**NEWS IN BRIEF**

**NK Cells Respond to Checkpoint Blockade**

Natural killer (NK) cells may play an important role in antitumor response to immune checkpoint blockade, according to a recent study (J Clin Invest 2018;128:4654–68). Using mouse models, researchers established that NK cells respond to PD-1 and PD-L1 inhibitors, information that could be used to develop immunotherapies that mobilize NK cells against cancer.

Cancers that are responsive to immune checkpoint inhibitors, such as melanoma and lung cancer, often have high MHC class I/II expression or mutation rates, making them a target for T cells, notes Michele Ardolino, PhD, of the Ottawa Hospital in Canada, co–senior author. However, that isn’t always the case.

“IT IS WELL KNOWN THAT HODGKIN lymphoma patients are very responsive to checkpoint blockade, and this is sort of a conundrum,” Ardolino says, “because their tumors have a loss of MHC class I expression. Consequently, he and his team decided to investigate whether there was a T cell–independent response that was initiated by immune checkpoint blockade,” with earlier research pointing to NK cells.

In a previous paper, the researchers investigated the activity of NK cells in tumors lacking MHC class I expression (J Clin Invest 2014;124:4781–94). In their recent study, the researchers found that when they treated mice that had tumors with low MHC class I expression—and were thus invisible to T cells—with PD-1 or PD-L1 inhibitors, the mice had reduced tumor growth and improved survival. However, the effect disappeared when they eliminated NK cells, “which to us suggested that in this tumor model, we could see a therapeutic effect that was linked to the presence of NK cells,” Ardolino says.

Finally, the researchers eliminated PD-L1 expression in mouse models of colon cancer and triple-negative breast cancer. They found that the PD-L1–deficient tumors did not grow as quickly as those that expressed PD-L1, though tumor growth was somewhat faster when the researchers depleted either T cells or NK cells. However, when they eliminated both T cells and NK cells, the tumors lacking PD-L1 grew more quickly than those expressing PD-L1. “Both T cells and NK cells seem to be playing a role in the response of these tumors, and both of them seem to be inhibited by the presence of PD-L1,” Ardolino explains.

“We think that this study really provides evidence that we may be able to use checkpoint blockade to help mobilize NK cells for immunotherapy,” says co–senior author David Raulet, PhD, of the University of California, Berkeley. He adds that NK cells may be a good target for immunotherapy because “they’re very much like T cells: They kill by the same types of mechanisms, they’re regulated by some of the same signals, including checkpoint receptors, and yet their recognition is different. Many of the types of tumors that may be resistant to T cell–focused immunotherapies will be sensitive to NK-based therapies.”

For Jeffrey Miller, MD, deputy director of the University of Minnesota’s Masonic Cancer Center in Minneapolis, who was not involved in the study, it “highlights the importance of immune checkpoints and goes beyond T cells, implicating the PD-1 axis as important for NK cells in the tumor microenvironment.”

André Veillette, MD, of the Montréal Clinical Research Institute in Canada, who was also not connected to the research, sees it as part of a larger trend: “There’s this rejuvenation in interest in NK cells as really bona fide players and serious contenders for being used for antitumor immunity,” he says. –**Catherine Caruso**

**Data Offer New Insights into AML**

A recently released dataset from a large cohort of patients with acute myeloid leukemia provided evidence that elevated telomerase levels are linked to poor outcome regardless of whether patients receive chemotherapy or immunotherapy. In a previous study, researchers showed that elevated levels of telomerase are associated with a poor prognosis in patients with acute myeloid leukemia. The current study, led by Padmanee Sharma, MD, PhD, of the University of Texas MD Anderson Cancer Center in Houston, won the Cancer Research Institute’s 2018 William B. Coley Award for Distinguished Research in Basic and Tumor Immunology. Sharma studies immune checkpoint inhibitors: She led clinical trials on bladder and prostate cancers that established the importance of the ICOS molecular pathway for promoting tumor destruction after anti-CTLA4 therapy. She is also investigating combinations of immune checkpoint inhibitors for prostate cancer.
leukemia (AML) offers new insights into the disease and provides information that will drive additional research efforts. The dataset, part of which was recently published, integrates genomic information about tumor samples with data on how cancer cells respond to drugs (Nature 2018;562:526–31). It was developed as an early iteration of the ongoing Beat AML Master Trial.

“AML is the most commonly diagnosed leukemia, and it’s also the one with the poorest prognosis,” explains Brian Druker, MD, director of the Knight Cancer Institute at Oregon Health & Science University in Portland and a senior author on the study. Although several therapies have been approved for AML in recent years, he says the standard of care has changed little, in part because “AML is an incredibly heterogeneous leukemia with a fair number of driver mutations that can occur in lots of different combinations.” Previous research has defined at least 11 distinct genetic subtypes of the disease (N Engl J Med 2016;374:2209–21).

