Capsule

Rev-erb-α modulates skeletal muscle oxidative capacity by regulating mitochondrial biogenesis and autophagy

The nuclear receptor Rev-erb-α modulates hepatic lipid and glucose metabolism, adipogenesis and the inflammatory response in macrophages. Woldt et al. show that Rev-erb-α is highly expressed in oxidative skeletal muscle and that its deficiency in muscle leads to reduced mitochondrial content and oxidative function, as well as upregulation of autophagy. These cellular effects resulted in both impaired mitochondrial biogenesis and increased clearance of this organelle, leading to compromised exercise capacity. On a molecular level, Rev-erb-α deficiency resulted in deactivation of the Lkb1-Ampk-Sirt1–Ppargc-1α signaling pathway. These effects were recapitulated in isolated fibers and in muscle cells after knockdown of the gene encoding Rev-erb-α, *Nr1d1*. In complementary experiments, Rev-erb-α overexpression in vitro increased the number of mitochondria and improved respiratory capacity, whereas muscle overexpression or pharmacological activation of Rev-erb-α in vivo increased exercise capacity. This study identifies Rev-erb-α as a pharmacological target that improves muscle oxidative function by modulating gene networks controlling mitochondrial number and function.

Nature Med 2013; 19: 1039

Eitan Israeli

Capsule

Origin and function of myofibroblasts in kidney fibrosis

Myofibroblasts are associated with organ fibrosis, but their precise origin and functional role remain unknown. LeBleu and collaborators used multiple genetically engineered mice to track, fate map and ablate cells to determine the source and function of myofibroblasts in kidney fibrosis. Through this comprehensive analysis, they identified that the total pool of myofibroblasts is split, with 50% arising from local resident fibroblasts through proliferation. The non-proliferating myofibroblasts derive through differentiation from bone marrow (35%), the endothelial-to-mesenchymal transition program (10%) and the epithelial-to-mesenchymal transition program (5%). Specific deletion of *Tgfbr2* in α-smooth muscle actin (αSMA)+ cells revealed the importance of this pathway in the recruitment of myofibroblasts through differentiation. Using genetic mouse models and a fate-mapping strategy, the authors determined that vascular pericytes probably do not contribute to the emergence of myofibroblasts or fibrosis. These data suggest that targeting diverse pathways is required to substantially inhibit the composite accumulation of myofibroblasts in kidney fibrosis.

Nature Med 2013; 19: 1047

Eitan Israeli

Capsule

The relationship of Asperger's syndrome to autism: a preliminary EEG coherence study

It has long been debated whether Asperger's Syndrome (ASP) should be considered part of the Autism Spectrum Disorders (ASD) or whether it constitutes a unique entity. Duffy et al. used EEG coherence, a measure of brain connectivity, to explore possible neurophysiological differences between ASP and ASD. Using prior EEG coherence-based DFA rules that successfully classified subjects as either controls or ASD, 96.2% of ASP subjects were classified as ASD. However, when ASP subjects were directly compared to ASD subjects using new DFA rules, 92.3% of ASP subjects were identified as separate from the ASD population. By contrast, five randomly selected subsamples of ASD subjects failed to reach significance when compared to the remaining ASD populations. When represented by the discriminant variable, both the ASD and ASD populations were normally distributed. Within a control-ASD dichotomy, an ASP population fell closer to ASD than controls. However, when compared directly with ASD, an ASP population was distinctly separate. The ASP population appears to constitute a neurophysiologically identifiable, normally distributed entity within the higher functioning tail of the ASD population distribution. These results must be replicated with a larger sample given their potentially immense clinical, emotional and financial implications for affected individuals, their families and their caregivers.

