Capsule

Dlk1 promotes a fast motor neuron biophysical signature required for peak force execution

Motor neurons, which relay neural commands to drive skeletal muscle movements, encompass types ranging from "slow" to "fast," whose biophysical properties govern the timing, gradation, and amplitude of muscle force. Muller et al. identify the non-canonical *Notch* ligand Delta-like homolog 1 (Dlk1) as a determinant of motor neuron functional diversification. Dlk1, expressed by ~30% of motor neurons, is necessary and sufficient to promote a fast biophysical signature in the mouse and chick. Dlk1 suppresses Notch signaling and activates expression of the K^+ channel subunit Kcng4 to modulate delayed-rectifier currents. Dlk1 inactivation comprehensively shifts motor neurons toward slow biophysical and transcriptome signatures, while abolishing peak force outputs. Our findings provide insights into the development of motor neuron functional diversity and its contribution to the execution of movements.

Science 2014; 343: 1264
Eitan Israeli

Capsule

Complement Is activated by IgG hexamers assembled at the cell surface

Complement activation by antibodies bound to pathogens, tumors, and self-antigens is a critical feature of natural immune defense, a number of disease processes, and immunotherapies. How antibodies activate the complement cascade, however, is poorly understood. Diebolder et al. found that specific non-covalent interactions between Fc segments of immunoglobulin G (IgG) antibodies resulted in the formation of ordered antibody hexamers after antigen binding on cells. These hexamers recruited and activated C1, the first component of complement, thereby triggering the complement cascade. The interactions between neighboring Fc segments could be manipulated to block, reconstitute, and enhance complement activation and killing of target cells, using all four human IgG subclasses. The authors offer a general model for understanding antibody-mediated complement activation and the design of antibody therapeutics with enhanced efficacy.

Science 2014; 343: 1260
Eitan Israeli

Capsule

Adaptation of innate lymphoid cells to a micronutrient deficiency promotes type 2 barrier immunity

How the immune system adapts to malnutrition to sustain immunity at barrier surfaces, such as the intestine, remains unclear. Vitamin A deficiency is one of the most common micronutrient deficiencies and is associated with profound defects in adaptive immunity. Spencer et al. found that type 3 innate lymphoid cells (ILC3s) are severely diminished in vitamin A-deficient settings, which results in compromised immunity to acute bacterial infection. However, vitamin A deprivation paradoxically resulted in dramatic expansion of interleukin-13 (IL-13)-producing ILC2s and resistance to nematode infection in mice, which revealed that ILCs are primary sensors of dietary stress. Further, these data indicate that, during malnutrition, a switch to innate type 2 immunity may represent a powerful adaptation of the immune system to promote host survival in the face of ongoing barrier challenges.

Science 2014; 343: 432

Eitan Israeli

Capsule

IL-35 producing B cells are critical regulators of immunity during autoimmune and infectious diseases

B lymphocytes have critical roles as positive and negative regulators of immunity. Their inhibitory function has been associated primarily with interleukin 10 (IL-10) because B cell-derived IL-10 can protect against autoimmune disease and increase susceptibility to pathogens. Shen et al. identify IL-35-producing B cells as key players in the negative regulation of immunity. Mice in which only B cells did not express IL-35 lost their ability to recover from the T cell-mediated demyelinating autoimmune disease experimental autoimmune encephalomyelitis (EAE). In contrast, these mice displayed a markedly improved resistance to infection with the intracellular bacterial pathogen *Salmonella enterica* serovar Typhimurium as shown by their superior containment of the bacterial growth and their prolonged survival after primary infection, and upon secondary challenge, compared to control mice. The increased immunity found in mice lacking IL-35 production by B cells was associated with a higher activation of macrophages and inflammatory T cells, as well as an increased function of B cells as antigen-presenting cells (APCs). During Salmonella infection, IL-35- and IL-10-producing B cells corresponded to two largely distinct sets of surface IgM^{+}CD138^{hi}TACI^{+}CXCR4^{+}CD1d^{int}Tim1^{int} plasma cells expressing the transcription factor Blimp1 (also known as Prdm1). During EAE, CD138^{+} plasma cells were also the main source of B cell-derived IL-35 and IL-10. Collectively, our data show the importance of IL-35-producing B cells in regulation of immunity and highlight IL-35 production by B cells as a potential therapeutic target for autoimmune and infectious diseases. This study reveals the central role of activated B cells, particularly plasma cells, and their production of cytokines in the regulation of immune responses in health and disease.