To investigate the relationship between genomics and drug responses in AML, Druker and his colleagues collected 672 tumor samples from 562 patients. They used whole-exome and RNA sequencing to identify mutations and gene expression profiles, and performed ex vivo drug sensitivity testing to determine how malignant cells responded to 122 different drugs. Then, they linked genomic data with drug response in each sample.

For example, the researchers found that tumors with combinations of \( \text{FLT3}, \text{NPM1}, \) and \( \text{DNMT3A} \) mutations were particularly sensitive to the Bruton tyrosine kinase inhibitor ibrutinib (Imbruvica; Johnson & Johnson and Pharmacyclics). Additionally, mutations in \( \text{TP53} \) or \( \text{ASXL1} \) resulted in a broad pattern of drug resistance, whereas mutations in both \( \text{BCOR} \) and \( \text{RUNX1} \) were associated with increased sensitivity to selective JAK inhibitors. The entire dataset is available via the Vizome platform (http://www.vizome.org/).

Shannon McWeeney, PhD, also of Oregon Health & Science University and a senior author on the study, notes that although massively parallel sequencing has allowed researchers to fully characterize the genomic architecture of AML, pairing genomics with drug response in the same patient samples provides functional context that has been missing in previous large-scale cohort studies. “That has huge implications for therapeutic stratification with regard to clinical trials and ultimately patient care,” she says.

One of those trials is the Beat AML Master Trial, a large umbrella trial spearheaded by the Leukemia and Lymphoma Society (LLS) that matches patients with first-line therapies based on genomic sequencing of tumors. “The goal is to take the data that we’ve just published and use that as a guide for some of the upcoming treatment arms that we’ll be adding,” explains Druker, a lead investigator of Beat AML Master Trial.

Monica Guzman, PhD, of Weill Cornell Medicine in New York, NY, who was not involved in the study, calls it “a wonderful resource for other researchers that are interested in identifying drugs that [might] target tumors that are difficult to eliminate.” Her lab, for example, is already exploring data relevant to their work on drug resistance in patients with a \( \text{PTPN11} \) mutation.

Ravi Majeri, MD, PhD, of Stanford University in California, who was also not connected to the study but has received research support from LLS, plans to integrate the data into his research on \( \text{IDH} \) mutations and drug sensitivity. For him, the study, along with the Beat AML Master Trial, supports a broader goal of quickly evaluating different drugs and drug combinations for AML.

He says that although several agents have recently been approved for AML and many more are in development, “we’re going to likely see that only a subset of patients will respond to any individual agent—the real hope is to be able to figure out which drug is right for which patient so that the entire population affected with this disease will have better outcomes.” – Catherine Caruso

**Resisting CAR T-cell Therapy: A Case Study**

Why some patients relapse months after responding to chimeric antigen receptor (CAR) T-cell therapy, and how to keep this development at bay, remain key questions with this immunotherapy. Several resistance mechanisms have now been uncovered, including one in a recent case report from the University of Pennsylvania in Philadelphia, tracing relapse to the inadvertent transduction of a single leukemic B cell with an anti-CD19 CAR (CAR19) gene (Nat Med 2018;24:1499–503).

A patient with acute lymphoblastic leukemia, in his third relapse after prior treatment, was enrolled in a phase I trial of then-investigational tisagenlecleucel (Kymriah; Novartis), which targets CD19 (N Engl J Med 2014;371:1507–17). Within 4 weeks of infusion with his own reprogrammed T cells, he experienced complete remission. However, he relapsed 9 months later with CD19-negative disease, and clinicians noticed a spike in CAR19 expression that, surprisingly, did not correlate with CAR19-bearing T cells. “We realized that this was actually a population of leukemic B cells expressing CAR19,” says Marco Ruella, MD, the case report’s first author.

Unraveling how these “CARB cells” came to exist, Ruella and colleagues determined that a lone leukemic B cell was accidentally transduced with the CAR19 gene. Unchecked proliferation of this one cell’s progeny—all resistant to further treatment—eventually led to disease progression and death.

The researchers probed this patient’s CD19-negative relapse, ruling out CD19 mutations and splicing variants. They reported that resistance to tisagenlecleucel occurred not because the leukemic blasts lost the target, but due to joint CAR19 and CD19 expression on their cell surface. CAR19 bound directly to CD19, hiding the latter from therapeutic T cells. Ruella and his team successfully modeled this phenomenon, called in cis epitope masking, both in vitro and in vivo. They