BMC Med 2013; 11: 175

Eitan Israeli

Capsule

An interleukin 17-mediated paracrine network promotes tumor resistance to anti-angiogenic therapy

Although angiogenesis inhibitors have provided substantial clinical benefit as cancer therapeutics, their use is limited by resistance to their therapeutic effects. While ample evidence indicates that such resistance can be influenced by the tumor microenvironment, the underlying mechanisms remain incompletely understood. Chung and team have uncovered a paracrine signaling network between the adaptive and innate immune systems that is associated with resistance in multiple tumor models: lymphoma, lung and colon. Tumor-infiltrating T helper type 17 (T_H17) cells and interleukin-17 (IL-17) induced the expression of granulocyte colony-stimulating factor (G-CSF) through nuclear factor κB (NF-κB) and extracellular-related kinase (ERK) signaling, leading to immature myeloid cell mobilization and recruitment into the tumor microenvironment. The occurrence of T_H17 cells and Bv8-positive granulocytes was also observed in clinical tumor specimens. Tumors resistant to treatment with antibodies to vascular endothelial growth factor (VEGF) were rendered sensitive in IL-17 receptor (IL-17R)-knockout hosts deficient in T_H17 effector function. Furthermore, pharmacological blockade of T_H17 cell function sensitized resistant tumors to therapy with antibodies to VEGF. These findings indicate that IL-17 promotes tumor resistance to VEGF inhibition, suggesting that immunomodulatory strategies could improve the efficacy of anti-angiogenic therapy.

Nature Med 2013; 19: 1114

Eitan Israeli

Capsule

The toxicity of anti-prion antibodies is mediated by the flexible tail of the prion protein

Prion infections cause lethal neurodegeneration. This process requires the cellular prion protein (PrP^C), which contains a globular domain hinged to a long amino-proximal flexible tail. Sonati et al. describe rapid neurotoxicity in mice and cerebellar organotypic cultured slices exposed to ligands targeting the α1 and α3 helices of the PrP^C globular domain. Ligands included seven distinct monoclonal antibodies, monovalent Fab_1 fragments and recombinant single-chain variable fragment mini-antibodies. Similar to prion infections, the toxicity of globular domain ligands required neuronal PrP^C, was exacerbated by PrP^C overexpression, was associated with calpain activation and was antagonized by calpain inhibitors. Neurodegeneration was accompanied by a burst of reactive oxygen species, and was suppressed by antioxidants. Furthermore, genetic ablation of the superoxide-producing enzyme NOX2 (also known as CYBB) protected mice from globular domain ligand toxicity. The authors also found that neurotoxicity was prevented by deletions of the octapeptide repeats within the flexible tail. These deletions did not appreciably compromise globular domain antibody binding, suggesting that the flexible tail is required to transmit toxic signals that originate from the globular domain and trigger oxidative stress and calpain activation. Supporting this view, various octapeptide ligands were not only innocuous to both cerebellar organotypic cultured slices and mice, but also prevented the toxicity of globular domain ligands while not interfering with their binding. The authors conclude that PrP^C consists of two functionally distinct modules, with the globular domain and the flexible tail exerting regulatory and executive functions, respectively. Octapeptide ligands also prolonged the life of mice expressing the toxic PrP^Cmutant^Z, PrP(Δ94–134), indicating that the flexible tail mediates toxicity in two distinct PrP^C-related conditions. Flexible tail-mediated toxicity may conceivably play a role in further prion pathologies, such as familial Creutzfeldt-Jakob disease in humans bearing supernumerary octapeptides.