Nature 2014; 507: 366

Eitan Israeli

Capsule

Structure-based programming of lymph-node targeting in molecular vaccines

In cancer patients, visual identification of sentinel lymph nodes (LNs) is achieved by the injection of dyes that bind avidly to endogenous albumin, targeting these compounds to LNs, where they are efficiently filtered by resident phagocytes. Liu et al. translate this "albumin hitchhiking" approach to molecular vaccines, through the synthesis of amphiphiles (amph-vaccines) comprising an antigen or adjuvant cargo linked to a lipophilic albumin-binding tail by a solubility-promoting polar polymer chain. Administration of structurally optimized CpG-DNA/peptide amph-vaccines in mice resulted in marked increases in LN accumulation and decreased systemic dissemination relative to their parent compounds, leading to 30-fold increases in T cell priming and enhanced anti-tumor efficacy while greatly reducing systemic toxicity. Amph-vaccines provide a simple, broadly applicable strategy to simultaneously increase the potency and safety of subunit vaccines.

Nature 2014; 507:5 19

Eitan Israeli

Capsule

Sessile alveolar macrophages communicate with alveolar epithelium to modulate immunity

The tissue-resident macrophages of barrier organs constitute the first line of defense against pathogens at the systemic interface with the ambient environment. In the lung, resident alveolar macrophages (AMs) provide a sentinel function against inhaled pathogens. Bacterial constituents ligate Toll-like receptors (TLRs) on AMs, causing AMs to secrete pro-inflammatory cytokines that activate alveolar epithelial receptors, leading to recruitment of neutrophils that engulf pathogens. Because the AM-induced response could itself cause tissue injury, it is unclear how AMs modulate the response to prevent injury. Using real-time alveolar imaging in situ, Westphalen et al. show that a subset of AMs attached to the alveolar wall form connexin 43 (Cx43)-containing gap junction channels with the epithelium. During lipopolysaccharide-induced inflammation, the AMs remained sessile and attached to the alveoli, and they established intercommunication through synchronized Ca^{2+} waves, using the epithelium as the conducting pathway. The intercommunication was immunosuppressive, involving Ca^{2+}-dependent activation of Akt, because AM-specific knockout of Cx43 enhanced alveolar neutrophil recruitment and secretion of pro-inflammatory cytokines in the bronchoalveolar lavage. A picture emerges of a novel immunomodulatory process in which a subset of alveolus-attached AMs intercommunicates immunosuppressive signals to reduce endotoxin-induced lung inflammation.

Nature 2014; 506: 503

Eitan Israeli

Capsule

Serial mutation

Mutations that affect gene function and, ultimately, the phenotype of an organism are grist to the mill of evolution. While examining the genetic basis for a stable polymorphism observed in bacteria during a long-term mutation experiment, Plucain et al. identified three specific, successive mutational events exhibiting synergistic epistatic and frequency-dependent interactions that enabled one lineage to invade the other and to be maintained. Thus, a series of specific mutations conferred the invasion phenotype and allowed the use of novel resources only when all mutations were present.

