Capsule

ABT-199, a potent and selective BCL-2 inhibitor, achieves antitumor activity while sparing platelets

Inhibition of prosurvival proteins of the BCL family is a promising anticancer strategy; however, the similarities between the family members make the development of specific agents difficult. Current compounds have been designed to target BCL-2, which is frequently elevated in tumors and is an important prosurvival factor, but also inhibit BCL-XL, which is required for the survival of platelets; thus, thrombocytopenia is a limiting toxic effect in patients. Souers et al. have engineered anti-BCL drugs to generate a more BCL-2-specific compound that has less affinity for BCL-XL and, therefore, reduced platelet toxicity. The compound is effective in several tumor models in vivo and had reduced toxicity in three patients with refractory leukemia, showing a promising activity and safety profile to refine and improve pro-apoptotic therapy in cancer.

Nature Med 2013; 19: 202

Eitan Israeli

Capsule

Epithelial-mesenchymal transition cells may facilitate tumor cell dissemination in humans

Epithelial-mesenchymal transition (EMT) is a developmental program that converts adherent epithelial cells to a migratory mesenchymal state. This cell-fate change has been linked to tumor metastasis in preclinical models. To investigate whether EMT occurs in human cancer, Yu et al. isolated circulating tumor cells (CTCs) from breast cancer patients and analyzed their expression of epithelial and mesenchymal markers by RNA in situ hybridization and RNA sequencing. Biphenotypic cells expressing both types of markers were rare in primary breast tumors but were enriched among CTCs, as were cells expressing only mesenchymal markers. Serial blood samples from one patient revealed that CTCs in the mesenchymal state declined in number when the patient responded to therapy but rebounded when the disease began to progress – a pattern repeated when a different therapy was administered. Thus, EMT may facilitate tumor cell dissemination in humans.

Science 2013; 339: 580

Eitan Israeli

Capsule

Plasma cells require autophagy for sustainable immunoglobulin production

The role of autophagy in plasma cells is unknown. Pengo et al. found notable autophagic activity in both differentiating and long-lived plasma cells and investigated its function through the use of mice with conditional deficiency in the essential autophagic molecule Atg5 in B cells. Atg5–/– differentiating plasma cells had a larger endoplasmic reticulum (ER) and more ER stress signaling than did their wild-type counterparts, which led to higher expression of the transcriptional repressor Blimp-1 and immunoglobulins and more antibody secretion. The enhanced immunoglobulin synthesis was associated with less intracellular ATP and more death of mutant plasma cells, which identified an unsuspected autophagy-dependent cytoprotective trade-off between immunoglobulin synthesis and viability. In vivo, mice with conditional deficiency in Atg5 in B cells had defective antibody responses, complete selection in the bone marrow for plasma cells that escaped Atg5 deletion, and fewer antigen-specific long-lived bone marrow plasma cells than did wild-type mice, despite having normal germinal center responses. Thus, autophagy is specifically required for plasma cell homeostasis and long-lived humoral immunity.

Nature Immunol 2013; 14: 298

Eitan Israeli

Capsule

Relative trends in hospitalizations and mortality among infants by the number of vaccine doses and age, based on VAERS, 1990–2010

Goldman and Miller investigated the Vaccine Adverse Event Reporting System (VAERS) database 1990–2010 and identified cases that specified either hospitalization or death among 38,801 reports of infants. Based on the types of vaccines reported, the actual number of vaccine doses administered, from 1 to 8, was summed for each case. Linear regression analysis of hospitalization rates as a function of the number of reported vaccine doses and patient age yielded a linear relationship with r2 ¼ 0.91 and r2 ¼ 0.95, respectively. The hospitalization rate increased linearly from 11.0% (107 of 969) for two doses to 23.5% (661 of 2817) for eight doses and decreased linearly from 20.1% (154 of 765) for children aged ‹ 0.1 year to 10.7% (86 of 801) for children aged 0.9 year. The rate ratio (RR) of the mortality rate for 5–8 vaccine doses to 1–4 vaccine doses is 1.5 (95% confidence interval 1.4–1.7), indicating a statistically significant increase from 3.6% (95% CI 3.2–3.9%) deaths associated with 1–4 vaccine doses to 5.5% (95% CI 5.2–5.7%) associated with 5–8 vaccine doses. The male-to-female mortality RR was 1.4 (95% CI 1.3–1.5). Their findings show a positive correlation between the number of vaccine doses administered and the percentage of hospitalizations and deaths. Since vaccines are given to millions of infants annually, it is imperative that health authorities have scientific data from synergistic toxicity studies on all combinations of vaccines that infants might receive. Finding ways to increase vaccine safety should be the highest priority.