Nature 2013; 501: 102

Eitan Israeli

Capsule

Safety and efficacy of RNAi therapy for transthyretin amyloidosis

Transthyretin amyloidosis is caused by the deposition of hepatocyte-derived transthyretin amyloid in peripheral nerves and the heart. A therapeutic approach mediated by RNA interference (RNAi) could reduce the production of transthyretin. Coelho et al. identified a potent anti-transthyretin small interfering RNA, which was encapsulated in two distinct first- and second-generation formulations of lipid nanoparticles, generating ALN-TTR01 and ALN-TTR02, respectively. Each formulation was studied in a single-dose, placebo-controlled phase 1 trial to assess safety and effect on transthyretin levels. The authors first evaluated ALN-TTR01 (at doses of 0.01 to 1.0 mg/kg of body weight) in 32 patients with transthyretin amyloidosis and then evaluated ALN-TTR02 (at doses of 0.01 to 0.5 mg/kg) in 17 healthy volunteers. Rapid, dose-dependent and durable lowering of transthyretin levels was observed in the two trials. At a dose of 1.0 mg/kg, ALN-TTR01 suppressed transthyretin, with a mean reduction at day 7 of 38%, as compared with placebo ($P = 0.01$); levels of mutant and non-mutant forms of transthyretin were lowered to a similar extent. For ALN-TTR02, the mean reductions in transthyretin levels at doses of 0.15–0.3 mg/kg ranged from 82.3 to 86.8%, with reductions of 56.6–67.1% at 28 days ($P < 0.001$ for all comparisons). These reductions were shown to be RNAi-mediated. Mild-to-moderate infusion-related reactions occurred in 20.8% and 7.7% of participants receiving ALN-TTR01 and ALN-TTR02, respectively.

N Engl J Med 2013; 369: 819

Eitan Israeli

Capsule

Vitamin D effects on musculoskeletal health, immunity, autoimmunity, cardiovascular disease, cancer, fertility, pregnancy, dementia and mortality

Optimal vitamin D intake and its status are important not only for bone and calcium-phosphate metabolism, but also for overall health and well-being. Vitamin D deficiency and insufficiency as a global health problem are likely to be a risk for a wide spectrum of acute and chronic illnesses. Reviewing randomized controlled trials, meta-analyses, and other evidence of vitamin D action on various health outcomes, Pludowski and colleagues found that adequate vitamin D status seems to be protective against musculoskeletal disorders (muscle weakness, falls, fractures), infectious diseases, autoimmune diseases, cardiovascular disease, type 1 and type 2 diabetes mellitus, several types of cancer, neurocognitive dysfunction and mental illness, and other diseases, as well as infertility and adverse pregnancy and birth outcomes. Vitamin D deficiency/insufficiency is associated with all-cause mortality. They concluded that adequate vitamin D supplementation and sensible sunlight exposure to reach optimal vitamin D status are among the front-line factors of prophylaxis for the spectrum of disorders. Supplementation guidance and population strategies for the eradication of vitamin D deficiency must be included in the priorities of physicians, medical professionals and healthcare policy-makers.

Autoimmun Rev 2013; 12: 976

Eitan Israeli

Capsule

Richness of human gut microbiome correlates with metabolic markers

We are facing a global metabolic health crisis provoked by an obesity epidemic. Le Chatelier and co-workers assessed the human gut microbial composition in a population sample of 123 non-obese and 169 obese Danish individuals. The authors found two groups of individuals differing by the number of gut microbial genes and thus gut bacterial richness, and containing known and previously unknown bacterial species at different proportions; individuals with a low bacterial richness (23% of the population) are characterized by more marked overall adiposity, insulin resistance and dyslipidemia and a more pronounced inflammatory phenotype when compared with individuals having high bacterial richness. The obese individuals among the lower bacterial richness group also gain more weight over time. Only a few bacterial species are sufficient to distinguish between individuals with high and low bacterial richness, and even between lean and obese participants. This classifications based on variation in the gut microbiome identify subsets of individuals in the general white adult population who may be at increased risk of progressing to adiposity-associated co-morbidities.

