Capsule

Melanoma genome sequencing reveals frequent PREX2 mutations

Melanoma is notable for its metastatic propensity, lethality in the advanced setting and association with ultraviolet exposure early in life. To obtain a comprehensive genomic view of melanoma in humans, Berger et al. sequenced the genomes of 25 metastatic melanomas and matched germline DNA. A wide range of point mutation rates was observed: lowest in melanomas whose primaries arose on non-ultraviolet-exposed hairless skin of the extremities (3 and 14 per megabase of genome), intermediate in those originating from hair-bearing skin of the trunk (5–55 per megabase), and highest in a patient with a documented history of chronic sun exposure (111 per megabase). Analysis of whole-genome sequence data identified *PREX2* (phosphatidylinositol-3,4,5-trisphosphate-dependent Rac exchange factor 2) – a PTEN-interacting protein and negative regulator of PTEN in breast cancer – as a significantly mutated gene with a mutation frequency of approximately 14% in an independent extension cohort of 107 human melanomas. *PREX2* mutations are biologically relevant, as ectopic expression of mutant PREX2 accelerated tumor formation of immortalized human melanocytes in vivo. Thus, whole-genome sequencing of human melanoma tumors revealed genomic evidence of ultraviolet pathogenesis and discovered a new recurrently mutated gene in melanoma.

Nature 2012; 485: 502

Eitan Israeli

Capsule

Immune self-reactivity triggered by drug-modified HLA-peptide repertoire

Human leukocyte antigens (HLAs) are highly polymorphic proteins that initiate immunity by presenting pathogen-derived peptides to T cells. HLA polymorphisms mostly map to the antigen-binding cleft, thereby diversifying the repertoire of self-derived and pathogen-derived peptide antigens selected by different HLA allotypes. A growing number of immunologically based drug reactions, including abacavir hypersensitivity syndrome (AHS) and carbamazepine-induced Stevens-Johnson syndrome (SJS), are associated with specific HLA alleles. However, little is known about the underlying mechanisms of these associations, including AHS, a prototypical HLA-associated drug reaction occurring exclusively in individuals with the common histocompatibility allele *HLA-B*57:01*, and with a relative risk of more than 1000. Illing et al. show that unmodified abacavir binds non-covalently to HLA-B*57:01, lying across the bottom of the antigen-binding cleft and reaching into the F-pocket, where a carboxy-terminal tryptophan typically anchors peptides bound to HLA-B*57:01. Abacavir binds with exquisite specificity to HLA-B*57:01, changing the shape and chemistry of the antigen-binding cleft, thereby altering the repertoire of endogenous peptides that can bind HLA-B*57:01. In this way, abacavir guides the selection of new endogenous peptides, inducing a marked alteration in 'immunological self'. The resultant peptide-centric 'altered self' activates abacavir-specific T cells, thereby driving polyclonal CD8 T cell activation and a systemic reaction manifesting as AHS. The authors also show that carbamazepine, a widely used anti-epileptic drug associated with hypersensitivity reactions in *HLA-B*15:02* individuals, binds to this allotype, producing alterations in the repertoire of presented self peptides. These findings simultaneously highlight the importance of HLA polymorphism in the evolution of pharmacogenomics and provide a general mechanism for some of the growing number of *HLA*-linked hypersensitivities that involve small molecule drugs.

Nature 2012: doi:10.1038/nature11147

Eitan Israeli

Capsule

Insights into amyloidogenesis

The amyloid-β (Aβ) peptides associated with Alzheimer's disease are generated by cleavage of the transmembrane C-terminal domain (C99) of the amyloid precursor protein by the enzyme γ-secretase. Barrett and co-researchers used nuclear magnetic resonance (NMR) and electron paramagnetic resonance spectroscopy to show that C99 contains surface-associated N- and C-terminal helices and a flexibly curved transmembrane helix that is well suited to processive cleavage by γ-secretase. Elevated cholesterol levels have been found to increase Aβ generation. NMR titration together with mutagenesis revealed a binding site for cholesterol within C99 that included a motif previously implicated in protein oligomerization.

