Capsule

A restricted cell population propagates glioblastoma growth after chemotherapy

Glioblastoma multiforme is the most common primary malignant brain tumor, with a median survival of about one year. This poor prognosis is due to therapeutic resistance and tumor recurrence after surgical removal. Precisely how recurrence occurs is unknown. Using a genetically engineered mouse model of glioma, Chen et al. identified a subset of endogenous tumor cells that are the source of new tumor cells after the drug temozolomide (TMZ) is administered to transiently arrest tumor growth. A *nestin-ΔTK-IRES-GFP* (*Nes-ΔTK-GFP*) transgene that labels quiescent subventricular zone adult neural stem cells also labels a subset of endogenous glioma tumor cells. On arrest of tumor cell proliferation with TMZ, pulse-chase experiments demonstrate a tumor regrowth cell hierarchy originating with the *Nes-ΔTK-GFP* transgene subpopulation. Ablation of the GFP^+ cells with chronic ganciclovir administration significantly arrested tumor growth, and combined TMZ and ganciclovir treatment impeded tumor development. Thus, a relatively quiescent subset of endogenous glioma cells, with properties similar to those proposed for cancer stem cells, is responsible for sustaining long-term tumor growth through the production of transient populations of highly proliferative cells.

Nature 2012; 488: 522

Eitan Israeli

Capsule

Zoonotic disease pathogens in fish used for pedicure

In a letter to the editor, Verner-Jeffreys et al. raise the question of infectious diseases in fish used for pedicure. "Doctor" fish might not be such good doctors after all. These fish are used for the increasingly popular spa treatment called fish pedicures. During these sessions, spa patrons immerse their feet in water, allowing the live fish to feed on dead skin, mainly for cosmetic reasons. However, examinations of doctor fish destined for these spas found that they can carry harmful bacteria. Thus, although reports of human infection after fish pedicures are few, there may be some risks. Spa patrons who have underlying medical conditions (such as diabetes, immunosuppression, or even simple breaks in the skin) are already discouraged from undergoing such treatments. However, spas that offer fish pedicures should also consider using only disease-free fish reared in controlled facilities under high standards of husbandry and welfare.

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Eitan Israeli

Capsule

A periciliary brush promotes the lung health by separating the mucus layer from airway epithelia

Mucus clearance is the primary defense mechanism that protects airways from inhaled infectious and toxic agents. In the current gel-on-liquid mucus clearance model, a mucus gel is propelled on top of a "watery" periciliary layer surrounding the cilia. However, this model fails to explain the formation of a distinct mucus layer in health or why mucus clearance fails in disease. Button and colleagues propose a gel-on-brush model in which the periciliary layer is occupied by membrane-spanning mucins and mucopolysaccharides densely tethered to the airway surface. This brush prevents mucus penetration into the periciliary space and causes mucus to form a distinct layer. The relative osmotic moduli of the mucus and periciliary brush layers explain both the stability of mucus clearance in health and its failure in airway disease.

Science 2012; 337: 937

Eitan Israeli

Capsule

Cancer stem cells in color

One of the liveliest debates in contemporary cancer research centers on whether cancer stem cells (CSCs) exist and, if so, how these cells are defined phenotypically. CSCs are hypothesized to be a small population of cells within a tumor that are endowed with the unique capacity to drive tumor growth – a scenario that in principle would offer important therapeutic opportunities. By studying mice expressing multicolor reporter genes, Schepers and team were able to visualize and monitor the fate of a candidate stem cell for intestinal adenomas, an early stage of cancer. This "lineage tracing" analysis suggests that tumor cells expressing the intestinal crypt stem cell marker Lgr5 (leucine-rich repeat containing G protein-coupled receptor 5) are the cells that fuel the growth of intestinal adenomas.

Science 2012; 337: 730

Eitan Israeli

Capsule

A selective jumonji H3K27 demethylase inhibitor modulates the pro-inflammatory macrophage response

The jumonji (JMJ) family of histone demethylases comprises Fe^{2+}- and α-ketoglutarate-dependent oxygenases that are essential components of regulatory transcriptional chromatin complexes. These enzymes demethylate lysine residues in histones in a methylation-state and sequence-specific context. Considerable effort has been devoted to gaining a mechanistic understanding of the roles of histone lysine demethylases in eukaryotic transcription, genome integrity and epigenetic inheritance, as well as in development, physiology and disease. However, because of the absence of any selective inhibitors, the relevance of the demethylase activity of JMJ enzymes in regulating cellular responses remains poorly understood. Kruidenier et al. present a structure-guided small molecule and chemoproteomics approach to elucidating the functional role of the H3K27me3-specific demethylase subfamily (KDM6 subfamily members JMJD3 and UTX). The liganded structures of human and mouse JMJD3 provide novel insight into the specificity determinants for cofactor, substrate and inhibitor recognition by the KDM6 subfamily of demethylases. We exploited these structural features to generate the first small molecule catalytic site inhibitor that is selective for the H3K27me3-specific JMJ subfamily. We demonstrate that this inhibitor binds in a novel manner and reduces lipopolysaccharide-induced pro-inflammatory cytokine production by human primary macrophages, a process that depends on both JMJD3 and UTX. These results resolve the ambiguity associated with the catalytic function of H3K27-specific JMJs in regulating disease-relevant inflammatory responses and provide encouragement for designing small-molecule inhibitors to allow selective pharmacological intervention across the JMJ family.

