Capsule

Cyclic GMP-AMP synthase is an innate immune sensor of HIV and other retroviruses

Retroviruses, including HIV, can activate innate immune responses, but the host sensors for retroviruses are largely unknown. Gao et al. show that HIV infection activates cyclic guanosine monophosphate-adenosine monophosphate (cGAMP) synthase (cGAS) to produce cGAMP, which binds to and activates the adaptor protein STING to induce type I interferons and other cytokines. Inhibitors of HIV reverse transcriptase, but not integrase, abrogated interferon-β induction by the virus, suggesting that the reverse-transcribed HIV DNA triggers the innate immune response. Knockout or knockdown of cGAS in mouse or human cell lines blocked cytokine induction by HIV, murine leukemia virus, and simian immunodeficiency virus. These results indicate that cGAS is an innate immune sensor of HIV and other retroviruses.

Science 2013; 341: 903

Eitan Israeli

Capsule

Notch2-dependent classical dendritic cells orchestrate intestinal immunity to attaching-and-effacing bacterial pathogens

Defense against attaching-and-effacing bacteria requires the sequential generation of interleukin 23 (IL-23) and IL-22 to induce protective mucosal responses. Although $CD4^+$ and $NKp46^+$ innate lymphoid cells (ILCs) are the critical source of IL-22 during infection, the precise source of IL-23 is unclear. Satpathy et al. used genetic techniques to deplete mice of specific subsets of classical dendritic cells (cDCs) and analyzed immunity to the attaching-and-effacing pathogen *Citrobacter rodentium*. The authors found that the signaling receptor Notch2 controlled the terminal stage of cDC differentiation. Notch2-dependent intestinal $CD11b^+$ cDCs were an obligate source of IL-23 required for survival after infection with *C. rodentium*, but $CD103^+$ cDCs dependent on the transcription factor Batf3 were not. These results demonstrate a non-redundant function for $CD11b^+$ cDCs in the response to pathogens in vivo.

Nature Immunol 2013; 14: 937

Eitan Israeli

Capsule

Macitentan and morbidity and mortality in pulmonary arterial hypertension

Current therapies for pulmonary arterial hypertension have been adopted on the basis of short-term trials with exercise capacity as the primary end-point. Pulido et al. assessed the efficacy of macitentan, a new dual endothelin receptor antagonist, using a primary end-point of morbidity and mortality in a long-term trial. A total of 250 patients were randomly assigned to placebo, 250 to the 3 mg macitentan dose, and 242 to the 10 mg macitentan dose. The primary end-point occurred in 46.4%, 38.0% and 31.4% of the patients in these groups, respectively. The hazard ratio for the 3 mg macitentan dose as compared with placebo was 0.70 (97.5% confidence interval 0.52–0.96, $P = 0.01$), and the hazard ratio for the 10 mg macitentan dose as compared with placebo was 0.55 (97.5%CI 0.39–0.76, $P < 0.001$). Worsening of pulmonary arterial hypertension was the most frequent primary end-point event. The effect of macitentan on this end-point was observed regardless of whether the patient was receiving therapy for pulmonary arterial hypertension at baseline. Adverse events more frequently associated with macitentan than with placebo were headache, nasopharyngitis, and anemia.

N Engl J Med 2013; 369: 809

Eitan Israeli

Capsule

Next generation gene therapy

Few disciplines in contemporary clinical research have experienced the high expectations directed at the gene therapy field. However, gene therapy has been challenging to translate to the clinic, often because the therapeutic gene is expressed at insufficient levels in the patient or because the gene delivery vector integrates near proto-oncogenes, which can cause leukemia. Biffi et al.(*Science* 2013:341;1233158, published online 11 July) and Aiuti et al. (1233151; published online 11 July) report progress on both fronts in gene therapy trials of three patients with metachromatic leukodystrophy (MLD), a neurodegenerative disorder, and three patients with Wiskott-Aldrich syndrome (WAS), an immunodeficiency disorder. Optimized lentiviral vectors were used to introduce functional *MLD* or *WAS* genes into the patients' hematopoietic stem cells (HSCs) ex vivo, and the transduced cells were then infused back into the patients, who were then monitored for up to 2 years. In both trials, the patients showed stable engraftment of the transduced HSC and high expression levels of functional *MLD* or *WAS* genes. Encouragingly, there was no evidence of lentiviral vector integration near proto-oncogenes, and the gene therapy treatment halted disease progression in most patients. A longer follow-up period will be needed to further validate efficacy and safety.

