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Dung T. Le, MD, discusses the use of mismatch repair deficiency to predict response to PD-1 blockade in colorectal and other cancers.

patients may not have a mutation that the immune system can recognize," explained Le, adding that researchers plan to further assess the MMR-deficient non-responders.

Although MMR deficiency can occur in many cancer types, including those in the uterus, stomach, biliary tract, pancreas, ovaries, prostate, and small intestine, in addition to colorectal cancer, Le said it is too early to recommend that all patients with cancer be tested for it. Researchers first need to confirm their findings in a larger group of patients. "This was a small study," she said. ■

Study May Yield Breakthrough for DIPG

A recent study suggests that a drug approved for the treatment of multiple myeloma may hold promise for treating diffuse intrinsic pontine glioma (DIPG), a pediatric brain tumor that currently has no effective treatment.

Researchers screened 16 human DIPG cell lines against a panel of 83 promising targeted agents and chemotherapies approved for pediatric brain tumors. The multihistone deacetylase inhibitor panobinostat (Farydak; Novartis) was selected for further study based on its efficacy in 12 of the 16 cell lines.

When the researchers injected the drug into mice implanted with DIPG tumors, they found that it slowed tumor growth. The findings set the stage for a phase I clinical trial of panobinostat, slated to begin by the end of this year (Nat Med 2015;21:555–9).

"This disease is the leading cause of brain tumor death in children, and we've made zero progress in treating it over the past several decades," says the study's senior author Michelle Monje, MD, PhD, a pediatric neuro-oncologist and assistant professor of neurology at Stanford University School of Medicine in Palo Alto, CA. "It's exciting that we have preclinical data that suggests a therapy."

Observing that DIPG cells eventually developed resistance to panobinostat, the researchers also experimented with a combination of panobinostat and GSK-J4 (GlaxoSmithKline), a development-stage demethylase inhibitor that has shown some potential for treating DIPG. They discovered that the two drugs work synergistically to counteract known mechanisms of epigenetic dysfunction in DIPG cells.

Panobinostat's potential as a therapeutic agent is consistent with earlier research showing that about 80% of DIPG tumors harbor recurrent K27M mutations in genes encoding histone H3 that prevent trimethylation, causing broad epigenetic dysregulation, says Monje. By inhibiting histone deacetylase, investigators expected panobinostat to increase acetylation, but they were surprised to discover that it also restored methylation and normalized gene expression.

DIPG has been difficult to study because tumors are enmeshed in the brain stem, cannot be removed, and are not typically biopsied. However, 5 years ago, Monje established the first cell culture of DIPG from an autopsy sample. Similar efforts to obtain tumor tissue for research have led to the development of additional DIPG cell cultures in Monje's lab and in several other labs internationally.

"In the past we would take adult glioblastoma tumors and test those cells for targets, but we now understand that the mutations found in DIPG are not the same as those found in adult tumors," says Mark Kieran, MD, PhD, clinical director, Brain Tumor Center, Dana-Farber/Boston Children's Cancer and Blood Disorders Center in Boston, MA, who was not involved with the study. "What makes this study so unique is that it uses the appropriate targeted cells from actual DIPG patients and shows that, *in vitro*, panobinostat can turn off tumor cell proliferation and, *in vivo*, it can cross into the brain and turn off tumor growth."

Kieran cautioned that many questions remain about panobinostat's potential in DIPG. For example, while systemic administration of the drug showed effectiveness in mice used in the study, it is not known whether it will cross the blood–brain barrier in children. Monje's team used convection-enhanced delivery to directly infuse panobinostat into the brain stem in mice, but that method has not yet been approved for humans.

"That one drug is suddenly going to knock out DIPG is unlikely, but for a disease where we've seen no progress in 50 years, this paper is an enormous advance in our understanding," says Kieran. "For the first time, we have at least some idea of how to start moving forward." ■

New Options for EGFR-Mutant Lung Cancer

Two new drugs that target the most common cause of acquired resistance to earlier EGFR inhibitors may offer a much-needed treatment option for patients with EGFR-mutated non–small cell lung cancer (NSCLC), according to findings from early-phase clinical trials.

AZD9291 (AstraZeneca) and rociletinib (Clovis Oncology) are third-generation EGFR tyrosine kinase inhibitors that are active against the T790M *EGFR* mutation, the most common mechanism of resistance in patients whose tumors progress after treatment with first-generation EGFR inhibitors, such as erlotinib (Tarceva; OSI Pharmaceuticals) and gefitinib (Iressa; AstraZeneca). In separate trials, AZD9291 and rociletinib were associated with response rates of 61% and 59%, respectively, among T790M-positive patients resistant to first-generation EGFR inhibitors, compared with 21% and 29% among patients without the mutation (N Engl J Med 2015;372:1689–99; N Engl J Med 2015;372:1700–9).