Nature 2012; 488: 404

Eitan Israeli

The man of action has to believe, the inquirer has to doubt; the scientific investigator is both

C.S. Pierce (1839-1914), American philosopher, logician, mathematician and scientist, sometimes known as “the father of pragmatism”

Capsule

Iatrogenic Creutzfeldt-Jakob disease, final assessment

The book on iatrogenic Creutzfeldt-Jakob disease (CJD) in humans is almost closed. This form of CJD transmission via medical misadventures was first detected in 1974. Today, only occasional CJD cases with exceptionally long incubation periods still appear. The main sources of the largest outbreaks were tissues from human cadavers with unsuspected CJD that were used for dura mater grafts and growth hormone extracts. A few additional cases resulted from neurosurgical instrument contamination, corneal grafts, gonadotropic hormone, and secondary infections from blood transfusions. Although the definitive answer to the problem of iatrogenic CJD is still not available (a laboratory test to identify potential donors who harbor the infectious agent), certain other measures have worked well: applying special sterilization of penetrating surgical instruments, reducing the infectious potential of donor blood and tissue, and excluding donors known to have higher than normal risk for CJD.

Emerg Infect Dis 2012; 18: 901

Eitan Israeli

Capsule

Restoring voluntary control of locomotion after paralyzing spinal cord injury

Half the human spinal cord injuries lead to chronic paralysis. van den Brand et al. have introduced an electrochemical neuroprosthesis and a robotic postural interface designed to encourage supraspinally mediated movements in rats with paralyzing lesions. Despite the interruption of direct supraspinal pathways, the cortex regained the capacity to transform contextual information into task-specific commands to execute refined locomotion. This recovery relied on the extensive remodeling of cortical projections, including the formation of brainstem and intraspinal relays that restored qualitative control over electrochemically enabled lumbosacral circuitries. Automated treadmill-restricted training, which did not engage cortical neurons, failed to promote translesional plasticity and recovery. By encouraging active participation under functional states, our training paradigm triggered a cortex-dependent recovery that may improve function after similar injuries in humans.

Science 2012; 36: 1182

Eitan Israeli

Don't be yourself. Be someone a little nicer

Mignon McLaughlin (1913-1983), American journalist and author

Capsule

The dynamics of B effector cell differentiation and homeostasis

In response to an infection, immunological B cells undergo a maturation process that results in the production of immunoglobulin (Ig) that is better able to bind and clear the invading pathogen. This occurs through somatic cell hypermutation and class switch recombination of the Ig gene and requires activation-induced deaminase (AID). Péron and collaborators observed that the 3' cis-regulatory region of the heavy chain locus is transcribed and undergoes AID-mediated mutation and recombination. The resulting deletion of the Ig heavy gene cluster generates B cells that are no longer able to express Ig on the cell surface. Because cell surface Ig expression is essential for B cell survival, this process is termed "locus suicide recombination" (LSR) and may be important in shaping the dynamics of B effector cell differentiation and homeostasis.

Science 2012; 336: 931

Eitan Israeli

An economist is an expert who will know tomorrow why the things he predicted yesterday didn't happen today

Laurence J. Peter (1919-1990), Canadian educator and "hierarchiologist," best known for the formulation of the Peter Principle: "In a hierarchy every employee tends to rise to his level of incompetence"

Capsule

APJ acts as a dual receptor in cardiac hypertrophy

Cardiac hypertrophy is initiated as an adaptive response to sustained overload but progresses pathologically as heart failure ensues. Scimia et al. report that genetic loss of APJ, a G-protein-coupled receptor, confers resistance to chronic pressure overload by markedly reducing myocardial hypertrophy and heart failure. In contrast, mice lacking apelin (the endogenous APJ ligand) remain sensitive, suggesting an apelin-independent function of APJ. Freshly isolated APJ-null cardiomyocytes exhibit an attenuated response to stretch, indicating that APJ is a mechanosensor. Activation of APJ by stretch increases cardiomyocyte cell size and induces molecular markers of hypertrophy. Whereas apelin stimulates APJ to activate $G\alpha_i$ and elicits a protective response, stretch signals in an APJ-dependent, G-protein-independent fashion to induce hypertrophy. Stretch-mediated hypertrophy is prevented by knockdown of β-arrestins or by pharmacological doses of apelin acting through $G\alpha_i$. Taken together, their data indicate that APJ is a bifunctional receptor for both mechanical stretch and the endogenous peptide apelin. By sensing the balance between these stimuli, APJ occupies a pivotal point linking sustained overload to cardiomyocyte hypertrophy.

Nature 2012; 488: 394

Eitan Israeli

Capsule

Bacterial virulence proteins as tools to rewire kinase pathways in yeast and immune cells

Bacterial pathogens have evolved specific effector proteins that, by interfacing with host kinase signaling pathways, provide a mechanism to evade immune responses during infection. Although these effectors contribute to pathogen virulence, it was realized that they might also serve as valuable synthetic biology reagents for engineering cellular behavior. Wei and collaborators exploit two effector proteins, the *Shigella flexneri* OspF protein and *Yersinia pestis* YopH protein, to rewire kinase-mediated responses systematically both in yeast and mammalian immune cells. Bacterial effector proteins can be directed to inhibit specific mitogen-activated protein kinase pathways selectively in yeast by artificially targeting them to pathway-specific complexes. Moreover, the authors show that unique properties of the effectors generate new pathway behaviors: OspF, which irreversibly inactivates mitogen-activated protein kinases, was used to construct a synthetic feedback circuit that shows novel frequency-dependent input filtering. Finally, they show that effectors can be used in T cells, either as feedback modulators to tune the T cell response amplitude precisely, or as an inducible pause switch that can temporarily disable T cell activation. These studies demonstrate how pathogens could provide a rich toolkit of parts to engineer cells for therapeutic or biotechnological applications.

Nature 2012; 488: 384

Eitan Israeli