Capsule

Association of ANXA11 genetic variation with sarcoidosis in African Americans and European Americans

A recent genome-wide association study in a German population and two subsequent studies in European populations found that a non-synonymous single-nucleotide polymorphism (SNP), rs1049550, within the annexin A11 (ANXA11) gene was associated with susceptibility to sarcoidosis. Levin et al. sought to identify additional ANXA11 variants independently associated with sarcoidosis, determine whether any sarcoidosis-associated ANXA11 variants were associated with chest radiographic phenotypes, and explore human leukocyte antigen (HLA) SNP–SNP interactions with ANXA11. A total of 209 SNPs spanning 100 kb including the 5' promoter, coding, and 3' untranslated regions of ANXA11 were genotyped for 1689 sarcoidosis cases and 1252 controls. After adjustment for rs1049550, two additional novel ANXA11 sarcoidosis associations were identified only in African Americans – rs61860052 (odds ratio (OR) = 0.62, 95% confidence interval (CI) = 0.40–0.97) and rs4377299 (OR=1.31; 95% CI=1.06–1.63). These associations were more pronounced in radiologically classified Scadding stage IV sarcoidosis cases. The authors also identified a significant SNP–SNP interaction between rs1049550 and a sarcoidosis risk SNP (rs9268839) near the HLA–DRA locus. This further genetic dissection of ANXA11 may provide additional insight into the immune dysregulation characteristic of sarcoidosis pathophysiology.

Genes Immun 2013; 14: 13

Eitan Israeli

Capsule

Ca2+ regulates T-cell receptor activation by modulating the charge property of lipids

Ionic protein-lipid interactions are critical for the structure and function of membrane receptors, ion channels, integrins and many other proteins. However, the regulatory mechanism of these interactions is largely unknown. Shi et al. show that Ca2+ can bind directly to anionic phospholipids and thus modulate membrane protein function. The activation of T cell antigen receptor-CD3 complex (TCR), a key membrane receptor for adaptive immunity, is regulated by ionic interactions between positively charged CD3ε/ζ cytoplasmic domains (CD3CD) and negatively charged phospholipids in the plasma membrane,. Crucial tyrosines are buried in the membrane and are largely protected from phosphorylation in resting T cells. It is not clear how CD3CD dissociates from the membrane in antigen-stimulated T cells. The antigen engagement of even a single TCR triggers a Ca2+ influx and TCR-proximal Ca2+ concentration is higher than the average cytosolic Ca2+ concentration. Our biochemical, live-cell fluorescence resonance energy transfer and NMR experiments showed that an increase in Ca2+ concentration induced the dissociation of CD3CD from the membrane and the solvent exposure of tyrosine residues. As a consequence, CD3 tyrosine phosphorylation was significantly enhanced by Ca2+ influx. Moreover, when compared with wild-type cells, Ca2+ channel-deficient T cells had substantially lower levels of CD3 phosphorylation after stimulation. The effect of Ca2+ on facilitating CD3 phosphorylation is primarily due to the charge of this ion, as demonstrated by the fact that replacing Ca2+ with the non-physiological ion Sr2+ resulted in the same feedback effect. Finally, 31P NMR spectroscopy showed that Ca2+ bound to the phosphate group in anionic phospholipids at physiological concentrations, thus neutralizing the negative charge of phospholipids. Rather than initiating CD3 phosphorylation, this regulatory pathway of Ca2+ has a positive feedback effect on amplifying and sustaining CD3 phosphorylation and should enhance T cell sensitivity to foreign antigens. This study thus provides a new regulatory mechanism of Ca2+ to T cell activation involving direct lipid manipulation.