Science 2104; 343: 1366

Eitan Israeli

Capsule

Endothelial *Notch* activity promotes angiogenesis and osteogenesis in bone

Blood vessel growth in the skeletal system and osteogenesis seem to be coupled, suggesting the existence of molecular crosstalk between endothelial and osteoblastic cells. Understanding the nature of the mechanisms linking angiogenesis and bone formation should be of great relevance for improved fracture healing or prevention of bone mass loss. Ramasamy et al. show that vascular growth in bone involves a specialized, tissue-specific form of angiogenesis. *Notch* signaling promotes endothelial cell proliferation and vessel growth in postnatal long bone, which is the opposite of the well-established function of *Notch* and its ligand Dll4 in the endothelium of other organs and tumors. Endothelial cell-specific and inducible genetic disruption of *Notch* signaling in mice not only impaired bone vessel morphology and growth, but also led to reduced osteogenesis, shortening of long bones, chondrocyte defects, loss of trabeculae and decreased bone mass. On the basis of a series of genetic experiments, the authors conclude that skeletal defects in these mutants involved defective angiocrine release of Noggin from endothelial cells, which is positively regulated by *Notch*. Administration of recombinant Noggin, a secreted antagonist of bone morphogenetic proteins, restored bone growth and mineralization, chondrocyte maturation, the formation of trabeculae and osteoprogenitor numbers in endothelial cell-specific *Notch* pathway mutants. These findings establish a molecular framework coupling angiogenesis, angiocrine signals and osteogenesis, which may prove significant for the development of future therapeutic applications.

Nature 2014; 507: 376

Eitan Israeli

Capsule

Active or passive exposure to tobacco smoking and allergic rhinitis, allergic dermatitis, and food allergy in adults and children

Allergic rhinitis, allergic dermatitis, and food allergy are extremely common diseases, especially among children, and are frequently associated with each other and with asthma. Smoking is a potential risk factor for these conditions, but so far results from individual studies have been conflicting. Saulyte et al. examined the evidence for an association between active smoking (AS) or passive exposure to second-hand smoke and allergic conditions. The authors retrieved 97 studies on allergic rhinitis, 91 on allergic dermatitis, and 8 on food allergy published in 139 different articles. When all studies were analyzed together (showing random effects model results and pooled odds ratios expressed as relative risk), allergic rhinitis was not associated with active smoking (pooled RR 1.02, 95% confidence interval (CI) 0.92–1.15), but was associated with passive smoking (pooled RR 1.10, 95% CI 1.06–1.15). Allergic dermatitis was associated with both active (pooled RR 1.21, 95% CI 1.14–1.29) and passive smoking (pooled RR 1.07, 95% CI 1.03–1.12). In children and adolescents, allergic rhinitis was associated with active (pooled RR 1.40, 95% CI 1.24–1.59) and passive smoking (pooled RR 1.09, 95% CI 1.04–1.14). Allergic dermatitis was associated with active (pooled RR 1.36, 95% CI 1.17–1.46) and passive smoking (pooled RR 1.06, 95% CI 1.01–1.11). Food allergy was associated with second-hand smoke (1.43, 1.12–1.83) when cohort studies only were examined, but not when all studies were combined. The findings are limited by the potential for confounding and bias, given that most of the individual studies used a cross-sectional design. Furthermore, the studies showed a high degree of heterogeneity and the exposure and outcome measures were assessed by self-report, which may increase the potential for misclassification.

PloS Med 2014; DOI: 10.1371/journal.pmed.1001611

Eitan Israeli

Capsule

Growing back hearing?

Hair cells do not normally regenerate in the mammalian ear, and it has been thought that permanent damage to human hair cells in the cochlea inexorably resulted in hearing loss. However, Bramhall et al. have found that supporting cells in the cochlea taken from newborn mice can turn into hair cells. In a chemical model of damage, explant cultures were treated with gentamycin, and lineage tracing was done to track cell populations. New hair cells arose at a low level from a subpopulation of supporting cells that expressed the *Lgr*5 (leucine-rich repeat-containing G protein-coupled receptor 5) marker, a protein in the *Wnt* signaling pathway. Previous studies had shown that inhibition of the *Notch* signaling pathway can help restore hearing in mice with noise-induced deafness. Here, Bramhall and colleagues found that *Notch* inhibition by a gamma secretase inhibitor increased the fraction of supporting cells that transdifferentiated into hair cells and that the effects of *Notch* were dependent on β-catenin. It is not yet known whether this process can be triggered in older animals.