Nature 2013; 500: 541

Eitan Israeli

Capsule

Worldwide research productivity in the field of rheumatology

Bibliometric studies on the quantity and quality of articles published in rheumatology journals are scarce. A study by Tao Cheng and Guoyou Zhang compared scientific production in the field of rheumatology between countries and evaluated the publication trend and citations worldwide. Articles published in 39 rheumatology journals from 1996 to 2010 were screened using the Scopus database. The number of articles, citations, Hirsch indices (h-indices) and international collaborations were determined for countries or regions. Publication activity was adjusted for the top 35 countries categorized by population size and gross domestic product (GDP). A total of 43 808 articles were identified. The time trend of the number of articles showed an increase of 2.95-fold between 1996 and 2010. Western Europe and northern America were the most productive world areas, producing 52.4% and 23.1% of the available literature, respectively. The USA published the most articles, followed by the UK and Germany. The USA, the UK and the Netherlands had the highest h-indices (169, 137 and 117, respectively) and ranked about the same when total citations were used. However, Ireland had the highest average citations per article (48.33), followed by Denmark (40.19) and the Netherlands (39.86). Positive associations between the total number of publications/citations and population/GDP were observed ($P < 0.01$). Scandinavian countries ranked the highest after adjusting for population and GDP. Israel ranked very high in all scores – third place in the number of publications per billion US $ GDP, fourth in the number of citations per billion US $ GDP, sixth in the number of publications per 10 million inhabitants and eleventh in citations per 10 million inhabitants.

Rheumatology 2013; 52: 1630

Eitan Israeli

Capsule

Use of oral fluconazole during pregnancy and the risk of birth defects

Case reports suggest that long-term high dose fluconazole treatment for severe fungal infections during pregnancy causes a pattern of birth defects. It is unclear whether commonly used lower doses increase the risk of specific birth defects. The majority of fluconazole-exposed pregnancies were in women who received common therapeutic doses of 150 mg (56% of pregnancies) or 300 mg (31%). Oral fluconazole exposure was not associated with an increased risk of birth defects overall: 210 birth defects among 7352 fluconazole-exposed pregnancies (prevalence, 2.86%) and 25,159 birth defects among 968,236 unexposed pregnancies (prevalence, 2.60%). The adjusted prevalence odds ratio (OR) was 1.06; 95% confidence interval (CI) 0.92–1.21. In addition, oral fluconazole exposure was not associated with a significantly increased risk of 14 of 15 types of birth defects previously linked to azole antifungal agents: craniosynostosis, other craniofacial defects, middle-ear defects, cleft palate, cleft lip, limb defects, limb-reduction defects, polydactyly, syndactyly, diaphragmatic hernia, heart defects overall, pulmonary artery hypoplasia, ventricular septal defects, and hypoplastic left heart. A significantly increased risk of tetralogy of Fallot was observed: 7 cases in fluconazole-exposed pregnancies (prevalence 0.10%) as compared with 287 cases in unexposed pregnancies (prevalence 0.03%); adjusted prevalence OR 3.16 and 95% CI 1.49–6.71.

N Engl J Med 2013; 369: 830

Eitan Israeli

Capsule

Completion of the entire hepatitis C virus life cycle in genetically humanized mice

More than 130 million people worldwide chronically infected with hepatitis C virus (HCV) are at risk of developing severe liver disease. Antiviral treatments are only partially effective against HCV infection, and a vaccine is not available. Development of more efficient therapies has been hampered by the lack of a small animal model. Building on the observation that CD81 and occludin (OCLN) comprise the minimal set of human factors required to render mouse cells permissive to HCV entry, Dorner et al. previously showed that transient expression of these two human genes is sufficient to allow viral uptake into fully immunocompetent inbred mice. Here the authors demonstrate that transgenic mice stably expressing human CD81 and OCLN also support HCV entry, but innate and adaptive immune responses restrict HCV infection in vivo. Blunting antiviral immunity in genetically humanized mice infected with HCV results in measurable viremia over several weeks. In mice lacking the essential cellular co-factor cyclophilin A (CypA), HCV RNA replication is markedly diminished, providing genetic evidence that this process is faithfully recapitulated. Using a cell-based fluorescent reporter activated by the NS3-4A protease we visualize HCV infection in single hepatocytes in vivo. Persistently infected mice produce de novo infectious particles, which can be inhibited with directly acting antiviral drug treatment, thereby providing evidence for the completion of the entire HCV life cycle in inbred mice. This genetically humanized mouse model opens new opportunities to dissect genetically HCV infection in vivo and provides an important preclinical platform for testing and prioritizing drug candidates and may also have utility for evaluating vaccine efficacy

