Priming for chemotherapy

Chemotherapy has been used to treat cancer for 60 years, despite an incomplete understanding of the mechanisms by which it is more toxic to cancer cells than normal cells. Now, Anthony Letai and colleagues show that a property called mitochondrial priming correlates with the clinical response to chemotherapy (*Science*, published online 27 October 2011; doi:10.1126/science.1206727). Chemotherapeutic drugs induce apoptosis or inactivate anti-apoptotic pathways. To measure a tumor cell's propensity to undergo mitochondrially mediated apoptosis, the authors exposed cells to BH3 peptides from pro-apoptotic proteins and monitored mitochondrial depolarization. The authors termed this property, which essentially measures the proximity of mitochondria to the apoptotic threshold, 'mitochondrial priming'. They then analyzed mitochondrial priming in 85 tumors before treatment. For each tumor type, the authors found evidence supporting a correlation between higher mitochondrial priming and a positive clinical response to chemotherapy. They tested whether modulating priming would alter chemosensitivity *in vitro*. Using ABT-737, a BH3-mimetic drug, to increase priming in a myeloid leukemia cell line, they observed an increase in sensitivity to three chemotherapeutic agents. The authors suggest that agents that selectively increase mitochondrial priming in cancer cells may enhance the clinical response to conventional chemotherapy. ***PF***

PTEN ceRNAs in melanoma

Pier Paolo Pandolfi and colleagues recently hypothesized that protein-coding RNA transcripts can compete for and sequester microRNAs (miRNAs), and they call these RNA transcripts competing endogenous RNAs (ceRNAs). In two recent studies, Pandolfi and colleagues identify ceRNAs that regulate the tumor suppressor *PTEN* and can promote melanoma in a mouse model (*Cell* **147**, 344–357, 2011, and *Cell* **147**, 382–395, 2011). The authors performed a Sleeping Beauty transposon screen to search for genes that promote melanoma in a B-RAF^{V619E} mouse. They identified 320 common insertion sites and searched for genes enriched for miRNA recognition elements (MREs) shared with *PTEN*. They identified 33 putative ceRNAs affecting *PTEN* and depleted them using RNA interference in human melanoma cells; the decreased levels of six of the putative ceRNAs reduced *PTEN* mRNA levels. None of the putative *PTEN* ceRNAs encode known tumor suppressors, but one gene identified, *ZEB2*, encodes an activator of the epithelial-to-mesenchymal transition (EMT). To test whether the regulation of *PTEN* by *ZEB2* depends on miRNA, the authors depleted *ZEB2* in a *Dicer*-null cell line. They found that *ZEB2* knockdown did not affect *PTEN* mRNA levels, indicating that *ZEB2* regulation of *PTEN* does depend on miRNA. Using bioinformatic analysis and RNA immunoprecipitations, the authors show that the *ZEB2* transcript binds at least four miRNAs in the regulation of *PTEN* expression. *PF*

Personalized asthma control

About a third of individuals with asthma who use inhaled glucocorticoids do not respond to this form of anti-inflammatory asthma control. Heterogeneity in the levels of endogenous glucocorticoids partially explains the observed variation, but family studies also suggest heritable components in the differential response to glucocorticoids. A new study reports that the promoter region of *GLCCI1* harbors two linked SNP markers associated with glucocorticoid response (*N. Engl. J. Med.* **365**, 1173–1183, 2011). The discovery was made using a family-based genome-wide screen in 403 child-parent trios, including 118 affected children who received budesonide, and was subsequently validated in four trial data sets. Individuals homozygous for the risk alleles have a 2.36-fold greater chance of poor response to inhaled glucocorticoids, and their mean improvement in a standard lung function measurement is only 30% of that of people with wild-type alleles. Reporter assays showed that the risk haplotype reduces *GLCCI1* transcription; however, the transcription factors involved and the function of the GLCCI1 protein remain unknown. Together with a recent report of a phase 2 trial for lebrikizumab, in which serum periostin level accurately predicted efficacy (*N. Engl. J. Med.* **365**, 1088–1098, 2011), this study brings us closer to personalized asthma treatment. *WP*

Written by Orli Bahcall, Pamela Feliciano, Wayne Peng, & Kyle Vogan

AKT2 mutations and hypoglycemia

Loss of AKT2 function in humans causes severe insulin resistance. A new study by Robert Semple and colleagues (*Science* **334**, 474, 2011) now shows that gain-of-function *AKT2* mutations result in severe hypoglycemia, weight gain and gross asymmetric overgrowth. The authors performed exome sequencing on a single individual with these phenotypic features and identified a heterozygous missense mutation in *AKT2* that was absent from the unaffected parents. They then sequenced two additional unrelated individuals with the same constellation of features and found the identical *AKT2* mutation in both individuals, of whom one was heterozygous for the mutation and one showed evidence of somatic mosaicism. In both instances, the mutation was absent from the unaffected parents. The mutation, which leads to a glutamate-to-lysine substitution at position 17 in the pleckstrin homology domain of AKT2, results in constitutive plasma membrane localization and activated signaling. Notably, somatic mosaicism for the *AKT1* variant encoding an identical p.Glu17Lys substitution was recently shown to underlie the characteristic skin and skeletal overgrowth in Proteus syndrome (*N. Engl. J. Med.* **365**, 611–619, 2011), highlighting the overlapping but distinct consequences of deregulated AKT1 and AKT2 signaling. *KV*

Leishmaniasis genomes

Visceral leishmaniasis, the most severe and potentially fatal form of leishmaniasis, is caused by the *Leishmania donovani* species complex. Matthew Berriman and colleagues report a high-quality reference genome sequence for a *L. donovani* strain from Nepal (*Genome Res.* published online, 28 October 2011; doi:10.1101/gr.123430.111). They also isolated and sequenced the genomes of 16 clinical strains from individuals in the same region with visceral leishmaniasis. The whole-genome sequence data set provides evidence of population structure beyond that detected using traditional multilocus typing, and there is evidence of adaptive evolution, including selection on genes with surface- and transport-related functions. Drug resistance was seen to emerge independently several times in the strains infecting this group of patients. In an accompanying paper, Jeremy Mottram and colleagues report a reference genome for *L. mexicana* and refine the three other *Leishmania* reference genomes (*Genome Res.* published online, 28 October 2011; doi:10.1101/gr.122945.111). Using comparative analyses, the authors identify a small number of genes and paralog groups unique to each of these species. They find high levels of gene copy-number variation between the species implicated in leishmaniasis. They also find that aneuploidy arises frequently, resulting in chromosome copy-number variation between leishmaniasis strains and species. ***OB***