

Cancer Genomics in the Era of Checkpoint Inhibition: Biomarkers to Predict Tumor Response to Checkpoint Inhibition Therapy

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Abstract

With their ground-breaking clinical success, immune checkpoint inhibitors (ICIs) have opened a new chapter in cancer treatment; however, not all patients have a response to ICI treatment. Current approaches to maximizing the efficacy of ICI treatment include combining it with conventional cancer treatments and identifying biomarkers that accurately predict tumor responses to ICI agents. This mini-review introduces genomic determinants of ICI efficacy and directions for future immunogenomic studies in the era of checkpoint inhibition.

Keywords: Antitumor immunity; Cytotoxic; Antibodies; Lung cancer, Kidney cancer, Hodgkin disease

Introduction

By targeting inhibitory checkpoint molecules with resultant rejuvenation of antitumor immunity, immune checkpoint inhibitors (ICIs) have opened a new chapter in cancer treatment [1]. The development of checkpoint-inhibiting molecules was enabled by unmasking the mechanisms of T cell activation. Full activation of T cells requires two signals: (i) binding of the T cell receptor (TCR) to the antigen presented by the MHC on antigen-presenting cells and (ii) co-stimulation by engagement of the CD28 on the T cell to CD80/86 on the antigen-presenting cell [2]. Upon activation, T cells express cytotoxic T lymphocyte-associated protein 4 (CTLA-4) on their surface, a CD28 homolog with higher affinity for CD80/86 than CD28, eventually attenuating and terminating T cell activation. Programmed death 1 (PD-1) is a surface molecule expressed on activated T cells, B cells, regulatory T cells, and natural killer cells. By binding PD-1 ligands (PD-L1 and -L2), PD-1 on activated T cells delivers inhibitory signals and attenuates T cell activity. PD-L1 and -L2 are also expressed in various tumor cells, comprising one of the mechanisms whereby tumor cells evade antitumor immunity. By rejuvenating antitumor T cells by inhibiting CTLA-4 and PD-1/PD-L1, anti-CTLA-4 antibody (ipilimumab) and anti-PD-1/PD-L1 antibodies (nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab) have shown enormous therapeutic benefits in multiple clinical trials [3]. The U.S. Food and Drug Administration approved anti-CTLA-4 antibody for the treatment of melanoma and anti-PD-1/PD-L1 antibodies for the treatment of melanoma, non-small cell lung cancer, kidney cancer, Hodgkin disease, head and neck cancer, and bladder cancer [4]. Other monoclonal antibodies to other immune checkpoints, including TIM3, LAG3, B7-H3, TIGIT, and OX40, are also under clinical investigation, in either a preclinical or clinical trial setting [5].

Literature Review

Despite unprecedented clinical success, however, only a fraction of patients achieves a durable long-lasting response to ICI treatment [6]. Concerted research efforts to identify biomarkers that can predict tumor response to ICI treatment have identified several genomic and cellular candidates [7]. For anti-CTLA-4 treatment, expansion of circulating inducible T cell co-stimulator (ICOS)⁺ CD4⁺ T cells early in the treatment can be used as a pharmacodynamic biomarker to indicate biologic activity of the treatment [8]. For anti-PD-1/PD-L1 agents, PD-L1 expression on tumor cells or intratumoral immune cells correlated with objective response to the treatment [9,10]. A recent