Stem Cell Rep 2014; 2: 311

Eitan Israeli

Capsule

Link between the complex phenotype of type 2 diabetes and epigenetic modifications

Methylation is a form of epigenetic regulation that can influence gene expression. Furthermore, methylation has been postulated to underlie some complex traits and diseases, especially those for which genetic factors have been poorly identified or functionally understood. In order to investigate the epigenetics of type 2 diabetes (T2D), Dayeh and team examined the genome-wide DNA methylation patterns in pancreatic islets in both diabetics and non-diabetics. They found that the degree of methylation was correlated with transcription, although overall levels of methylation did not differ between diabetics and non-diabetics. Differentially methylated regions between individuals with and without T2D were identified. Of the more than 800 genes exhibiting differential methylation, 102 showed differential mRNA expression, including 17 candidate T2D genes expressed in islets. Furthermore, functional analyses provided support that these observed methylation differences may underlie differences in gene expression and potentially link the complex phenotype of T2D with epigenetic modifications.

PLOS Genet 2014; 10: e1004160

Eitan Israeli

Capsule

Gut immune tolerance

With the constant assault of food antigens and its billions of resident microbes, the gut is an important site of immune tolerance. By studying specific intestinal immune cell populations in genetically modified mice, Mortha and co-authors found that gut macrophages produce the cytokine interleukin-1 (IL-1) in response to signals derived from the microbiota. IL-1 acts on type 3 innate lymphoid cells in the intestine, which then produce the cytokine, colony-stimulating factor 2 (Csf2). Csf-2, in turn, induces myeloid cells (including dendritic cells and macrophages) to produce regulatory factors like retinoic acid and interleukin-10, which support the conversion and expansion of regulatory T cells, a population of cells known to be critical for maintaining immune tolerance in the gut.

Science 2014 10.1126/science.1249288, published online 13 March

Eitan Israeli

Capsule

Health care-associated infection after red blood cell transfusion

The association between red blood cell (RBC) transfusion strategies and health care-associated infection is not fully understood. Rohde et al. evaluated whether RBC transfusion thresholds are associated with the risk of infection and whether risk is independent of leukocyte reduction. The pooled risk of all serious infections was 11.8% (95%CI, 7.0–16.7%) in the restrictive group and 16.9% (95%CI 8.9–25.4%) in the liberal group. The risk ratio (RR) for the association between transfusion strategies and serious infection was 0.82 (95%CI 0.72–0.95) with little heterogeneity ($I^2 = 0\%$, $\tau^2 < 0.0001$). The number needed to treat (NNT) with restrictive strategies to prevent serious infection was 38 (95%CI 24–122). The risk of infection remained reduced with a restrictive strategy, even with leukocyte reduction (RR 0.80, 95%CI 0.67–0.95). For trials with a restrictive hemoglobin threshold of < 7.0 g/dl, the RR was 0.82 (95%CI 0.70–0.97) with NNT of 20 (95%CI 12–133). With stratification by patient type, the RR was 0.70 (95%CI 0.54–0.91) in patients undergoing orthopedic surgery and 0.51 (95%CI 0.28–0.95) in patients presenting with sepsis. There were no significant differences in the incidence of infection by RBC threshold for patients with cardiac disease, the critically ill, those with acute upper gastrointestinal bleeding, or for infants with low birth weight.