Hum Exp Toxicol 2012; 31: 1012

Eitan Israeli

Capsule

Microbiota restricts trafficking of bacteria to mesenteric lymph nodes by CX3CR1hi cells

The intestinal microbiota has a critical role in immune system and metabolic homeostasis, but it must be tolerated by the host to avoid inflammatory responses that can damage the epithelial barrier separating the host from the luminal contents. Breakdown of this regulation and the resulting inappropriate immune response to commensals are thought to lead to the development of inflammatory bowel diseases such as Crohn's disease and ulcerative colitis. Diehl and co-workers propose that the intestinal immune system is instructed by the microbiota to limit responses to luminal antigens. They demonstrated in mice that, at steady state, the microbiota inhibits the transport of both commensal and pathogenic bacteria from the lumen to a key immune inductive site, the mesenteric lymph nodes (MLNs). However, in the absence of Myd88 or under conditions of antibiotic-induced dysbiosis, non-invasive bacteria were trafficked to the MLNs in a CCR7-dependent manner, and induced both T cell responses and immunoglobulin A production. Trafficking was carried out by CX3CR1hi mononuclear phagocytes, an intestinal cell population previously reported to be non-migratory. These findings define a central role for commensals in regulating the migration to the MLNs of CX3CR1hi mononuclear phagocytes endowed with the ability to capture luminal bacteria, thereby compartmentalizing the intestinal immune response to avoid inflammation.

Nature 2013; 494: 116

Eitan Israeli

Capsule

Crystal structure of the entire respiratory complex I

Complex I is the first and largest enzyme of the respiratory chain and has a central role in cellular energy production through the coupling of NADH:ubiquinone electron transfer to proton translocation. It is also implicated in many common human neurodegenerative diseases. Baradaran and team report the first crystal structure of the entire, intact complex I (from Thermus thermophilus) at 3.3Å resolution. The structure of the 536 kDa complex comprises 16 different subunits, with a total of 64 transmembrane helices and 9 iron-sulphur clusters. The core fold of subunit Nqo8 (ND1 in humans) is, unexpectedly, similar to a half-channel of the antiporter-like subunits. Small subunits nearby form a linked second half-channel, which completes the fourth proton-translocation pathway (present in addition to the channels in three antiporter-like subunits). The quinone-binding site is unusually long, narrow and enclosed. The quinone headgroup binds at the deep end of this chamber, near iron-sulphur cluster N2. Notably, the chamber is linked to the fourth channel by a 'funnel' of charged residues. The link continues over the entire membrane domain as a flexible central axis of charged and polar residues, and probably has a leading role in the propagation of conformational changes, aided by coupling elements. The structure suggests that a unique, out-of-the-membrane quinone-reaction chamber enables the redox energy to drive concerted long-range conformational changes in the four antiporter-like domains, resulting in translocation of four protons per cycle.

Nature 2013; 494: 443

Eitan Israeli

Capsule

Epigenetic silencing of retinoblastoma gene regulates pathologic differentiation of myeloid cells in cancer

Two major populations of myeloid-derived suppressor cells (MDSCs), monocytic MDSCs (M-MDSCs) and polymorphonuclear MDSCs (PMN-MDSCs) regulate immune responses in cancer and other pathologic conditions. Under physiologic conditions, Ly6ChiLy6G– inflammatory monocytes, which are the normal counterpart of M-MDSCs, differentiate into macrophages and dendritic cells. PMN-MDSCs are the predominant group of MDSCs that accumulates in cancer. Youn at al. show that a large proportion of M-MDSCs in tumor-bearing mice acquired phenotypic, morphological and functional features of PMN-MDSCs. Acquisition of this phenotype, but not the functional attributes of PMN-MDSCs, was mediated by transcriptional silencing of the retinoblastoma gene through epigenetic modifications mediated by histone deacetylase 2 (HDAC-2). These data demonstrate a new regulatory mechanism of myeloid cells in cancer.

Nature Immunol 2013; 14: 211

Eitan Israeli

Capsule

New insights into doxorubicin cellular effects

Doxorubicin (Dox) is a chemotherapeutic drug with efficacy in many cancers, yet after 40 years of clinical use there are lingering mysteries about its mechanism of action. The prevailing hypothesis is that Dox forms a complex with topoisomerase II, a DNA-unwinding enzyme, and this leads to DNA strand breaks that induce cell cycle arrest. Although much evidence supports this model, not all data are consistent with it. New insights into Dox's cellular effects could help optimize its antitumor activity, reduce its adverse side effects, and/or help oncologists identify which patients are most likely to respond to the drug. Denard et al. propose that the membrane-associated transcription factor CREB3L1 plays a key role in Dox's antitumor activity. In cultured cells, Dox increased synthesis of the lipid ceramide, which in turn caused proteolytic activation of CREB3L1 and its entry into the nucleus, where it increased transcription of cell cycle-inhibitory genes. When CREB3L1 levels were experimentally suppressed, cancer cells became resistant to Dox. These results suggest that CREB3L1 may be a biomarker of Dox-responsive cancer cells or even a druggable target itself.

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Eitan Israeli