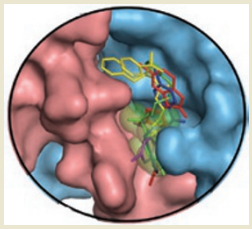
Taking aim at transcription factors



The transcription factor BCL6 facilitates the generation of antibody diversity in B cells by repressing the DNA damage–sensing apparatus, thereby creating genomic instability. But when BCL6 activity goes awry by mutation or translocation, unregulated B-cell growth can ensue and is often associated with diffuse large B-cell lymphomas (DLBCL). Now Cerchietti and colleagues have isolated small molecules that interfere with the interaction between BCL6 and its co-repressors that show activity against DLBCL cells *in vitro* and *in vivo*. Although one of a family of transcription factors with a particular binding region called BTB, BCL6 has a unique lateral groove that interacts with co-repressor molecules. Using computer-aided design, the researchers screened over a million commercially available small molecules for those that might bind that region; molecules were grouped according to their structure, and some from the largest group were chosen for testing. The selected molecules were found to specifically bind BCL6; no binding was observed with other BTB-containing transcription factors. In BCL6-positive cell lines, the molecules blocked repression of several BCL6 targets, among them *tp53, cd69* and *cd44*, which are involved in checkpoint maintenance. Finally, the molecules killed BCL6-dependent lymphoma cells in culture and when transplanted into severe combined immune-deficient mice. Whereas small molecules that target protein-protein interactions have been previously described, this is the first to target a transcription factor. Although more work needs to be done to maximize the potential of the active molecules, this study does suggest a new approach to treating B-cell lymphomas. (*Cancer Cell* **17**, 400–411, 2010) *LD*

Deeper tumor-specific drug delivery

The efficacy of many anti-cancer drugs is compromised by their inability to penetrate tumors more than a few cell diameters from the vasculature. The tumor-penetrating peptide iRGD is known to home to tumors by binding to αv integrins, and to then penetrate cancerous tissue by virtue of exposure of a motif that confers affinity for neuropilin-1. Chemical conjugation of iRGD to drugs can promote tumor-selective uptake, but it is laborious, may not be feasible for the full range of approved chemotherapies and might even impair drug activities. Ruoslahti and colleagues show that systemic coadministration of unconjugated iRGD with either free doxorubicin, liposome-borne doxorubicin, trastuzumab (Herceptin) or nanoparticle albumin-bound paclitaxel (Abraxane) promotes drug uptake by tumors as much as 40-fold in mouse models of breast and prostate cancer. Free iRGD also boosts uptake of both iron oxide and phage-based nanoparticles by prostate tumor xenografts in mice. There is no evidence that the peptide increases tumor metastasis. (*Science* **328**, 1031–1035, 2010) *PH*

Targeting hepatitis C assembly

More than 20 years after the discovery of hepatitis C virus, no drug specifically targeting viral proteins is approved for clinical use. Gao *et al.* and Lemm *et al.* have now identified compounds that target the viral protein NS5A. Whereas most previous anti-viral molecules have targeted viral enzymes, NS5A has no known enzymatic function. It is involved in amplification of viral DNA and regulates the assembly of infectious particles, although details remain unknown. The lead compound, BMS-790052, is active against all hepatitis genotypes tested in cell culture. Early clinical trial results in eight individuals infected with genotype 1a or 1b viruses are promising. Oral administration of a single dose leads to an almost 2,000-fold reduction of viral titers and the low levels are maintained for 1 week. The mechanism of action of BMS-790052 still needs to be elucidated. However, the location of resistance mutations suggests that it might disrupt the formation of dimers of NS5A. *In vitro* results imply synergistic effects between BMS-790052 and inhibitors of the viral protease NS3 or the DNA polymerase NS5B. (*Nature* **465**, 96–100, 2010; *J. Virol.* **84**, 482–491, 2010) *ME*

miRNAs in cancer networks

It is widely appreciated that single microRNAs (miRNAs) frequently control expression of multiple genes and that single mRNA transcripts can be controlled by multiple miRNAs. Yet, instead of aiming to comprehend the complex coordination of miRNA activities, most efforts to elucidate the functions of miRNAs have studied them in isolation. Croce and colleagues illustrate the potential of a systems biology approach to understanding the roles of miRNAs in gene regulation. Using miRNA expression profiles from ~1,000 human samples collected from 50 normal tissues, they show that each cell type is characterized by a distinctive network, with certain miRNAs playing a more critical role than others. Comparison of these networks with those obtained after analysis of >3,000 neoplastic samples from 51 cancer types reveals that all tested cancer types fragment the miRNA network found in healthy cells into several smaller clusters of miRNAs with coordinated activities. The authors conclude that independently regulated miRNAs defined by discrete miRNA subnetworks in cancer cells identify genes involved in cancer-related pathways. They validate this proposal by showing that deregulated miRNAs associated with leukemia in a *Mir155* transgenic mouse model map to the vicinity of the miR155 hub in the cancer network. (*Genome Res.* **20**, 589–599, 2010) *PH*

Cancer metabolism modulator

In the 1920s, biochemist Otto Warburg identified a puzzling feature of cancer metabolism. Whereas normal cells catabolize glucose through oxidative phosphorylation, generating >30 molecules of ATP per molecule of glucose, cancer cells favor the less-efficient fermentation pathway, which yields only 2 molecules of ATP. Why this is so remains elusive nearly a century later, but the possibility of exploiting this difference in molecularly targeted therapies appears promising. Building on their earlier preclinical studies, Michelakis *et al.* have begun to test one such approach in a small-scale clinical trial for glioblastoma. The compound dichloroacetate was known to shift metabolism away from fermentation toward oxidative phosphorylation (by inhibiting an inhibitor of the mitochondrial pyruvate dehydrogenase complex) and has been studied as a treatment for lactic acidosis in metabolic disorders unrelated to cancer. Working with five patients, the authors identified a dosing regimen that altered glioblastoma cell metabolism *in vivo* without causing serious side effects. Although the trial was not designed to measure anti-tumor efficacy, by comparing patient samples from different time points, the authors documented increased activity of pyruvate dehydrogenase, depolarization of mitochondria, increased apoptosis of glioblastoma cells, activation of p53 and decreased angiogenesis. (*Sci. Transl. Med.* **2**, 31ra34, 2010) *KA*

Written by Kathy Aschheim, Laura DeFrancesco, Markus Elsner & Peter Hare