Eitan Israeli

Capsule

Efficacy of remission-induction regimens for ANCA-associated vasculitis

The 18 month efficacy of a single course of rituximab as compared with conventional immunosuppression with cyclophosphamide followed by azathioprine in patients with severe (organ-threatening) antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis is unknown. Specks and team enrolled 197 patients. As reported previously, 64% of the patients in the rituximab group, as compared with 53% of the patients in the cyclophosphamide-azathioprine group, had a complete remission by 6 months. At 12 and 18 months, 48% and 39%, respectively, of the patients in the rituximab group had maintained the complete remissions, as compared with 39% and 33%, respectively, in the comparison group. Rituximab met the prespecified criteria for non-inferiority ($P < 0.001$, with a non-inferiority margin of 20%). There was no significant difference between the groups in any efficacy measure, including the duration of complete remission and the frequency or severity of relapses. Among the 101 patients who had relapsing disease at baseline, rituximab was superior to conventional immunosuppression at 6 months ($P = 0.01$) and at 12 months ($P = 0.009$) but not at 18 months ($P = 0.06$), at which time most patients in the rituximab group had reconstituted B cells. There was no significant between-group difference in adverse events. In patients with severe ANCA-associated vasculitis, a single course of rituximab was as effective as continuous conventional immunosuppressive therapy for the induction and maintenance of remissions over the course of 18 months.

N Engl J Med 2013; 369: 417

Eitan Israeli

Capsule

Model therapies for cancer

If cellular signaling pathways were discrete and linear, controlling signals gone awry – like those from growth-promoting receptor tyrosine kinases often linked to cancer – would be straightforward. But these pathways form entangled and dynamic networks, and inhibiting signal transmission at one node, although successful in the short term, is often thwarted by regulatory mechanisms that keep cells healthy by rendering them robust to perturbations. Two groups have used a combination of mathematical modeling and experiments to identify strategies that may more effectively fight excess signaling by the ErbB family of receptors, which is associated with breast cancer. Kirouac et al. used their model to search for combinations of two or three inhibitors that would overcome adaptive feedback and validated these effects in cell and animal models of cancer. Meyer et al. used a model, data from public databases, and their own experiments to identify a second receptor, AXL, which allowed cancer cells to resist the effects of ErbB receptor inhibitors. In this scenario, ligand-independent activating interactions between receptors of the ErbB family and AXL appeared to be crucial, suggesting that reducing receptor number or activity is more likely to be effective than treatments that target ligand-induced activation of the receptors.

Sci Signal 2013; 6, ra68; ra66

Eitan Israeli

Capsule

Severe hypoglycemia and cardiovascular disease: systematic review and meta-analysis with bias analysis

Goto at al. provide a systematic and quantitative summary of the association between severe hypoglycemia and risk of cardiovascular disease in people with type 2 diabetes and examine the sensitivity of the association to possible uncontrolled confounding by unmeasured comorbid severe illness using a bias analysis. Of 3443 citations screened, 6 eligible studies with 903,510 participants were identified. In the conventional random effects meta-analysis, severe hypoglycemia was strongly associated with a higher risk of cardiovascular disease (relative risk 2.05, 95% confidence interval 1.74–2.42, $P < 0.001$). The excess fraction of cardiovascular disease incidence that was attributable to severe hypoglycemia (the population attributable fraction) was 1.56% (95%CI 1.32–1.81%, $P < 0.001$). Although moderate heterogeneity across the studies was suggested (I2=73.1%, $P = 0.002$ for heterogeneity), most subgroups showed similar results in stratified analyses. The bias analysis indicated that comorbid severe illness alone may not explain the association between hypoglycemia and cardiovascular disease; to explain this association, comorbid severe illness would have had to be extremely strongly associated with both severe hypoglycemia and cardiovascular disease. These findings suggest that severe hypoglycemia is associated with a higher risk of cardiovascular disease; they also support the notion that avoiding severe hypoglycemia may be important to prevent cardiovascular disease in people with type 2 diabetes.

BMJ 2013; 347: f4533

Eitan Israeli

Capsule

BCAT1 promotes cell proliferation through amino acid catabolism in gliomas carrying wild-type IDH1

Tönjes et al. show that glioblastoma express high levels of branched-chain amino acid transaminase 1 (BCAT1), the enzyme that initiates the catabolism of branched-chain amino acids (BCAAs). Expression of BCAT1 was exclusive to tumors carrying wild-type isocitrate dehydrogenase 1 (IDH1) and IDH2 genes and was highly correlated with methylation patterns in the BCAT1 promoter region. BCAT1 expression was dependent on the concentration of α-ketoglutarate substrate in glioma cell lines and could be suppressed by ectopic overexpression of mutant IDH1 in immortalized human astrocytes, providing a link between IDH1 function and BCAT1 expression. Suppression of BCAT1 in glioma cell lines blocked the excretion of glutamate and led to reduced proliferation and invasiveness in vitro, as well as significant decreases in tumor growth in a glioblastoma xenograft model. These findings suggest a central role for BCAT1 in glioma pathogenesis, making BCAT1 and BCAA metabolism attractive targets for the development of targeted therapeutic approaches to treat patients with glioblastoma.