JAMA 2014; 311: 1317

Eitan Israeli

Capsule

Adenoma detection rate and risk of colorectal cancer and death

The proportion of screening colonoscopic examinations performed by a physician that detect one or more adenomas (the adenoma detection rate) is a recommended quality measure. However, little is known about the association between this rate and patients' risks of a subsequent colorectal cancer (interval cancer) and death. Using data from an integrated health care delivery organization, Corley et al. evaluated the associations between the adenoma detection rate and the risks of colorectal cancer diagnosed 6 months to 10 years after colonoscopy and of cancer-related death. They evaluated 314,872 colonoscopies performed by 136 gastroenterologists; the adenoma detection rates ranged from 7.4 to 52.5%. During the follow-up period, they identified 712 interval colorectal adenocarcinomas, including 255 advanced-stage cancers, and 147 deaths from interval colorectal cancer. The unadjusted risks of interval cancer according to quintiles of adenoma detection rates, from lowest to highest, were 9.8, 8.6, 8.0, 7.0, and 4.8 cases per 10,000 person-years of follow-up, respectively. Among patients of physicians with adenoma detection rates in the highest quintile, as compared with patients of physicians with detection rates in the lowest quintile, the adjusted hazard ratio for any interval cancer was 0.52 (95% confidence interval [CI] 0.39–0.69), for advanced-stage interval cancer, 0.43 (95%CI 0.29–0.64), and for fatal interval cancer, 0.38 (95%CI 0.22–0.65). Each 1.0% increase in the adenoma detection rate was associated with a 3.0% decrease in the risk of cancer (hazard ratio 0.97, 95%CI 0.96–0.98).

N Engl J Med 2014; 370: 1298

Eitan Israeli

Capsule

Humans can discriminate more than 1 trillion olfactory stimuli

Humans can discriminate several million different colors and almost half a million different tones, but the number of discriminable olfactory stimuli remains unknown. The lay and scientific literature typically claims that humans can discriminate 10,000 odors, but this number has never been empirically validated. Bushdid et al. determined the resolution of the human sense of smell by testing the capacity of humans to discriminate odor mixtures with varying numbers of shared components. On the basis of the results of psychophysical testing, they calculated that humans can discriminate at least 1 trillion olfactory stimuli. This is far more than previous estimates of distinguishable olfactory stimuli. It demonstrates that the human olfactory system, with its hundreds of different olfactory receptors, far outperforms the other senses in the number of physically different stimuli it can discriminate.

Science 2014; 343: 1370

Eitan Israeli

Capsule

A randomized trial of hyperimmune globulin to prevent congenital cytomegalovirus

Congenital infection with human cytomegalovirus (CMV) is a major cause of morbidity and mortality. In an uncontrolled study published in 2005, administration of CMV-specific hyperimmune globulin to pregnant women with primary CMV infection significantly reduced the rate of intrauterine transmission, from 40% to 16%. Revello et al. evaluated the efficacy of hyperimmune globulin in a phase 2, randomized, placebo-controlled, double-blind study. A total of 123 women could be evaluated in the efficacy analysis (1 woman in the placebo group withdrew). The rate of congenital infection was 30% (18 fetuses or infants of 61 women) in the hyperimmune globulin group and 44% (27 fetuses or infants of 62 women) in the placebo group (a difference of 14 percentage points; 95% confidence interval −3 to 31, $P = 0.13$). There was no significant difference between the two groups or within each group, between the women who transmitted the virus and those who did not, with respect to levels of virus-specific antibodies, T cell-mediated immune response, and viral DNA in the blood. The clinical outcome of congenital infection at birth was similar in the two groups. The number of obstetric adverse events was higher in the hyperimmune globulin group than in the placebo group (13% vs. 2%). The authors conclude that in this study of 123 women who could be evaluated, treatment with hyperimmune globulin did not significantly modify the course of primary CMV infection during pregnancy.

