Washington University School of Medicine

Digital Commons@Becker

Open Access Publications

2019

Predicting tumor response to PD-1 blockade

Li Ding

Washington University School of Medicine in St. Louis

Feng Chen

Washington University School of Medicine in St. Louis

Follow this and additional works at: https://digitalcommons.wustl.edu/open_access_pubs

Please let us know how this document benefits you.

Recommended Citation

Ding, Li and Chen, Feng, "Predicting tumor response to PD-1 blockade." *New England Journal of Medicine*. 381, 5. 477 - 479. (2019).

https://digitalcommons.wustl.edu/open_access_pubs/8028

This Open Access Publication is brought to you for free and open access by Digital Commons@Becker. It has been accepted for inclusion in Open Access Publications by an authorized administrator of Digital Commons@Becker. For more information, please contact vanam@wustl.edu.

CLINICAL IMPLICATIONS OF BASIC RESEARCH

Elizabeth G. Phimister, Ph.D., *Editor***Predicting Tumor Response to PD-1 Blockade**

Li Ding, Ph.D., and Feng Chen, Ph.D.

The outcomes of traditional therapy, targeted therapy, or immunotherapy for cancer are influenced by the differences in cancer mutational profiles. Tumors with mismatch-repair deficiency have specific mutational profiles characterized by high microsatellite instability (MSI). (Microsatellites are stretches of DNA made up of short tandem repeats scattered throughout the human genome; the number of repeats composing any given microsatellite varies from person to person.) A study recently reported by Mandal and colleagues¹ shows that both the degree of MSI in tumor tissue and the resultant tumor mutational burden, especially the burden of a particular type of mutation, correlate with and therefore may help predict a response to antibodies against programmed death 1 (anti-PD-1) immunotherapy.

Microsatellites are prone to DNA replication errors, which are usually repaired in normal cells. In cells with defective DNA mismatch-repair genes, however, the “errors” accumulate, leading to somatic microsatellite polymorphisms, or MSI.² MSI has been observed in many types of cancer but is most prevalent in colorectal, endometrial, and gastric cancers. Findings of general correlations among mismatch-repair deficiency, high tumor mutational burden, high MSI, and responses to immune checkpoint inhibition led to the approval of anti-PD-1 therapy solely according to the status of MSI and mismatch repair, rather than cancer type.³ However, responses to anti-PD-1 therapy vary considerably among patients who have both mismatch-repair deficiency and MSI; nearly half these patients have only limited benefit. To further delineate the mechanistic details of interactions among these factors and to reveal the best predictors of benefit of anti-PD-1 therapy in patients with mismatch-repair deficiency, Mandal et al. carried

out experiments in mice. These experiments were followed by analyses of sequencing results from the Cancer Genome Atlas project and clinical data from two patient cohorts.

The high degree of genetic heterogeneity in mismatch repair-deficient human tumors presents challenges in identifying causal relationships and in quantifying contributions of individual elements to the response to PD-1 checkpoint inhibitors. Mandal and colleagues started out by inactivating the gene *Msh2*, which is indispensable for normal mismatch repair, in poorly immunogenic mouse melanoma and mouse colon-carcinoma cell lines (Fig. 1). The longer the cell lines were cultured after becoming mismatch repair-deficient, the more mutations they accrued: the MSI scores (with higher scores indicating greater genomic instability)⁴ of cells cultured for 1 month after *Msh2* inactivation were intermediate, whereas the scores of cells cultured for an additional 3 months were much higher. Cells with a high MSI score had significantly higher percentages of newly acquired indel mutations (insertions or deletions of DNA sequence) than those with an intermediate MSI score.

In mice treated with anti-PD-1, tumors grown from the parental and MSI-intermediate lines had limited responses, but tumors from MSI-high cells had drastic reductions in volume. These reductions were accompanied by immune-activation gene-expression signatures in tumor tissue and by much greater T-cell infiltrations than those in tumors grown from MSI-intermediate and parental cells. The immune response had a strong effect on the immunogenic subpopulation within a tumor, leading to the disappearance of some of the mutation-bearing cells in a phenomenon termed “immunoediting.” Consistent with the hypothesis that cells with indel

mutations have a higher probability of generating immunogenic neoantigens than do those with more single-nucleotide variants, and that the former are more likely to be targeted by T cells, there was a greater loss of indels than single-nucleotide variants in the MSI-high tumors in mice treated with anti-PD-1.

With these new findings from their murine models, the investigators next looked for the best predictor of outcomes of anti-PD-1 therapy in cohorts of human patients. They observed a general trend of higher cytolytic scores (indicating increased cytolytic activity of T cells) in MSI-high tumors than in MSI-low tumors across 14 different types of cancer in the Cancer Genome Atlas data set. The authors focused on 9 patients who had MSI-high colorectal tumors with a wide range of MSI scores, and they looked for correlations between clinical outcomes of anti-PD-1 therapy (pembrolizumab⁵) and the mutational characteristics of the tumors. These analyses showed that both a higher MSI score and a higher indel load in tumors were associated with better clinical outcomes in patients who received immune checkpoint blockade therapy. In contrast, they observed no significant association between numbers of single-nucleotide variants and clinical outcomes. In another small, retrospective analysis, 33 patients — each with a mismatch repair–deficient tumor (colorectal or esophagogastric carcinoma) and all of whom received a PD-1 checkpoint inhibitor — had longer survival if they had an MSI-high tumor than if they had an MSI-intermediate tumor.

Although immunostaining of mismatch-repair proteins in tumor tissue and detection of MSI markers by the polymerase chain reaction will continue to be helpful in clinical testing, the results reported by Mandal et al. support the use

of MSI scoring and tumor mutational burden (especially the indel load), which can be quantified by next-generation DNA sequencing, to predict the outcome of anti-PD-1 immunotherapy. These new approaches require validation in larger, independent clinical studies, and a key area for further investigation will be their clinical validity in predicting long-term responses. Although MSI-high tumors with a high load of indel mutations shrank with immune checkpoint blockade in mice, they were not entirely eradicated, nor were they eliminated in most of the human patients. Immunoediting during therapy may preferentially remove the more immunogenic cancer subclones, leaving behind less immunogenic subclones that go on to form a recurrent tumor — in which case, a combinatorial therapy with a treatment method other than immunotherapy would appear to be warranted.

Disclosure forms provided by the authors are available at NEJM.org.

From the Department of Medicine (L.D., F.C.), McDonnell Genome Institute (L.D.), the Department of Genetics (L.D.), Siteman Cancer Center (L.D., F.C.), and the Department of Cell Biology and Physiology (F.C.) — all at Washington University School of Medicine, St. Louis.

1. Mandal R, Samstein RM, Lee KW, et al. Genetic diversity of tumors with mismatch repair deficiency influences anti-PD-1 immunotherapy response. *Science* 2019;364:485-91.
2. Baretta M, Le DT. DNA mismatch repair in cancer. *Pharmacol Ther* 2018;189:45-62.
3. Ganesh K, Stadler ZK, Cercek A, et al. Immunotherapy in colorectal cancer: rationale, challenges and potential. *Nat Rev Gastroenterol Hepatol* 2019;16:361-75.
4. Niu B, Ye K, Zhang Q, et al. MSIsensor: microsatellite instability detection using paired tumor-normal sequence data. *Bioinformatics* 2014;30:1015-6.
5. Le DT, Uram JN, Wang H, et al. PD-1 blockade in tumors with mismatch-repair deficiency. *N Engl J Med* 2015;372:2509-20.

DOI: 10.1056/NEJMcibr1906340

Copyright © 2019 Massachusetts Medical Society.