INSIDE THE USCAP JOURNALS

doi:10.1038/labinvest.2016.59

MODERN PATHOLOGY

Gene panel for tumor classification

See page 546

Xu *et al* sought to tackle the ongoing difficulty surrounding the approximately 3–5% of all tumor diagnoses that, despite multiple diagnostic workups, remain unclassified as to primary origin. They have established a database of microarray and sequencing gene expression profiles of 16,674 tumor samples encompassing 22 common human tumor types. They thus identified a 154-gene expression signature that identified the tissue of origin with 96.5% accuracy. Knowing the tissue of origin of a patient's tumor can significantly impact his or her care and outcome, making more accurate identification of primary site of tumors an advantage. The panel performed well in a large independent cohort of tumors, including diagnostically challenging cases. Although further study is necessary, the use of gene expression-based tests to refine diagnoses in difficult cases and perhaps improve treatment outcomes is promising.

Profiling small intestinal neuroendocrine tumors

See page 616

Andersson *et al* performed genome-wide expression profiling on tumor biopsies from 33 patients with well-differentiated neuroendocrine tumors. Their goal was to define the transcriptome and identify clinically relevant subgroups of tumors, prognostic markers, and novel targets for treatment. High expression of neuroendocrine markers such as *SSR2* were characterized in half of the tumors, which were from the patients with the longest survival. Patients with shorter

survival showed increased expression of cell cycle-promoting genes. The authors showed that tumor grade was associated with altered expression of genes related to proliferation and microenvironment, such as upregulation of FOXM1 expression. Other cell cycle regulators, such as E2Fs, TBX1, and FOXM1 as well as PTGER2, which promotes tumor cell proliferation, invasion, and angiogenesis, were also affected. HDAC inhibitors as well as inhibitors of HSP90 and AKT were found to effectively suppress the growth of neuroendocrine tumor cells, although clinical evaluation is needed.

LABORATORY INVESTIGATION

Liver myofibroblast test for antifibrotic drugs

See page 672

Aoudjehane *et al* used normal human liver myofibroblasts obtained from 31 subjects to develop a cell culture model to assess antifibrotic drugs. The goal of developing a preclinical model is to replace the currently used animal models, which are expensive, time-intensive, and sometimes poorly predictive. The authors' model of fibrogenesis can be evaluated on a cell level in terms of both myofibroblastic differentiation as reflected by α -smooth muscle actin

(α -SMA) expression and extracellular matrix production as reflected by collagen 1 (Coll1) production. The group was able to determine intersubject variability of fibrogenesis, allowing them to illustrate polymorphism of liver fibrogenesis in the human population. They measured α -SMA and Coll1 expression in four patients to test the potential antifibrotic effects of pirfenidone and losartan. The results indicated that their model could provide data and determine biomarkers that could be accessible in blood for use in future studies of liver fibrosis and trials of antifibrotic drugs.

Cancer and virus-related microRNA profiling

See page 661

Treece *et al* investigated gastric adenocarcinoma microRNA expression. Analyses of formalin-fixed paraffin-embedded tissue and plasma were evaluated. The authors compared human Epstein-Barr virus (EBV)-encoded and control microRNAs to provide insight into alterations of expression and insight into the specific expression signatures of viral-associated tumors. Selected human and viral microRNAs in normal versus cancer tissue were differentially expressed and could be distinguished; even circulating cell-free microRNA exhibited unique expression patterns that could distinguish cancer from noncancer patient groups. hsa-miR-155, -185, and -378 were upregulated in infected cancer, whereas hsa-miR-196b was downregulated. The authors propose that the development of these technologies, and a deeper understanding of these profiles and the cellular pathways they regulate, could support clinical trials. In plasma samples, microRNA profiling could allow monitoring of tumor burden during therapy and might identify predictive markers as well.

Laboratory Investigation | Volume 96 June 2016

nature.com/pathology

High-throughput genotype-specific compound screening

Yu *et al* recently described in *Nature Biotechnology* the development of a method, called PRISM, for labeling multiple cell lines with a unique 24 nucleotide bead-based bar code. The bar codes allow cell lines to be pooled prior to the introduction of various compounds, and the data extracted show the efficacy of the compound with respect to cell killing. A total of 8,000 diversity-oriented synthesis compounds were screened against 102 cell lines. One of the targets from an eight-point PRISM dose-response assay exhibited a promising cytotoxicity profile, BRD-7880. The authors showed that BRD-7880 had aurora kinase inhibitor activity similar to that of the existing inhibitor tozasertib, and that it was more targeted than all other known inhibitors in its class. The rapid identification of a molecular target using these barcoded tumor cell lines has the potential to provide a large-scale resource for faster testing of compounds across the diversity of human cancer types.

Nature Biotechnology 2016;34:419–423; doi:10.1038/nbt.3460

Genetic predisposition to diabetes

As reported in *Nature Genetics*, Dooley and colleagues investigated mechanistic links between type 1 (T1D) and type 2 (T2D) diabetes in a mouse model. Their findings point toward a genetic predisposition to diabetes caused by genetic variation in

Xrcc40 and *Glis3* causing altered response by nonobese diabetic (NOD) mouse β -cells to unfolded protein stress that results in apoptosis and senescence. *Glis3* expression was reduced in islet expression of NOD mice, and in INS-1 cell knockdown models there was increased susceptibility to apoptosis. Their data identified β -cell failure as a mechanistic commonality between T1D and T2D. The model enables investigation of β -cell death and the negative effects of compensatory upregulation of insulin in the absence of autoimmunity or insulin resistance. Validation of their data in human islets supports the use of the model for the development of therapeutics to prevent the decline of β -cells.

Nature Genetics 2016;48:519–527; doi:10.1038/ng.3531

Targeting fatty acid oxidation in TNBC

Camarda *et al* explored the role of the MYC transcription factor in triple-negative breast cancer (TNBC) metabolism. Using an MYC-driven model of TNBC, described recently in *Nature Medicine*, they demonstrated that fatty acid oxidation (FAO) intermediates were dramatically upregulated. Univariate analysis of 336 fatty acid metabolism genes in their patient cohort showed that decreased expression of ACACB (the ACC2 enzyme that produces malonyl-coenzyme A to directly inhibit CPT1A and CPT1B and therefore FAO) was associated with a poorer prognosis for all patients, as well as for the TNBC cohort. This fatty acid signature was hypothesized to contribute to aggressiveness in breast tumors in general, with the worst outcomes in TNBC. Pharmacologic inhibition of FAO catastrophically decreased energy metabolism in an MYC-driven transgenic TNBC model, illustrating a bioenergetic reliance on FAO in TNBC. This supports a strategy of targeting FAO in TNBC patients.

Nature Medicine 2016;48:519–527; doi:10.1038/nm.4055

Emma Judson contributed to these reviews.