1300

Eitan Israeli

Capsule

Cystathionine γ-lyase deficiency mediates neurodegeneration in Huntington's disease

Huntington's disease is an autosomal dominant disease associated with a mutation in the gene encoding huntingtin (Htt), leading to expanded polyglutamine repeats of mutant Htt (mHtt) that elicit oxidative stress, neurotoxicity, and motor and behavioral changes. Huntington's disease is characterized by highly selective and profound damage to the corpus striatum, which regulates motor function. Striatal selectivity of Huntington's disease may reflect the striatally selective small G protein Rhes binding to mHtt and enhancing its neurotoxicity. Specific molecular mechanisms by which mHtt elicits neurodegeneration have been hard to determine. Paul et al. show a major depletion of cystathionine γ-lyase (CSE), the biosynthetic enzyme for cysteine, in Huntington's disease tissues, which may mediate Huntington's disease pathophysiology. The defect occurs at the transcriptional level and seems to reflect influences of mHtt on specificity protein 1, a transcriptional activator for CSE. Consistent with the notion of loss of CSE as a pathogenic mechanism, supplementation with cysteine reverses abnormalities in cultures of Huntington's disease tissues and in intact mouse models of Huntington's disease, suggesting therapeutic potential.

Nature 2014; 509: 96

Eitan Israeli

Capsule

Signaling dynamics for B cell receptor

The signaling pathways that activate the transcription factor NF-κB are key regulatory pathways in cells of the immune system, and their dynamic properties are still being elucidated. In B cells, analysis of single-cell responses has shown that the stimulation of the B cell receptor causes a "digital" all-or-none response of cells to a stimulus. Shinohara and colleagues used a combination of mathematical modeling and experiments to show that this property of the system results from the presence of a positive feedback loop among the signaling components activated in response to the receptor. Studies in cells expressing mutated signaling components resolved key phosphorylation events that provide the threshold responses observed and identified potential molecular modifications that might modify the threshold or other aspects of the dynamic response.

Science 2014; 344: 760

Eitan Israeli