Science 2012; 336: 1168

Eitan Israeli

Capsule

CIITA promoter I CARD-deficient mice express functional MHC class II genes in myeloid and lymphoid compartments

Three distinct promoters control the master regulator of major histocompatibility complex (MHC) class II expression, class II transactivator (CIITA), in a cell type-specific manner. Promoter I (pI) CIITA, expressed primarily by dendritic cells (DCs) and macrophages, expresses a unique isoform that contains a caspase-recruitment domain (CARD). The activity and function of this isoform are not understood but are believed to enhance the function of CIITA in antigen-presenting cells. To determine whether isoform I of CIITA has specific functions, Zinzow-Kramer and team created *CIITA* mutant mice in which isoform I was replaced with isoform III sequences. Mice in which pI and the CARD-encoding exon were deleted were also created. No defect in the formation of CD4 T cells, the ability to respond to a model antigen or bacterial or viral challenge was observed in mice lacking CIITA isoform I. Although CIITA and MHC-II expression was decreased in splenic DCs, pI knockout animals expressed CIITA from downstream promoters, suggesting that control of pI activity is mediated by unknown distal elements that could act at pIII, the B cell promoter. Thus, no critical function is linked to the CARD domain of CIITA isoform I with respect to basic immune system development, function and challenge.

Genes Immunity 2012; 13: 299

Eitan Israeli

Capsule

Heart repair by reprogramming non-myocytes with cardiac transcription factors

The adult mammalian heart possesses little regenerative potential following injury. Fibrosis due to activation of cardiac fibroblasts impedes cardiac regeneration and contributes to loss of contractile function, pathological remodeling and susceptibility to arrhythmias. Cardiac fibroblasts account for a majority of cells in the heart and represent a potential cellular source for restoration of cardiac function following injury through phenotypic reprogramming to a myocardial cell fate. Song and fellow authors show that four transcription factors, GATA4, HAND2, MEF2C and TBX5, can cooperatively reprogram adult mouse tail-tip and cardiac fibroblasts into beating cardiac-like myocytes in vitro. Forced expression of these factors in dividing non-cardiomyocytes in mice reprograms these cells into functional cardiac-like myocytes, improves cardiac function and reduces adverse ventricular remodeling following myocardial infarction. These results suggest a strategy for cardiac repair through reprogramming fibroblasts resident in the heart with cardiogenic transcription factors or other molecules.

Nature 2012; 485: 599

Eitan Israeli

Capsule

Sustained translational repression by eIF2α-P mediates prion neurodegeneration

The mechanisms leading to neuronal death in neurodegenerative disease are poorly understood. Many of these disorders, including Alzheimer's, Parkinson's and prion diseases, are associated with the accumulation of misfolded disease-specific proteins. The unfolded protein response is a protective cellular mechanism triggered by rising levels of misfolded proteins. One arm of this pathway results in the transient shutdown of protein translation, through phosphorylation of the α-subunit of eukaryotic translation initiation factor, eIF2. Activation of the unfolded protein response and/or increased eIF2α-P levels are seen in patients with Alzheimer's, Parkinson's and prion diseases, but how this links to neurodegeneration is unknown. Moreno et al. show that accumulation of prion protein during prion replication causes persistent translational repression of global protein synthesis by eIF2α-P, associated with synaptic failure and neuronal loss in prion-diseased mice. Further, the authors show that promoting translational recovery in hippocampi of prion-infected mice is neuroprotective. Overexpression of GADD34, a specific eIF2α-P phosphatase, as well as reduction of levels of prion protein by lentivirally mediated RNA interference, reduced eIF2α-P levels. As a result, both approaches restored vital translation rates during prion disease, rescuing synaptic deficits and neuronal loss, thereby significantly increasing survival. In contrast, salubrinal, an inhibitor of eIF2α-P dephosphorylation, increased eIF2α-P levels, exacerbating neurotoxicity and significantly reducing survival in prion-diseased mice. Given the prevalence of protein misfolding and activation of the unfolded protein response in several neurodegenerative diseases, these results suggest that manipulation of common pathways such as translational control, rather than disease-specific approaches, may lead to new therapies preventing synaptic failure and neuronal loss across the spectrum of these disorders.

