Xiling Shen, Duke University

molecule TNFα does play a role during inflammation. normal conditions. that the switch is not necessary under conditions, suggesting that the switch is not necessary under normal conditions. However, they found that the switch does play a role during inflammation. Adding the inflammation-promoting molecule TNFα to cultured intestinal stem cells increased the rate of asymmetric division from 4.6% to 19%. To determine whether that increase also occurs in vivo, the team stimulated intestinal inflammation in mice that do or do not express miR-34a. The frequency of asymmetric divisions among intestinal stem cells rose from 2% to 13% in normal mice, but this increase didn’t occur in miR-34a-deficient mice. Given that inflammation may be a cause of colorectal cancer, the authors suggest that the shift to asymmetric division may be a safeguard against too much stem-cell self-renewal after inflammation-induced damage—and possibly under oncogenic stress—and thus may serve as a tumor-suppressive mechanism. Indeed, when Shen and colleagues compared healthy and cancerous intestinal tissue from patients with colorectal tumors, they found that asymmetric division was more common in the tumor samples. Although the switch can curb division, it may not be successful in preventing tumors. If they form, they eventually eliminate miR-34a, restoring symmetric division and accelerating cellular proliferation, says Shen. “That unleashes the badness.”

The symmetric division of normal intestinal stem cells has been “a paradox,” says Sharon Pine, PhD, of Rutgers University in New Brunswick, NJ, who wasn’t connected to the study. “This work adds a new element to the equation—inflammation” and suggests that asymmetric division “is a mechanism to curb expansion of the stem cells during injury and repair.”

The work also offers an explanation for how miR-34a controls tumor growth, adds Tannishtha Ray, PhD, of the University of California, San Diego. “This study suggests that miR-34a could act as a tumor suppressor in part by regulating asymmetric division.” –Mitch Leslie

**Analysis of ALL Subtypes May Improve Treatment**

A new study identifies the underpinnings of a genomic alteration that occurs in children and young adults with a particularly aggressive form of acute lymphoblastic leukemia (ALL), potentially leading to targeted treatment options for those whose tumors progress on standard therapy. The findings will aid in designing clinical trials in which patients with Philadelphia chromosome–like (Ph-like) ALL will receive a combination of chemotherapy and approved drugs.

In previous studies, researchers from St. Jude Children’s Research Hospital in Memphis, TN, identified chromosomal rearrangements of the erythropoietin receptor (EPOR) gene in Ph-like ALL, but they did not understand how the rearrangements occurred or how they activated the JAK–STAT signaling pathway in ALL.

In this study, the researchers analyzed 3,115 cases of childhood, adolescent, and young adult B-cell precursor ALL, 212 of which had a gene expression profile of Ph-like ALL (Cancer Cell 2016;29:186–200). Of the latter, 19 had EPOR rearrangements, including those identified in previous research, representing about 9% of their Ph-like ALL cases.

Each EPOR rearrangement results in overexpression of a truncated form of the receptor, which is hypersensitive to erythropoietin, says the study’s senior investigator, Charles Mullighan, MD, co-leader of the Hematological Malignancies Program at St. Jude. Erythropoietin then binds to the overexpressed receptors, leading to heightened activation of the JAK–STAT pathway.

The researchers demonstrated that combining the JAK–STAT inhibitor ruxolitinib (Jakafi; Incyte)—currently approved to treat myelofibrosis—with conventional chemotherapy slowed tumor growth in engineered mouse cells and human leukemic cells.

“We found that JAK–STAT inhibitors were active and that they synergized with the chemotherapy drugs that we routinely use now,” including dexamethasone, vincristine, and daunorubicin, Mullighan says. “We saw remarkable and dramatic improvements in tumor cells that were often refractory or partially resistant to active chemotherapy.”

St. Jude is now working with the Children’s Oncology Group (COG) to design trials using whole-genome sequencing to detect targetable alterations and guide patients with leukemia into appropriate clinical trials. As part of their research, Mullighan’s team developed a diagnostic test using gene expression assays that could be used to screen for EPOR rearrangements.

The findings will help inform research on many Ph-like ALL alterations, which tend to increase with age and are present in about 27% of all patients with ALL between ages 21 and 39, says Lee Greenberger, PhD, chief scientific officer of the Leukemia and Lymphoma Society, based in White Plains, NY. The EPOR rearrangements, which are found in 3% to 4% of Ph-like ALL tumors, are among many chromosomal rearrangements that are targetable by inhibiting the JAK–STAT or other signaling pathways.