N Engl J Med 2014; 370: 316

Eitan Israeli

three key proteins that are biomarkers and/or drug targets for breast cancer: the estrogen receptor, the progesterone receptor, and HER2 (a member of the epidermal growth factor receptor family). Triple-negative tumors are aggressive and more likely to metastasize than other breast cancers, and there is no effective treatment. To acquire new insights into the biology and possible therapy of these tumors, Feigin et al. looked for aberrant expression of G protein-coupled receptors, cell signaling proteins that have been successfully targeted for treatment but not in other breast cancer types. In cell culture, high expression levels of GPR161 induced proliferation of mammary epithelial cells, disrupted the acinar structures formed by these cells, and enhanced their invasive capacity. GPR161 was shown to activate the mTORC1/S6K signaling pathway. These observations suggest that GPR161 dysfunction contributes to the development of triple-negative breast cancers.

Proc Natl Acad Sci USA 2014; 10.1073/pnas.1320239111

Eitan Israeli

Capsule

Misfolded proteins can be targets for autoantibodies

MHC class II molecules can rescue endoplasmic reticulum-localized misfolded proteins from protein degradation and transport them to the cell surface intact by associating with the misfolded protein. MHC class II allelic polymorphisms are associated with susceptibility to many autoimmune diseases. Jin et al. now found that cellular misfolded autoantigens rescued and complexed with MHC class II molecules can become targets for autoantibodies in patients with rheumatoid arthritis (RA). By analyzing sera from some RA patients in which autoantibodies against correctly folded intact proteins were not detectable, autoantibodies specific to misfolded proteins complexed with MHC class II molecules of disease-susceptible alleles but not disease-resistant MHC class II alleles were observed. This suggested that misfolded proteins complexed with MHC class II molecules are natural autoantigens for autoantibodies. Autoantibody binding to misfolded proteins transported by MHC class II molecules was strongly correlated with susceptibility to RA. Thus, misfolded proteins, which normally would not be exposed to the immune system, can be targets for autoantibodies when they avoid protein degradation.

Proc Natl Acad Sci USA 2014; 111: 3787

Eitan Israeli

Capsule

Multitarget stool DNA testing for colorectal cancer screening

An accurate, non-invasive test could improve the effectiveness of colorectal cancer screening. Imperiale and colleagues compared a no-ninvasive, multitarget stool DNA test with a fecal immunochemical test (FIT) in persons at average risk for colorectal cancer. The DNA test includes quantitative molecular assays for *KRAS* mutations, aberrant *NDRG*4 and *BMP*3 methylation, and β-actin, plus a hemoglobin immunoassay. Of the 9989 participants who could be evaluated, 65 (0.7%) had colorectal cancer and 757 (7.6%) had advanced precancerous lesions (advanced adenomas or sessile serrated polyps measuring ≥ 1 cm in the greatest dimension) on colonoscopy. The sensitivity for detecting colorectal cancer was 92.3% with DNA testing and 73.8% with FIT ($P = 0.002$). The sensitivity for detecting advanced precancerous lesions was 42.4% with DNA testing and 23.8% with FIT ($P < 0.001$). The rate of detection of polyps with high grade dysplasia was 69.2% with DNA testing and 46.2% with FIT ($P = 0.004$); the rates of detection of serrated sessile polyps measuring 1 cm or more were 42.4% and 5.1%, respectively ($P < 0.001$). Specificities with DNA testing and FIT were 86.6% and 94.9%, respectively, among participants with non-advanced or negative findings ($P < 0.001$) and 89.8% and 96.4%, respectively, among those with negative results on colonoscopy ($P < 0.001$). The numbers of persons who would need to be screened to detect one cancer were 154 with colonoscopy, 166 with DNA testing, and 208 with FIT.

