Genetics and immunology: reinvigorated

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Immune checkpoint blockade therapy is changing oncology by improving the outcome of patients with advanced malignancies. Our research has revealed the genetic features of tumors present in patients who initiate a successful antitumor immune response and derive clinical benefit from immune checkpoint blockade therapy versus non-responders.

Introduction

By mobilizing the immune system against each patient’s tumor, immune checkpoint blockade agents can cause tumor regression or long-term disease control in advanced stage cancers. Immune checkpoint agents that block cytotoxic T- lymphocyte-associated protein 4 (CTLA-4) and programmed cell death-1 (PDCD1, better known as PD-1) are examples of such agents. These agents can result in durable remissions in some patients. Prior to our work, the tumor features that initiate a clinical response following treatment with checkpoint blockade therapy were unknown. Furthermore, only a minority of patients responds to single agent immune checkpoint blockade and biomarkers to predict which patients would benefit from these therapies were lacking.

Tumor Genomics and Efficacy of Immune Checkpoint Blockade

The concept that tumor mutations can elicit an immune response leading to immune surveillance and elimination was proposed as early as 1950. More recently the fact that neoantigens may represent important targets for T-cell recognition of cancers was revisited by multiple groups using in silico and mouse models to determine the effects of neoantigens on immune responses.2 We recently sought to determine how the genomic landscape of tumors affects a patient’s immunologic and clinical response to immune checkpoint therapy. In two recent studies, we elucidated the tumor genetic features that impact clinical benefit from checkpoint blockade therapy. In the first study, we examined tumor whole exome sequencing data from 64 melanoma tumors of patients treated with anti-CTLA-4 antibody.3 We found that an increased mutational burden strongly correlated with immunotherapy clinical benefit. Interestingly, we noted that there were striking similarities among the neoantigens that occurred only in responders. Some of these predicted neoantigens appeared to harbor putative T-cell receptor (TCR) recognition motifs that were homologous to known antigens of pathogens.

In a second study, we examined tumors from patients with metastatic lung cancers treated with the anti-PD1 agent pembrolizumab.4 As in our first study on anti-CTLA4-treated patients, we found that high mutational burden predicted clinical response. Interestingly, tumors characterized by the mutational smoking signature were selectively sensitive to anti-PD1 treatment, suggesting that the specific mutational processes that generate somatic mutations can influence immunotherapy response. Strikingly, responders with the highest mutational burden frequently possessed mutations in POLD1 or POLE, alterations known to lead to hypermutation.6 PD-L1 expression was used as a biomarker for these studies and the mutation load appears to be a better predictor of clinical responses since most of these tumors maintain PD-L1 expression.

In both studies, we were able to validate CD8+ T cell reactivity against neoantigens using autologous peripheral blood from treated patients. This finding has several important implications. First, it illustrates that, although these drugs are thought to act primarily at the tumor site, their immunologic activity appears to be systemic and can be detected in the peripheral blood. In this regard, antitumor immune responses may be similar to immune responses against pathogens such as viruses. Second, the anti-neoantigen response appears to track with clinical antitumor activity. Therefore, once clinically validated, T-cell reactivity assays hold promise of peripheral blood-based screening for outcome without the need for invasive biopsies.

Together, these studies illustrate the importance of tumor genetics in contributing to an effective antitumor response in patients treated with immune checkpoint blockade therapies. Importantly, the mutations that are predicted to generate neoantigens are not the classical “driver mutations” promoting cancer cell growth. Rather, our work suggests that mutations previously characterized as “passenger mutations” may in fact represent immunogenic determinants during tumor growth and treatment.
Academic Collaboration Reflects Biological Complexity

A unique depth and breadth of collaboration was required in order to execute these studies. Dissecting the genomic determinants underlying immuno-oncologic processes required extensive multidimensional approaches merging advanced genetic and immunologic analyses. In the last decade, applying high throughput genomic analyses to immunologic questions was largely outside mainstream immunology research. Ironically, the beginnings of modern immunology were steeped in genetics (i.e., VDJ recombination, somatic hypermutation, etc.). In recent years, we are seeing a resurgence of the application of rigorous genetic analysis to immunologic questions in both science and health, a trend that will undoubtedly accelerate advances in medicine.

Future Directions

Despite recent progress, much work remains to be done. First, as tumor genomic analyses improve, interpretation of the data generated increasingly becomes the bottleneck. Improvements are needed in many areas such as the ability to predict TCR reactivity and the ability to link TCR sequence to the peptide antigen sequences they target. Second, a broad understanding of how neoantigen repertoires differ between different cancer types is lacking. Comparisons of mutational landscapes of diverse cancer types from patients treated with immunotherapies will be needed to address this important question. Third, it will be important to determine how the process of cancer cell clonality affects immunoediting and the sculpting of the neoantigen landscape. We are in the process of incorporating intratumoral and peripheral T-cell receptor diversity data to determine whether an effective antitumor response is characterized by oligoclonal dominance or polyclonal diversity in neoantigen repertoires. Lastly, we must improve our ability to predict T cell cross-reactivity and the impact of environmental and prior pathogen exposure on response.

An understanding of these critical issues will allow us to improve the efficacy of immunotherapy in cancer patients. Through the integration of tumor immunologic and genomic data, we are confident that progress can be made toward broadening the efficacy of immunotherapy in cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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