“There could be other kinase inhibitors that might work for these patients,” he says. “This paper shows that diagnostic tools for specific rearrangements can be developed and
could guide the use of precision therapeutics to treat patients with such genetic alterations.” –Janet Colwell

**Diagnostic Advances Made for CNS-PNET**

A recently published study concludes that a majority of children diagnosed with primitive neuroectodermal tumors of the central nervous system (CNS-PNET) may have other CNS cancers instead (Cell 2016;164:1060–72). The findings may lead to more accurate diagnoses and better-tailored treatment plans based on the molecular profiles of their tumors.

Historically, it has been difficult to distinguish CNS-PNETs from other CNS tumors because diagnoses have been based solely upon their appearance under the microscope, says the study’s co-first author Brent Orr, MD, PhD, of St. Jude Children’s Research Hospital in Memphis, TN. As a result, patients with CNS-PNETs have often been lumped together with patients with medulloblastoma in clinical trials because of the histopathologic similarities of their tumors.

In the new study, an international team of researchers analyzed DNA methylation patterns from 323 tumors classified as CNS-PNET and from 211 other well-defined brain tumors. They determined that 61% of the CNS-PNETs could be reclassified as other types of tumors based on their molecular profiles.

They also found that the remaining fraction fell into one of four new molecular subtypes of CNS-PNETs: CNS neuroblastoma with FOXR2 activation, CNS Ewing sarcoma family tumor with CIC alteration, CNS high-grade neuroepithelial tumor with MNI alteration, and CNS high-grade neuroepithelial tumor with ECOR alteration.

Subsequently, the researchers performed next-generation sequencing on tumors from each group and identified specific genetic fusions, deletions, and rearrangements underlying each of the four molecular subtypes. Some of these alterations were shared or similar to abnormalities found in other cancers, including Ewing sarcoma and clear cell sarcomas of the kidney, and patients whose tumors have these alterations could potentially be treated with existing approved drugs.

“The findings have significant therapeutic implications,” says Jim Olson, MD, PhD, professor of pediatric hematology/oncology at the University of Washington School of Medicine in Seattle. CNS-PNETs, which account for about 1% of pediatric brain tumors and primarily affect young children, are treated with very high doses of craniospinal radiation and more-toxic chemotherapy than is typically used to treat other types of CNS tumors.

“Some children could receive other, less-toxic treatments if we know the correct diagnosis from the start, and these new genomic analyses allow us to do that,” says Olson, who leads an international phase III Children’s Oncology Group (COG) clinical trial for patients with high-risk medulloblastoma. “We can also now identify patients with CNS-PNETs and potentially guide them towards targeted therapies that are aligned with the genetic drivers of their disease.”

The COG clinical trial is testing the efficacy of treating patients with high-risk medulloblastoma with carboplatin radiosensitization in combination with cisplatin-based chemotherapy. Olson closed the CNS-PNET arm of the trial about 2 years ago based on the data emerging from the St. Jude study showing that some patients originally diagnosed with PNETs might have different types of tumors. Researchers are now analyzing tumor samples from patients in the discontinued arm to determine how patients with the four PNET subtypes responded to treatment. They expect to release their findings within the next year.

“The data analysis will allow us to look at patients who actually had CNS-PNETs and determine what fraction of them survived,” Olson says. “We hope that will help us to identify trends that can help us shape future clinical trials.” –Janet Colwell

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**NOTED**

The genetic testing company Ambry Genetics launched AmbryShare, a disease-specific public database that includes anonymized, aggregated data from 10,000 patient samples. The company sequenced the exomes of deidentified patients with hereditary breast and ovarian cancers and found 10-fold more genes implicated in these conditions than previously known.

A report issued by the California Life Sciences Association and Boston Consulting Group found that FDA review times for new drugs have steadily declined since 2009, when a review took 21 months on average. That average was cut to 9 months by 2014, with cancer treatments receiving some of the fastest reviews.

Microsoft cofounder Paul Allen will launch an eponymous foundation with $100 million to advance biologic research. His Paul G. Allen Frontiers Group announced several grants, including a $20 million grant to fund the Allen Discovery Center at Tufts University that will help researchers understand the “biological code that determines anatomical structure and function during embryogenesis, regeneration, and tumor suppression.”

Developed by researchers at The University of Texas MD Anderson Cancer Center in Houston, a new staging system for breast cancer considers five factors—preclinical stage, estrogen receptor status, HER2 status, grade, and posttreatment pathologic stage. Researchers say that the new tool will refine prognostic stratification and help clinicians decide which patients would benefit from additional therapy (JAMA Oncol 2016;March 17 [Epub ahead of print]).

Of 2,211 doctors recently polled, 64% thought that regular colon cancer screenings should begin before age 50, the current recommendation. The poll was conducted in response to two recent studies—one found that nearly 15% of patients with colorectal cancer are diagnosed before age 50, and another concluded that younger patients are more likely to have advanced disease (Cancer Med 2015;4:1863–70; Cancer 2016;122:929–34).