study using melanoma tumor samples demonstrated that intratumoral T cell infiltration in early treatment with anti-PD-1 antibody is highly predictive of tumor response [11]. Whole-exome sequencing analysis of tumor samples before ICI treatment showed that mutational burden and neoantigen load are positively correlated with clinical benefits of ICI treatment, a finding that has been reproduced in multiple independent cohorts with various primary tumors [10,12-16]. Patients with colorectal cancer with mismatch-repair deficiency (MMR) and resultant higher mutational burden and neoantigen load had better tumor responses to anti-PD-1 antibody treatment than colorectal cancer patients without MMR deficiency [15]. A follow-up expanded trial to evaluate anti-PD-1 antibody efficacy across 12 different solid tumors with MMR deficiency revealed that MMR-deficient cancers are sensitive to anti-PD-1 antibody treatment regardless of the cancer's origin [16]. Notably, in three patients who had a response to the anti-PD-1 antibody, mutation-associated neoantigen-specific T cells were expanded in blood 2-4 weeks after starting anti-PD-1 antibody treatment, indicating that certain mutations and subsequent neoantigens can elicit antitumor T cell responses and that such T cells could be a marker of tumor response. A recent integrated analysis of intratumoral heterogeneity (ITH) in non-small cell lung cancer samples suggested that clonal neoantigen (present in all tumor cells from a given biopsy) may elicit a T cell response [17]. In the same study, 16 of 18 tumors with a high fraction (> 5%) of subclonal neoantigens or low clonal neoantigen level did not respond to ICI treatment, indicating that subclonal antigens are not as immunogenic as clonal neoantigens.

Discussion

How alteration of specific genes determines tumor response to ICI treatment is also of interest? For example, PTEN loss in tumor cells inhibits T cell trafficking into tumors and inhibits autophagy in

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tumor cells, reducing T cell-mediated tumor cell killing [18]. Notably, PTEN suppresses PI3K expression, and PTEN loss results in altered PI3K β expression; targeting PI3K β with an antibody enhanced tumor response to anti-PD-1 antibody in mouse models of melanoma with PTEN loss, suggesting the therapeutic potential of such combinations in melanoma patients with PTEN loss. A case report of one patient with metastatic lung adenocarcinoma who had an extraordinary response to anti-PD-1 antibody treatment revealed somatic and germline JAK3 mutations at the same allele [19]. Transduction of these mutants enhanced PD-L1 expression on lung cells, suggesting a mechanism for the patient's exceptional tumor response to anti-PD-1 antibody. Finally, both *in vitro* and *in vivo* experiments demonstrated that anti-CTLA-4 antibody synergizes with PARP inhibition in BRCA-deficient ovarian cancer, most likely mediated by interferon gamma from intratumoral T cells [20].

ICIs are associated with potentially disabling immune-related adverse events (irAEs), characterized by inflammation of one or more organs. Up to 80% of patients receiving an ICI develop at least one irAE. irAEs are clinically important as they may be life-threatening and/or result in early termination of ICI treatment; however, the molecular and immunologic mechanisms of irAEs have not been fully elucidated. Our group and others reported successful treatment of irAEs with interleukin-6 receptor antibody (tocilizumab), suggesting that the Th17-regulatory T (Treg) cell axis might play a critical role in development of irAEs [21,22]. Recently, immunogenomic analysis of postmortem tumor (melanoma), skeletal muscle, and cardiac muscle from two patients who died of ICI-induced myocarditis revealed identical clonal expansion of T cells reactive to melanoma, inflamed skeletal muscles, and inflamed heart muscles [23]. Considering that cancer cells are an antigenic source after ICI treatment, it is speculated that the intratumoral genomic landscape might also regulate development of irAEs. It would be very interesting to investigate how such neoantigens activate cross-reactive T cells and result in irAEs, focusing on the Th17-Treg axis.

Conclusion

This brief review summarizes the findings of selected studies attempting to identify biomarkers predictive of response to ICI treatment. High pretreatment mutational burden, high neoantigen load, intratumoral T cell infiltration during early treatment, and early treatment expansion of circulating ICOS⁺ CD4⁺ T cells are related to favorable antitumor responses to ICI treatment. Further studies are needed, not only for detecting more sensitive and specific predictive biomarkers, but also to elucidate in detail the molecular mechanisms whereby mutations result in neoantigen production and how T cells rejuvenated by ICI treatment detect the neoantigens and/or normal tissues. Comprehensive immunogenomic analyses with clinical samples and preclinical mouse models will provide insights that will support identification of biomarkers and understanding of the corresponding mechanisms. In addition, comprehensive immunogenomic approaches will also enable us to develop novel therapeutic strategies with ICIs combined with genomically targeted agents to achieve better median survival with long-term durable responses.

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