Nature Med 2013; 19: 901

Eitan Israeli

Capsule

Meat consumption and mortality: results from the European Prospective Investigation into Cancer and Nutrition

Recently, some U.S. cohorts showed a moderate association between red and processed meat consumption and mortality, supporting the results of previous studies among vegetarians. Rohrmann and co-authors examined the association of red meat, processed meat, and poultry consumption with the risk of early death in the European Prospective Investigation into Cancer and Nutrition (EPIC). Included in the analysis were 448,568 men and women without prevalent cancer, stroke, or myocardial infarction, and with complete information on diet, smoking, physical activity and body mass index, who were between 35 and 69 years old at baseline. Cox proportional hazards regression was used to examine the association of meat consumption with all-cause and cause-specific mortality. As of June 2009, 26,344 deaths were observed. After multivariate adjustment, a high consumption of red meat was related to higher all-cause mortality (hazard ratio = 1.14, 95% confidence interval 1.01–1.28, 160+ vs. 10 to 19.9 g/day), and the association was stronger for processed meat (HR = 1.44, 95%CI 1.24–1.66, 160+ vs. 10 to 19.9 g/day). After correction for measurement error, higher all-cause mortality remained significant only for processed meat (HR = 1.18, 95%CI 1.11–1.25, per 50 g/day). We estimated that 3.3% (95%CI 1.5%–5.0%) of deaths could be prevented if all participants had a processed meat consumption of less than 20 g/day. Significant associations with processed meat intake were observed for cardiovascular diseases, cancer, and 'other causes of death'. The consumption of poultry was not related to all-cause mortality.

BMC Med 2013; 11: 63

Eitan Israeli

Capsule

Frequency of nut consumption and mortality risk in the PREDIMED nutrition intervention trial

Prospective studies in non-Mediterranean populations have consistently related increasing nut consumption to lower coronary heart disease mortality. A small protective effect on all-cause and cancer mortality has also been suggested. To examine the association between frequency of nut consumption and mortality in individuals at high cardiovascular risk from Spain, a Mediterranean country with a relatively high average nut intake per person. Guasch-Ferre et al. evaluated 7216 men and women aged 55 to 80 years randomized to one of three interventions (Mediterranean diets supplemented with nuts, olive oil, or control diet) in the PREDIMED ('PREvención con DIeta MEDiterránea') study. Nut consumption was assessed at baseline and mortality was ascertained by medical records and linkage to the National Death Index. During a median follow-up of 4.8 years, 323 total deaths, 81 cardiovascular deaths and 130 cancer deaths occurred. Nut consumption was associated with a significantly reduced risk of all-cause mortality (*P* for trend ‹ 0.05, all). Compared to non-consumers, subjects consuming › 3 servings of nuts/week (32% of the cohort) had a 39% lower mortality risk (hazard ratio 0.61, 95% confidence interval 0.45–0.83). A similar protective effect against cardiovascular and cancer mortality was observed. Participants allocated to the Mediterranean diet with nuts group who consumed › 3 nut servings/week at baseline had the lowest total mortality risk (HR 0.37, 95% CI 0.22–0.66).

BMC Med 2013, 11: 164

Eitan Israeli

Capsule

Integrative genomics identifies APOE4 effectors in Alzheimer's disease

Late-onset Alzheimer's disease (LOAD) risk is strongly influenced by genetic factors such as the presence of the apolipoprotein E ε4 allele (referred to here as APOE4), as well as non-genetic determinants including ageing. To pursue mechanisms by which these affect human brain physiology and modify LOAD risk, Rhinn et al. initially analyzed whole-transcriptome cerebral cortex gene expression data in unaffected APOE4 carriers and LOAD patients. APOE4 carrier status was associated with a consistent transcriptomic shift that broadly resembled the LOAD profile. Differential co-expression correlation network analysis of the APOE4 and LOAD transcriptomic changes identified a set of candidate core regulatory mediators. Several of these – including APBA2, FYN, RNF219 and SV2A – encode known or novel modulators of LOAD-associated amyloid beta A4 precursor protein (APP) endocytosis and metabolism. Furthermore, a genetic variant within RNF219 was found to affect amyloid deposition in human brain and LOAD age of onset. These data implicate an APOE4 associated molecular pathway that promotes LOAD.

Nature 2013; 500: 45