Nature 2013; 493: 111

Eitan Israeli

Capsule

Crosstalk between neutrophils, B-1a cells and plasmacytoid dendritic cells initiates autoimmune diabetes

Type 1 diabetes develops over many years and is characterized ultimately by the destruction of insulin-producing pancreatic beta cells by autoreactive T cells. Nonetheless, the role of innate cells in the initiation of this disease remains poorly understood. Diana et al. show that in young female non-obese diabetic mice, physiological beta cell death induces the recruitment and activation of B-1a cells, neutrophils and plasmacytoid dendritic cells (pDCs) to the pancreas. Activated B-1a cells secrete IgGs specific for double-stranded DNA. IgGs activate neutrophils to release DNA-binding cathelicidin-related antimicrobial peptide (CRAMP), which binds self DNA. Then, self DNA, DNA-specific IgG and CRAMP peptide activate pDCs through the Toll-like receptor 9–myeloid differentiation factor 88 pathway, leading to interferon-alpha (IFNα) production in pancreatic islets. The authors further demonstrate through the use of depleting treatments that B-1a cells, neutrophils and IFNα-producing pDCs are required for the initiation of the diabetogenic T cell response and type 1 diabetes development. These findings reveal that an innate immune cell crosstalk takes place in the pancreas of young NOD mice and leads to the initiation of T1D.

Nature Med 2013; 19: 65

Eitan Israeli

Capsule

Exaggerated translation causes synaptic and behavioral aberrations associated with autism

Autism spectrum disorders (ASDs) are an early-onset heterogeneous group of heritable neuropsychiatric disorders with symptoms that include deficits in social interaction skills, impaired communication abilities, and ritualistic-like repetitive behaviors. One of the hypotheses for a common molecular mechanism underlying ASDs is altered translational control, resulting in exaggerated protein synthesis. Genetic variants in chromosome 4q, which contains the EIF4E locus, have been described in patients with autism. Importantly, a rare single nucleotide polymorphism has been identified in autism that is associated with increased promoter activity in the EIF4E gene. Santini and collaborators show that genetically increasing the levels of eukaryotic translation initiation factor 4E (eIF4E) in mice results in exaggerated cap-dependent translation and aberrant behaviors reminiscent of autism, including repetitive and perseverative behaviors and social interaction deficits. Moreover, these autistic-like behaviors are accompanied by synaptic pathophysiology in the medial prefrontal cortex, striatum and hippocampus. The autistic-like behaviors displayed by the eIF4E-transgenic mice are corrected by intracerebroventricular infusions of the cap-dependent translation inhibitor 4EGI-1.These findings demonstrate a causal relationship between exaggerated cap-dependent translation, synaptic dysfunction and aberrant behaviors associated with autism.

Nature 2013; 493: 411

Eitan Israeli

Capsule

Influence of intragenic CCL3 haplotypes and CCL3L copy number in HIV-1 infection in a sub-Saharan African population

Two CCL3 haplotypes (Hap-A1 and Hap-A3) and two polymorphic positions shared by the haplotypes (Hap-2SNP, single nucleotide polymorphism) were investigated together with CCL3L copy number (CN), for their role in HIV-1 disease. Hap-A1 was associated with protection from in utero HIV-1 infection: exposed uninfected (EU) infants had higher representation of wild-type (WT)/Hap-A1 than infected infants (excluding intrapartum-infected infants), which maintained significance post-maternal Nevirapine (mNVP) and viral load (MVL) correction ($P = 0.04$, odds ratio (OR) = 0.33). Mother-infant pair analyses showed the protective effect of Hap-A1 is dependent on its presence in the infant. Hap-A3 was associated with increased intrapartum transmission: WT/Hap-A3 was increased in intrapartum -transmitting vs. non-transmitting (NT) mothers, and remained significant post mNVP and MVL correction ($P = 0.02$, OR = 3.50). This deleterious effect of Hap-A3 seemed dependent on its presence in the mother. Hap-2SNP was associated with lower CD4 count in the NT mothers (P = 0.03). CCL3 Hap-A1 was associated with high CCL3L CN in total ($P = 0.001$) and EU infants ($P = 0.006$); the effect was not additive, however, having either Hap-A1 or high CCL3L CN was more significantly ($P = 0.0008$) associated with protection from in utero infection than Hap-A1 ($P = 0.028$) or high CCL3L CN (P = 0.002) alone. Linkage disequilibrium between Hap-A1 and high CCL3L CN appears unlikely given that a Nigerian population showed an opposite relationship.

