can confer vulnerabilities specific to cancer cells,” says senior author Ronald DePinho, MD, president of The University of Texas MD Anderson Cancer Center in Houston. “Our proof-of-concept was ENO1, a key glycolytic gene that’s lost as part of the 1p36 deletion in glioblastoma—the cells did just fine until we silenced ENO2 [Nature 2012;488:337–42]. This current work in pancreatic cancer is our second example of collateral lethality.”

The malic enzymes ME2 and ME3 reside in the mitochondria, where they help keep reactive oxygen species (ROS) levels in check. Examining four PDAC cell lines, all lacking SMAD4 and, consequently, ME2, DePinho and his team observed a compensatory increase in ME3 expression. Knockdown of the latter significantly reduced cell proliferation and increased apoptosis; in transplanted PDAC-bearing mice, it also suppressed tumor growth and improved survival.

Mechanistically, in PDAC cells lacking both mitochondrial malic enzymes, “we showed that NADPH production is diminished, ROS levels rise, and this stress signal then activates AMPK,” says first author Prasenjit Dey, PhD. AMPK then prevents another protein, SREBP1, from upregulating BCAT2, which is normally involved in regenerating glutamate—an amino acid critical for the cells’ survival, Dey adds.

“Glutamate-derived amino acids are necessary for new nucleotide synthesis,” DePinho explains. “Our study revealed a very important function for malic enzymes in sustaining the replicative potential of cancer cells.”

Nabeel Bardeesy, PhD, of Massachusetts General Hospital Cancer Center in Boston, notes that SMAD4’s absence marks a particularly metastatic subset of PDAC. However, there are no established therapies targeting this loss. The latest findings from DePinho’s group “help crystallize collateral lethality as a way to identify treatment strategies based not on a deleted tumor suppressor’s function, but that of its neighbors on the same chromo-

some,” Bardeesy says. “I think this compelling concept will be explored in many more studies.”

Designing a highly specific ME3 inhibitor would be ideal, DePinho says, but he acknowledges that structural similarities within the active sites of all malic enzymes make this challenging. “To avoid inadvertently inhibiting family members in normal cells, we’ll want to look for other regions of ME3 that may be easier to target,” he says. “With delivery technology continuing to improve, RNAi-based strategies to silence ME3 could also be clinically feasible.” A third, broader approach involves going after additional components of this malic enzyme–regulated metabolic pathway that PDAC cells depend on to survive.

DePinho points out that the SMAD4 locus is also eliminated in approximately 14% of head and neck squamous cell carcinomas, and in up to 10% of gastric and esophageal cancers. “Basically, there are multiple ME2-deficient cancers for which collateral lethality may present a new therapeutic avenue,” he says. —Alissa Poh

NIH Extends Support for Genomics Catalog

The NIH announced earlier this month that it has issued new awards totaling up to $31.5 million in fiscal year 2017 for its Encyclopedia of DNA Elements (ENCODE) Project. The funds will expand the catalog of candidate gene regulatory elements and support new efforts to characterize biological roles of the candidate elements in various cell types and model systems. Additionally, project awards will allow the ENCODE catalog to incorporate data provided by researchers and will allow the use of biological samples from research participants who have agreed to share their genomic data. The resource is available to researchers free of charge at www.encodeproject.org.

“We’re broadening the scope to try to better understand the catalog we’re generating,” says Elise Feingold, PhD, a program director at the National Human Genome Research Institute, part of the NIH.

As cancer disease drivers continue turning up in oft-ignored noncoding stretches, ENCODE “could shine a light on this ‘dark matter’ and allow researchers to pay more attention to these parts of the genome,” says Bing Ren, PhD, an investigator at the Ludwig Institute for Cancer Research at the University of California, San Diego. Ren co-leads one of ENCODE’s newly funded characterization centers, which will study gene regulatory elements in a range of biological contexts. Other centers include the University of California, San Francisco (UCSF); University of Washington in Seattle; Stanford University in Palo Alto, CA; Cornell University in Ithaca, NY; and Lawrence Berkeley National Laboratory in CA.

Since ENCODE launched 14 years ago, researchers not funded by ENCODE have published more than 1,700 papers using its data and tools. Roughly one third of these publications focus on disease applications, says Feingold, and about a third of those relate to cancer.