Nature 2012; 485: 507

Eitan Israeli

Capsule

Potential therapeutic target for the treatment of bone-destructive diseases and malignancies

Osteoclasts are cells that promote bone remodeling, and their hyperactivity is linked to bone-destructive disorders, including osteoporosis. Activated osteoclast precursors develop columnar actin structures, known as podosomes, which are similar to the invadopodia observed in invasive cancer cells. During osteoclast differentiation, cells can fuse with one another to create multinucleate cells. Oikawa et al. found that in osteoclastic cell cultures, a protein known to be involved in Src-induced cancer cell invadopodia production, Tks5, was also induced during osteoclastogenesis. Tyrosine phosphorylation of Tks5 by Src was required for the generation of circumferential podosomes in osteoclasts and for their fusion. Knockdown of Tks5 in osteoclasts interfered with circumferential podosome formation and cell-cell fusion, whereas polarized membrane extensions seemed to be unaffected. Tks5-expressing osteoclasts were also able to fuse with melanoma cells. Similar osteoclast-cancer cell hybrid cells have been detected in bone lesions in myeloma patients. Thus, Src-Tks5 signaling may represent a potential therapeutic target for the treatment of bone-destructive diseases and malignancies.

J Cell Biol 2012; 197: 553

Eitan Israeli

Capsule

How a viral infection makes you more susceptible to bacterial infection

It is well known that viral infection can leave you susceptible to bacterial infections – a bad cold or flu followed by pneumonia is a well-known and oft-experienced example. But why? Negishi et al. reveal a potential mechanism. They found that triggering of RIG-I-like receptors (RLR), which are most often triggered by viruses, can inhibit Toll-like receptor (TLR) signaling, which is essential for some antibacterial responses. In particular, RLR signaling induces the transcription factor IRF3, which binds to and blocks the transcriptional activation of *Il12b*. *Il12b* encodes the p40 subunit of the cytokine interleukin (IL)-12 – a molecule that is essential for the defense against bacterial infections. In mice, activation of RLR led to attenuated TLR signaling and consequently, decreased T cell responses dependent on IL-12 and another cytokine that uses p40, IL-23. The consequence of such reduced immunity was that mice succumbed to sub-lethal doses of a bacterial infection if they were first infected with a virus.

Nature Immunol 2012; 13: 659

Eitan Israeli

Capsule

Pretransplant fecal carriage of extended-spectrum β-lactamase–producing Enterobacteriaceae and infection after liver transplant

Bacterial infection after liver transplant is fairly common, mostly because liver transplant patients are severely ill and the surgery is very complex. Adding to the seriousness of this situation is that some bacteria are resistant to many antimicrobial drugs. However, treating all infections as drug resistant would lead to even more drug resistance, so only patients at highest risk should receive the most powerful drugs. But who is at highest risk? A recent study in France screened fecal samples of liver transplant candidates and found that post-operative infections were most likely for those patients who already had certain bacteria in their feces before surgery. Thus, fecal screening for those multiresistant bacteria should be considered for all liver transplant candidates so that if postoperative infection develops, those at high risk can receive the most specific drugs right away.

