Predicting tumor response to PD-1 blockade

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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 colleagues 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. 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. 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) 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
Figure 1. Microsatellite Instability, Mutation, and Immune Checkpoint Inhibition.

As shown in Panel A, the engagement of programmed death 1 (PD-1) on T cells by the PD-1 ligand (PD-L1) leads to suppression of the immune response. Antibodies against programmed death 1 (anti–PD-1) disrupt this interaction, allowing the T cells to recognize and attack tumor cells expressing immunogenic neoepitopes. As shown in Panel B, mismatch repair–deficient tumor cells were created from competent parental cell lines through CRISPR-Cas9 (clustered regularly interspaced short palindromic repeats associated with Cas9 endonuclease)–mediated knockout of Msh2. These mismatch repair–deficient cells were cultured for 1 month, during which time they accumulated mutations and became microsatellite instability (MSI)–intermediate cells. Those cultured for 4 months became MSI-high cells. MSI-high cells accumulated more mutations (indels in particular) than did MSI-intermediate cells. After implantation into immunocompetent mouse hosts and treatment with control or anti–PD-1 antibodies, T-cell infiltration was greater in tumor grafts with anti–PD-1 treatment. In addition, the relative reduction of novel indels in the shrunken anti–PD-1-treated, MSI-high tumors (as compared with the number of novel indels in the control-treated MSI-high tumors) is consistent with “immunoediting.” The numbers of new variants were determined with the use of the genome sequence of the parental cell line as a control. The bar graphs are meant to convey trends and are not intended to be precise. MHC denotes major histocompatibility complex, and SNV single-nucleotide variant.
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 (pembrolizumab) 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 esophageal 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.

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