Genes Immun 2013; 14: 42

Eitan Israeli

Capsule

Negligible immunogenicity of terminally differentiated cells derived from induced pluripotent or embryonic stem cells

The advantages of using induced pluripotent stem cells (iPSCs) instead of embryonic stem (ES) cells in regenerative medicine center around circumventing concerns about the ethics of using ES cells and the likelihood of immune rejection of ES cell-derived tissues. However, partial reprogramming and genetic instabilities in iPSCs could elicit immune responses in transplant recipients even when iPSC-derived differentiated cells are transplanted. iPSCs are first differentiated into specific types of cells in vitro for subsequent transplantation. Although model transplantation experiments have been conducted using various iPSC-derived differentiated tissues and immune rejections have not been observed, careful investigation of the immunogenicity of iPSC-derived tissue is becoming increasingly critical, especially as this has not been the focus of most studies done so far. A recent study reported immunogenicity of iPSC but not ES cell-derived teratomas and implicated several causative genes. Nevertheless, some controversy has arisen regarding these findings. Araki et al. examined the immunogenicity of differentiated skin and bone marrow tissues derived from mouse iPSCs. To ensure optimal comparison of iPSCs and ES cells, the authors established 10 integration-free iPSC and 7 ES cell lines using an inbred mouse strain, C57BL/6. They observed no differences in the rate of success of transplantation when skin and bone marrow cells derived from iPSCs were compared with ES cell-derived tissues. Moreover, they observed limited or no immune responses, including T cell infiltration, for tissues derived from either iPSCs or ES cells, and no increase in the expression of the immunogenicity-causing Zg16 and Hormad1 genes in regressing skin and teratoma tissues. Their findings suggest limited immunogenicity of transplanted cells differentiated from iPSCs and ES cells.

Nature 2013; 494: 100

Eitan Israeli

Capsule

NLRP3 is activated in Alzheimer's disease and contributes to pathology in APP/PS1 mice

Alzheimer's disease is the world's most common dementing illness. Deposition of amyloid-β peptide drives cerebral neuroinflammation by activating microglia. Indeed, amyloid-β activation of the NLRP3 inflammasome in microglia is fundamental for interleukin-1β maturation and subsequent inflammatory events. However, it remains unknown whether NLRP3 activation contributes to Alzheimer's disease in vivo. Heneka et al. demonstrate strongly enhanced active caspase-1 expression in human mild cognitive impairment and brains with Alzheimer's disease, suggesting a role for the inflammasome in this neurodegenerative disease. Nlrp3−/− or Casp1−/− mice carrying mutations associated with familial Alzheimer's disease were largely protected from loss of spatial memory and other sequelae associated with Alzheimer's disease, and demonstrated reduced brain caspase-1 and interleukin-1β activation as well as enhanced amyloid-β clearance. Furthermore, NLRP3 inflammasome deficiency skewed microglial cells to an M2 phenotype and resulted in the decreased deposition of amyloid-β in the APP/PS1 model of Alzheimer's disease. These results show an important role for the NLRP3/caspase-1 axis in the pathogenesis of Alzheimer's disease, and suggest that NLRP3 inflammasome inhibition represents a new therapeutic intervention for the disease.

Nature 2013; 493: 674

Eitan Israeli

Capsule

Mammalian heart renewal by pre-existing cardiomyocytes

Although recent studies have revealed that heart cells are generated in adult mammals, the frequency of generation and the source of new heart cells are not yet known. Some studies suggest a high rate of stem cell activity with differentiation of progenitors to cardiomyocytes. Other studies suggest that new cardiomyocytes are born at a very low rate, and that they may be derived from the division of pre-existing cardiomyocytes. Senyo et al. show, by combining two different pulse-chase approaches – genetic fate-mapping with stable isotope labeling, and multi-isotope imaging mass spectrometry M – that the genesis of cardiomyocytes occurs at a low rate by the division of pre-existing cardiomyocytes during normal aging, a process that increases adjacent to areas of myocardial injury. The authors found that cell cycle activity during normal aging and after injury led to polyploidy and multinucleation, but also to new diploid, mononucleate cardiomyocytes. These data reveal pre-existing cardiomyocytes as the dominant source of cardiomyocyte replacement in normal mammalian myocardial homeostasis as well as after myocardial injury.

Nature 2013; 493: 433

Eitan Israeli