ENCODE helps scientists form or refine hypotheses about the biological underpinnings of susceptibility alleles identified by genome-wide association analyses. In a study published last fall, researchers used the genomics catalog to identify tissue-specific effects of two APOBEC3 germ-line variants in bladder and breast cancers (Nat Genet 2016;48:1330–8). Also last year, ENCODE helped scientists discover a surprising mechanism behind certain gliomas: Mutations in IDH, which encodes an enzyme involved in energy production, trigger local hypermethylation that disrupts the regulation of the oncogene PDGFRA (Nature 2016; 529:110–4).
Cervical Cancer Analysis Reveals New Mutations

A comprehensive analysis of cervical cancer, a project of the Cancer Genome Atlas (TCGA), has revealed new molecular characteristics that might serve as biomarkers for identifying clinically important patient subgroups in this disease (Nature 2017 Jan 23 [Epub ahead of print]).

So far, only one targeted therapy, the VEGF inhibitor bevacizumab (Avastin, Genentech), which blocks angiogenesis, has received FDA approval for patients with metastatic or recurrent cervical cancer. To uncover other potential targets and better understand how this disease develops, scientists with TCGA used a variety of techniques to profile 228 cervical tumors, including whole-genome and whole-exome sequencing, as well as analyses of copy number, protein levels, mRNA and miRNA expression data, and DNA methylation.

The team reported that these tumors fell into three broad categories: adenocarcinomas, or squamous cell carcinomas with high or low expression of genes in the keratin family. Although previous studies had noted the split within squamous cell carcinomas, this study pinpointed differences “that may serve as key markers for these subgroups,” says co-author Christopher Vellano, PhD, of The University of Texas MD Anderson Cancer Center in Houston. For example, the two subgroups differed in expression of genes such as ARID1A, PIK3CA, and SPRR3.

Approximately 95% of cervical cancers result from persistent human papillomavirus (HPV) infection. However, the researchers pinpointed a subgroup of tumors that were usually HPV-negative and resembled endometrial cancer. This subgroup had high frequencies of ARID1A, KRAS, and PTEN mutations and “may require a different subset of therapeutic options,” says co-author Akinyemi Ojesina, MD, PhD, of the University of Alabama at Birmingham.

The team uncovered five mutant genes not previouly implicated in cervical cancer: SHKBPI, ERBB3, CASP8, HLA-A, and TGFBR2. They also determined that most mutations in the profiled tumors appeared to have been caused by APOBEC proteins. Although these enzymes are part of the innate immune system, altering the genetic material of viruses to ward off infection, they are also a major source of mutagenesis if misregulated.

Overall, “we have identified new markers underlying cervical cancer subgroups which may translate to novel clinical therapies,” says Vellano. Additionally, he notes that CD274 and PDCD1LG2—encoding the programmed cell death ligands PD-L1 and PD-L2, respectively—were often amplified in the study tumors, suggesting a potential therapeutic role for immune checkpoint inhibitors.

Like previous TCGA analyses of endometrial and high-grade serous ovarian cancer, this study “is a tremendous reference guide for the rational development of new therapeutic strategies,” says Ursula Matulonis, MD, of Dana-Farber Cancer Institute in Boston, MA, who wasn’t connected to the work. She notes that several immunotherapies have already reached clinical trials for advanced cervical cancer, including the PD-1 blocker pembrolizumab (Keytruda; Merck), and the findings on CD274 and PDCD1LG2 amplification “justify further work” on these approaches.

Jocelyn Chapman, MD, of the University of California, San Francisco, who also wasn’t involved with the study, adds that it “gives us some ideas about where to pursue novel targets.” For example, the findings suggest that the normally beneficial APOBEC enzymes “have been hijacked by cancer,” she says. –Mitch Leslie

Sequencing Errors Rife in Genome Databases

Many low-frequency somatic variants included in The Cancer Genome Atlas (TCGA) may actually be sequencing errors, not necessarily rare driver mutations, as often suspected. Rather, they could be artifacts of DNA damage introduced by routine sample preparation, according to a recent study (Science 2017;355:752–6).

“This is a very timely paper,” says Trevor Pugh, PhD, a cancer geneticist at Princess Margaret Cancer Centre in Toronto, Canada, who was not involved in the new study. “Today, we’re sequencing much, much more deeply than we used to, so we’re going to start confounding mutations like these oxidative-damage mutations with real tumor-driving variants.”

Archived samples are known to be riddled with mutagenic changes that could be confused for tumor-driving mutations, but fresh tumor samples were thought to be mostly fine. Then in 2013, a team from the Broad Institute, which included Pugh, was sequencing tumors from children with neuroblastoma and found hundreds to thousands of mutations when they expected just...
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