Emerg Infect Dis 2012; 18: 908

Eitan Israeli

Capsule

The mutational landscape of lethal castration-resistant prostate cancer

Characterization of the prostate cancer transcriptome and genome has identified chromosomal rearrangements and copy number gains and losses, including ETS gene family fusions, *PTEN* loss and androgen receptor (*AR*) amplification, which drive prostate cancer development and progression to lethal, metastatic castration-resistant prostate cancer (CRPC). However, less is known about the role of mutations. Grasso et al. sequenced the exomes of 50 lethal, heavily pretreated metastatic CRPCs obtained at rapid autopsy (including three different foci from the same patient) and 11 treatment-naive, high grade localized prostate cancers. The authors identified low overall mutation rates even in heavily treated CRPCs (2.00 per megabase) and confirmed the monoclonal origin of lethal CRPC. Integrating exome copy number analysis identified disruptions of *CHD1* that define a subtype of ETS gene family fusion-negative prostate cancer. Similarly, they demonstrated that *ETS2*, which is deleted in approximately one-third of CRPCs (commonly through *TMPRSS2:ERG* fusions), is also deregulated through mutation. Furthermore, they identified recurrent mutations in multiple chromatin- and histone-modifying genes, including *MLL2* (mutated in 8.6% of prostate cancers) and demonstrated interaction of the MLL complex with the AR, which is required for AR-mediated signaling. They also identified novel recurrent mutations in the *AR* collaborating factor *FOXA1*, which is mutated in 5 of 147 (3.4%) prostate cancers (both untreated localized prostate cancer and CRPC), and showed that mutated *FOXA1* represses androgen signaling and increases tumor growth. Proteins that physically interact with the AR, such as the *ERG* gene fusion product, FOXA1, MLL2, UTX (also known as KDM6A) and ASXL1 were found to be mutated in CRPC. In summary, the authors describe the mutational landscape of a heavily treated metastatic cancer, identify novel mechanisms of AR signaling deregulated in prostate cancer, and prioritize candidates for future study.

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Eitan Israeli

Capsule

Working on borrowed time: the social jet lag

Many of us are sleeping less than we used to because of the demands of work and the enticements of the Internet, television, and digital social networking. It is also true that we are increasingly sleeping outside of the times normally dictated by our internal circadian clocks (our "chronotype"). This difference between circadian and social clocks has been termed "social jet lag." Roenneberg and co-workers analyzed data from the Munich ChronoType Questionnaire (MCTQ), which assesses sleep behavior on work and free days. They calculated that one-third of the 65,000 European participants in the MCTQ suffered from at least 2 hours of social jet lag, with teenagers suffering the largest deficiencies. Reduced amounts of sleep are known to be correlated with increased body mass index (BMI) and obesity. The results showed that social jet lag is an equally important predictor of BMI. Furthermore, the average chronotype has shifted later into the night over the past decade, exacerbating social jet lag. This change in chronotype has probably been driven by a weakening of the external cues that normally entrain our circadian clocks, with increasing numbers of people living and working in cities being exposed to less light during the day and more light during the night, and spending less time outdoors. People who regularly sleep outside of their circadian window can show an imbalance in glucose metabolism normally associated with type 2 diabetes.

Curr Biol 2012; 22: 939

Eitan Israeli

Capsule

Neural tissue supports the continued formation of neuronal structures while maintaining a pool of progenitors

During development of the cortex of the mammalian brain, radial glia divide asymmetrically to give rise to apical progenitor cells that continue to divide and cells that differentiate into neurons. Thus, the tissue supports the continued formation of neuronal structures while maintaining a pool of progenitors. Tsunekawa et al. report on a mechanism that influences the fate of the daughter cells. Radial glial cells have long thin apical and basal processes that extend from either end of the cell. mRNA encoding the cell cycle regulator cyclin D2 was preferentially localized and translated in the basal process because of a regulatory sequence in the 3' untranslated region of the mRNA. The daughter cell that inherited the basal process thus got most of the cyclin D2 and continued to proliferate. The other daughter cell, perhaps because of a prolonged cell cycle, or effects of other sequestered factors, underwent neuronal differentiation. A causal role of cyclin D2 was supported by experiments depleting or overexpressing the protein, which caused the accumulation of proliferating progenitor cells or increased neurogenesis, respectively.

EMBO J 2012; 31: 1879

Eitan Israeli