of HLA-A*0201, a cell-surface protein responsible for presenting antigens to the immune system, were also observed.

Next, the team synthesized 707 potential neoantigen peptides and evaluated them in both groups; no significant differences in peptide binding to HLA-A*0201 were found. They randomly assessed 40 peptides for their ability to elicit cytotoxic T-cell responses in vitro, and confirmed that approximately a quarter were immunogenic—five from the inflamed cohort, and six from the noninflamed cohort.

“The main question we addressed in our study was, ‘Does T cell–driven inflammation in tumors depend on mutational load and neoantigen density?’” says co–lead author Stefani Spranger, PhD. “It appears the answer is no.” The findings substantiate clinical observations that immunotherapy can be effective even in tumor types with a low number of neoantigens, such as renal cell carcinoma, adds Jason Luke, MD, the study’s other co–lead author. One reason why some tumors are devoid of infiltrating T cells and are noninflamed may be because they also lack Batf3-lineage CD103+ dendritic cells, Spranger notes. She and Gajewski have shown that tumor-intrinsic β-catenin signaling hinders the recruitment and activation of this dendritic cell subset; this in turn keeps T cells from being activated and entering the tumor microenvironment (Nature 2015;523:231–5).

Another culprit that suppresses T-cell trafficking to tumors is PTEN loss and concomitant activation of PI3K signaling, reported by Patrick Hwu, MD, chair of the department of melanoma medical oncology at The University of Texas MD Anderson Cancer Center in Houston, and his colleagues (Cancer Discov 2016;6:202–16). This, together with the findings from Gajewski’s group, demonstrates that “mutational load may be an important factor for immunogenicity in some cases, but there are many other elements that are underappreciated by our field,” Hwu says.

Luke and Spranger also examined the correlation between mutational load and T-cell–driven inflammation in cancers besides melanoma. The team developed a 160-gene signature of T-cell inflammation and applied it to 30 different solid tumor samples from TCGA, including prostate cancer and lung adenocarcinoma. “The number of mutations present in a given tumor type had little bearing on whether or not inflammation occurred,” Luke says. “It’s a relief to know that mutational load is not the be all and end all of immunotherapy responsiveness,” he adds. “We’re now exploring therapeutic interventions, including β-catenin inhibitors, that may improve T-cell trafficking into noninflamed tumors and ultimately increase the number of patients who benefit from immune checkpoint blockade.” –Alissa Poh ■

Pinpointing Cancer Stem Cells in Oligodendroglioma

Cancer stem cells may drive the development of oligodendroglioma, an incurable brain tumor characterized by IDH1 or IDH2 mutations, a new study reveals (Nature 2016;539:309–13).

Researchers led by Mario Suva, MD, PhD, of Massachusetts General Hospital in Boston, and Aviv Regev, PhD, of the Broad Institute in Cambridge, MA, weren’t trying to track down cancer stem cells when they began their study. Instead, Suva says, “we wanted to understand the composition of oligodendrogliomas early in their development in an unbiased way.”

The researchers used RNA sequencing to profile individual cells from six untreated low-grade tumors, analyzing a total of 4,347 cells. Gene expression patterns indicated that the cells fell into three categories. One group had high levels of oligodendrocyte markers such as OLG1 and OMG. Expression of these markers was low in the second group, which instead featured high levels of astrocyte markers such as APOE and ALDOC. Overall, the differentiation paths of these two groups of cancer cells resembled lineage maturation in oligodendrocytes and astrocytes.

The third group caught the researchers’ attention. These cells were undifferentiated and expressed transcription factors required by stem cells, such as SOX4 and SOX2, suggesting that they could be cancer stem or progenitor cells. Supporting that inference, the gene expression patterns in these cells were very similar to those of mouse neural stem cells and human neural progenitor cells. Within each of the six tumors, the scientists pinpointed a small proportion (1.5% to 8%) of actively proliferating cells, which they determined mostly belonged to this third category of stem/progenitor cells.

“We think that we’ve identified a cancer stem cell population that is responsible for fueling the growth of these tumors,” Suva says. Other studies have discovered likely cancer stem cells in glioblastoma, he says, but whether they occur in low-grade, IDH1- or IDH2-mutant gliomas has been unclear.

When the researchers used copy-number variation and point mutation analyses to sort their cells into subclones, they found that many subclones contained cells from all three categories identified through RNA sequencing. These results imply that the identity of oligodendroglioma cells is not primarily determined by genetic events, but rather by nongenetic developmental programs.

Suva acknowledges one caveat of the study: Because low-grade oligodendroglioma xenografts don’t grow in mice, the researchers couldn’t functionally validate the stem/progenitor cell category they found. However, he thinks it might be possible to curb oligodendroglioma growth by targeting the stem/progenitor cells with immunotherapies, such as CAR T cells engineered to home in on markers on the stem cells.