Nature 2013; 501: 237

Eitan Israeli

Capsule

Activation of the Nlrp3 inflammasome in infiltrating macrophages by endocannabinoids mediates beta cell loss in type 2 diabetes

Type 2 diabetes mellitus (T2DM) progresses from compensated insulin resistance to beta cell failure resulting in uncompensated hyperglycemia, a process replicated in the Zucker diabetic fatty (ZDF) rat. The Nlrp3 inflammasome has been implicated in obesity-induced insulin resistance and beta cell failure. Endocannabinoids contribute to insulin resistance through activation of peripheral CB_1 receptors (CB_1Rs) and also promote beta cell failure. Jourdan et al. show that beta cell failure in adult ZDF rats is not associated with CB_1R signaling in beta cells, but rather in M1 macrophages infiltrating into pancreatic islets, and that this leads to activation of the Nlrp3-ASC inflammasome in the macrophages. These effects are replicated in vitro by incubating wild-type human or rodent macrophages, but not macrophages from CB_1R-deficient (*Cnr*1$^{-/-}$) or *Nlrp*3$^{-/-}$ mice, with the endocannabinoid anandamide. Peripheral CB_1R blockade, in vivo depletion of macrophages or macrophage-specific knockdown of CB_1R reverses or prevents these changes and restores normoglycemia and glucose-induced insulin secretion. These findings implicate endocannabinoids and inflammasome activation in beta cell failure and identify macrophage-expressed CB_1R as a therapeutic target in T2DM.

Nature Med 2013; 19: 1132

Eitan Israeli

Capsule

Bacteria activate sensory neurons that modulate pain and inflammation

Nociceptor sensory neurons are specialized to detect potentially damaging stimuli, protecting the organism by initiating the sensation of pain and eliciting defensive behaviors. Bacterial infections produce pain by unknown molecular mechanisms, although they are presumed to be secondary to immune activation. Chiu et al. demonstrated that bacteria directly activate nociceptors, and that the immune response mediated through TLR2, MyD88, T cells, B cells, and neutrophils and monocytes is not necessary for *Staphylococcus aureus*-induced pain in mice. Mechanical and thermal hyperalgesia in mice is correlated with live bacterial load rather than tissue swelling or immune activation. Bacteria induce calcium flux and action potentials in nociceptor neurons, in part via bacterial *N*-formylated peptides and the pore-forming toxin α-hemolysin, through distinct mechanisms. Specific ablation of Nav1.8-lineage neurons, which include nociceptors, abrogated pain during bacterial infection, but concurrently increased local immune infiltration and lymphadenopathy of the draining lymph node. Thus, bacterial pathogens produce pain by directly activating sensory neurons that modulate inflammation, an unsuspected role for the nervous system in host–pathogen interactions.

Nature 2013; 501: 52

Eitan Israeli

Capsule

The scavenger receptor SCARF1 mediates the clearance of apoptotic cells and prevents autoimmunity

The clearance of apoptotic cells is critical for the control of tissue homeostasis; however, the full range of receptors on phagocytes responsible for the recognition of apoptotic cells has yet to be identified. Ramirez-Ortiz et al. found that dendritic cells, macrophages and endothelial cells used the scavenger receptor SCARF1 to recognize and engulf apoptotic cells via the complement component C1q. Loss of SCARF1 impaired the uptake of apoptotic cells. Consequently, in SCARF1-deficient mice, dying cells accumulated in tissues, which led to a lupus-like disease, with the spontaneous generation of autoantibodies to DNA-containing antigens, activation of cells of the immune system, dermatitis and nephritis. The discovery of such interactions of SCARF1 with C1q and apoptotic cells provides insight into the molecular mechanisms involved in the maintenance of tolerance and prevention of autoimmune disease.