N Engl J Med 2014; 370: 1287

Eitan Israeli

Capsule

Tweaking a switch in mechanisms of gene regulation

Transcription factors regulate gene expression by binding to specific chromosomal operator sites. Many transcription factors are repressors, with transcription turned off when the repressor is bound. A simple operator occupancy model assumes that the level of repression is determined only by the equilibrium binding of the repressor to its operator. Hammar et al. used a single-molecule chase assay to directly test this in living cells. They measured the time that the lac repressor protein LacI remained bound to the natural $lacO_1$ operator and to a stronger, artificial $lacO_{sym}$ operator. It is assumed that transcription is turned off during this time, so this is termed τ_{off}. They also measured the average time that the operators remained unbound so that transcription can be on (τ_{on}). The repression ratio in the simple occupancy model would be given by $RR = (\tau_{on} + \tau_{off})/\tau_{on}$. The calculated repression ratios were compared with repression ratios measured based on an enzymatic reporter assay, thus monitoring protein expression rather than repressor binding. There was agreement for the $lacO_1$ operator, but for the $lacO_{sym}$, more repression was seen than would be expected based on a simple occupancy model. This could be accounted for either by promoter-specific cooperative interactions between LacI and RNA polymerase or simply by transcription initiation driving the system out of equilibrium; fast transcription initiation could lead to the synthesis of transcripts before the repressor has equilibrated with DNA. Such effects need to be considered in examining mechanisms of gene regulation.

Nat Genet 2014; 10.1038/ng.2905

Eitan Israeli

Capsule

Regulating DNA repair

Chromosomes carry the intricate code that makes and organizes cells and organisms. But chromosomes can break, causing a serious potential threat to cell and organismal survival. Repairing such breaks is vital, but repair can come with its own dangers, as certain repair pathways are necessarily error-prone – restoring chromosome integrity at the cost of introducing mutations into the genome. Microhomology-mediated end joining (MMEJ) is an error-prone form of repair that relies on very small (~5 to 25 base pairs) fortuitous homologies near the broken ends of chromosomes, which allow them to come together and be rejoined. A microhomology signature is often seen in breakpoints in chromosome arrangements in cancers and other diseases, suggesting that MMEJ is commonly involved in such genome derangement. Deng and collaborators investigated MMEJ in the budding yeast *Saccharomyces cerevisiae*. They found that although resection [the trimming back of one of the DNA stands to generate a single-stranded DNA (ssDNA) tail] at the ends of the breaks is important to expose regions of microhomology internal to the break, it is not rate-limiting for repair. On the other hand, replication protein A, which binds ssDNA, actively prevents spontaneous annealing between the microhomologies and suppresses MMEJ.

Nat Struct Mol Biol 2014; 10.1038/nsmb.2786

Eitan Israeli

Capsule

REST and stress resistance in aging and Alzheimer's disease

Human neurons are functional over an entire lifetime, yet the mechanisms that preserve function and protect against neurodegeneration during aging are unknown. Lu and colleagues show that induction of the repressor element 1-silencing transcription factor (REST, also known as neuron-restrictive silencer factor, NRSF) is a universal feature of normal aging in human cortical and hippocampal neurons. REST is lost, however, in mild cognitive impairment and Alzheimer's disease. Chromatin immunoprecipitation with deep sequencing and expression analysis show that REST represses genes that promote cell death and Alzheimer's disease pathology, and induces the expression of stress response genes. Moreover, REST potently protects neurons from oxidative stress and amyloid β-protein toxicity, and conditional deletion of REST in the mouse brain leads to age-related neurodegeneration. A functional orthologue of REST, *Caenorhabditis elegans* SPR-4, also protects against oxidative stress and amyloid β-protein toxicity. During normal aging, REST is induced in part by cell non-autonomous Wnt signaling. However, in Alzheimer's disease, frontotemporal dementia and dementia with Lewy bodies, REST is lost from the nucleus and appears in autophagosomes together with pathological misfolded proteins. Finally, REST levels during aging are closely correlated with cognitive preservation and longevity. Thus, the activation state of REST may distinguish neuroprotection from neurodegeneration in the aging brain.

Nature 2014; 507: 448

Eitan Israeli