The single-cell RNA-sequencing technique that Suva’s team used provides strong evidence that cells in this category are indeed cancer stem cells, says Justin Lathia, PhD, of the Cleveland Clinic Lerner College of Medicine in Ohio, who wasn’t connected to the study. “What’s really exciting is to see the stem cell signature within this tumor type.” Now, he adds, the researchers will need to determine how this population responds to treatment and also figure out individual cells’ role in resistance. –Mitch Leslie ■

Bringing Precision Medicine to Community Oncologists

Quest Diagnostics has teamed up with Memorial Sloan Kettering Cancer Center (MSKCC) in New York, NY, and with IBM Watson Health in Cambridge, MA, to create IBM
Oncologist Norman Sharpless, MD, and pathologist Nirali Patel, MD, of the University of North Carolina Lineberger Comprehensive Cancer Center, review cancer treatment insights from Watson Genomics.

Watson Genomics, a new service that combines cognitive computing with genomic tumor sequencing. The initiative is aimed at advancing precision medicine beyond large cancer centers to thousands of community oncologists across the country.

“The real innovation is making this data clinically actionable for community oncologists,” says Jay Wohlgemuth, MD, chief medical officer and senior vice president of research and development at Quest Diagnostics, based in Madison, NJ. “Oncologists can now get a report that summarizes all of the relevant literature, data, and expert opinion surrounding a patient’s specific tumor mutations, along with any potential drug and clinical trial options.”

IBM Watson Health is a cloud-based platform that searches tumor sequencing data, uploaded by oncologists, for actionable mutations, while simultaneously reviewing the most current evidence-based guidelines, clinical trials, journal articles, and patient outcomes.

The program is already being used at many large cancer centers, whose experts have been helping to “train” Watson by providing both clinical data and feedback on the quality of the platform’s analyses. This new partnership with Quest, which has relationships with half of the country’s hospitals, marks the first time that Watson will be made widely available to community cancer centers.

With the new service, oncologists can send a patient’s solid-tumor biopsy sample to Quest, where it will be sequenced and the results fed into Watson. Watson will then compare the findings against its clinical and research databases and uncover any available drug therapies that target the patient’s mutations.

MSKCC is contributing its existing precision oncology knowledge base, OncoKB, to Watson’s trove of data. OncoKB contains detailed information about specific alterations in 418 cancer genes, including their biological effects and prevalence, based on sequencing data collected at MSKCC and curated by its expert panel.

“Sequencing data are complex and need expert interpretation,” says Paul Sabbatini, MD, deputy physician-in-chief for clinical research at MSKCC. “Some of the information surrounding genomic alterations is too new to be described in the published literature. However, we’re able to provide input on what we know today.”

Community oncologists have often struggled to interpret the basic information provided in a patient’s tumor sequencing report, Sabbatini says. Through IBM Watson Genomics, in addition to a list of mutations, they will also receive the benefit of expert guidance on prognostic and treatment implications, which he considers a giant step forward.

IBM Watson Genomics is available immediately to all physicians and hospitals that use Quest Diagnostics’ services, says Wohlgemuth. The entire process—from ordering the test to analyzing the data—takes 2 to 3 weeks.

Besides better informing treatment decisions, collaborators expect the initiative will help advance targeted drug development, adds Wohlgemuth.

“To date, sequencing has largely been performed at major cancer centers, which has limited trial enrollment,” he says. “We hope this new service will speed up the patient matching process and reach people in the community who may not otherwise be connected with many clinical trials.” –Janet Colwell

China is rapidly becoming a powerhouse in cancer research, with more than 17% of the global share of cancer-related publications, according to a report from the scientific publisher Elsevier (available at https://www.elsevier.com/connect/cancer-moonshot-resource-center).

This output matches that of the United States in 2005 and is driven by increased R&D spending along with “a shift from socialist economic planning to a more market-driven system,” the report says.

New guidelines for HER2 testing in patients with gastroesophageal adenocarcinoma were issued (J Clin Oncol 2016 Nov 14 [Epub ahead of print]). Members of the American Society of Clinical Oncology, the College of American Pathologists, and the American Society for Clinical Pathology developed 11 evidence-based recommendations to establish standards for when and how to accurately assess HER2 status—and to help clinicians identify patients most likely to benefit from HER2-targeted therapy.

The tobacco industry’s efforts to quash various state cigarette tax hike initiatives met with mixed results on Election Day. Voters in California approved Proposition 56, which will increase the state cigarette tax by $2.00 per pack. However, Colorado and North Dakota rejected similar measures, which would have resulted in per-pack tax increases of $1.75 and $1.76, respectively.

Also on Election Day, three states approved marijuana for medical use. Voters in Florida, North Dakota, and Arkansas approved initiatives legalizing its use for patients with diseases such as cancer, HIV/AIDS, amyotrophic lateral sclerosis, and post-traumatic stress disorder.

The FDA approved nivolumab (Opdivo; Bristol-Myers Squibb) for patients with recurrent or metastatic head and neck squamous cell carcinoma previously treated with platinum chemotherapy. The agency’s nod was based on a phase III trial of 361 patients, who were randomly assigned to receive the PD-1 inhibitor or investigator’s choice of chemotherapy (N Engl J Med 2016;375:1856-67). A 2.4-month improvement in median overall survival was seen in the nivolumab arm.