Nature immunol 2013; 14: 917

Eitan Israeli

Capsule

Bacterial colonization factors control specificity and stability of the gut microbiota

Mammals harbor a complex gut microbiome, comprising bacteria that confer immunological, metabolic and neurological benefits. Despite advances in sequence-based microbial profiling and myriad studies defining microbiome composition during health and disease, little is known about the molecular processes used by symbiotic bacteria to stably colonize the gastrointestinal tract. Lee and co-researchers sought to define how mammals assemble and maintain the *Bacteroides*, one of the most numerically prominent genera of the human microbiome. They found that, whereas the gut normally contains hundreds of bacterial species, germ-free mice mono-associated with a single *Bacteroides* species are resistant to colonization by the same, but not different, species. To identify bacterial mechanisms for species-specific saturable colonization, the authors devised an in vivo genetic screen and discovered a unique class of polysaccharide utilization loci that is conserved among intestinal *Bacteroides*. They named this genetic locus the commensal colonization factors (*ccf*). Deletion of the *ccf* genes in the model symbiont, *Bacteroides fragilis*, results in colonization defects in mice and reduces horizontal transmission. The *ccf* genes of *B. fragilis* are upregulated during gut colonization, preferentially at the colonic surface. When they visualize microbial biogeography within the colon, *B. fragilis* penetrates the colonic mucus and resides deep within crypt channels, whereas *ccf* mutants are defective in crypt association. Notably, the CCF system is required for *B. fragilis* colonization following microbiome disruption with *Citrobacter rodentium* infection or antibiotic treatment, suggesting that the niche within colonic crypts represents a reservoir for bacteria to maintain long-term colonization. These findings reveal that intestinal *Bacteroides* have evolved species-specific physical interactions with the host that mediate stable and resilient gut colonization, and the CCF system represents a novel molecular mechanism for symbiosis.

Nature 2013; 501: 426

Eitan Israeli

Capsule

Topoisomerases facilitate transcription of long genes linked to autism

Topoisomerases are expressed throughout the developing and adult brain and are mutated in some individuals with autism spectrum disorder (ASD). However, how topoisomerases are mechanistically connected to ASD is unknown. King et al. found that topotecan, a topoisomerase 1 (TOP1) inhibitor, dose-dependently reduces the expression of extremely long genes in mouse and human neurons, including nearly all genes that are longer than 200 kilobases. Expression of long genes is also reduced after knockdown of *Top*1 or *Top2b* in neurons, highlighting that both enzymes are required for full expression of long genes. By mapping RNA polymerase II density genome-wide in neurons, the authors showed that this length-dependent effect on gene expression was due to impaired transcription elongation. Interestingly, many high confidence ASD candidate genes are exceptionally long and were reduced in expression after TOP1 inhibition. These findings suggest that chemicals and genetic mutations that impair topoisomerases could commonly contribute to ASD and other neurodevelopmental disorders.

Nature 2013; 501: 58

Eitan Israeli

Capsule

Usp16 contributes to somatic stem cell defects in Down's syndrome

Down's syndrome results from full or partial trisomy of chromosome 21. However, the consequences of the underlying gene-dosage imbalance on adult tissues remain poorly understood. Adorno et al. show that in Ts65Dn mice, which are trisomic for 132 genes homologous to genes on human chromosome 21, triplication of *Usp16* reduces the self-renewal of hematopoietic stem cells and the expansion of mammary epithelial cells, neural progenitors and fibroblasts. In addition, Usp16 is associated with decreased ubiquitination of Cdkn2a and accelerated senescence in Ts65Dn fibroblasts. Usp16 can remove ubiquitin from histone H2A on lysine 119, a critical mark for the maintenance of multiple somatic tissues. Down-regulation of Usp16, either by mutation of a single normal *Usp16* allele or by short interfering RNAs, largely rescues all of these defects. Furthermore, in human tissues over-expression of USP16 reduces the expansion of normal fibroblasts and postnatal neural progenitors, whereas down-regulation of USP16 partially rescues the proliferation defects of Down's syndrome fibroblasts. Taken together, these results suggest that USP16 has an important role in antagonizing the self-renewal and/or senescence pathways in Down's syndrome and could serve as an attractive target to ameliorate some of the associated pathologies.

Nature 2013; 501: 380

Eitan Israeli