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

Kim S*

Section of Rheumatology and Clinical Immunology, Department of General Internal Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA

Abstract

With their ground-breaking clinical success, 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 reactivating tumor 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, andOX40, are also under clinical investigation, in either a preclinical or clinical trial setting [5].

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 reactivating tumor 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, andOX40, 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...
tumor cells, reducing T cell–mediated tumor cell killing [18]. Notably, PTEN suppresses PI3K expression, and PTEN loss results in altered PI3Kβ expression; targeting PI3Kβ with an antibody enhanced tumor response to anti-CD-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-CD-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-CD-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].

ICls 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.

References

1. Couzin-Frankel J (2013) Breakthrough of the year 2013. Cancer immunotherapy. Science 342: 1432-1433.
2. Suarez-Almazor ME, Kim ST, Abdel-Wahab N, Diab A (2017) Review on immune-related adverse events with use of checkpoint inhibitors for immunotherapy of cancer. Arthritis Rheumatol 69: 687-699.
3. Alexander W (2016) The checkpoint immunotherapy revolution: What started as a trickle has become a flood, despite some daunting adverse effects; new drugs, indications, and combinations continue to emerge. PT 41: 185-191.
4. Sharpe AH (2017) Introduction to checkpoint inhibitors and cancer immunotherapy. Immunological reviews 276: 5-8.
5. Mandal R, Chan TA (2016) Personalized oncology meets immunology: The path toward precision immunotherapy. Cancer Discov 6: 703-713.
6. Sharma P, Allison JP (2016) Immune checkpoint targeting in cancer therapy: Towards combination strategies with curative potential. Cell 161: 205-214.
7. Miao D, Allen VEM (2016) Genomic determinants of cancer immunotherapy. Curr Opin Immunol 41: 32-38.
8. Ng Tang D, Shen Y, Sun J, Wen S, Wolchok JD, et al. (2013) Increased frequency of ICOS+ CD4 T cells as a pharmacodynamic biomarker for anti-CTLA-4 therapy. Cancer Immunol Res 1: 229-234.
9. Taube JM, Klein A, Brahmer JR, Xu H, Pan X, et al. (2014) Association of PD-1 PD-1 ligands, and other features of the tumor immune microenvironment with response to anti-PD-1 therapy. Clin Cancer Res 20: 5064-5074.
10. Rosenberg JE, Hoffman-Censits J, Powles T, Heidjen MS, Balar AV, et al. (2016) Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: A single-arm, multicentre, phase 2 trial. Lancet 387: 1909-1920.
11. Chen PL, Ruh W, Reuben A, Cooper ZA, Spencer CN, et al. (2016) Analysis of immune signatures in longitudinal tumor samples yields insight into biomarkers of response and mechanisms of resistance to immune checkpoint blockade. Cancer Discov 6: 827-837.
12. Snyder A, Makarov V, Hellmann M, Rizvi N, Merghoub T, et al. (2015) Genetics and immunology reinvigorated. Oncoimmunology 4: e1029705.
13. Rizvi NA, Hellmann MD, Snyder A, Kvistborg P, Makarov V, et al. (2015) Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. Science 348: 124-128.
14. Van Allen EM, Miao D, Schilling B, Shukla SA, Blank C, et al. Genomic correlates of response to CTLA-4 blockade in metastatic melanoma. Science 350: 207-211.
15. Le DT, Uram JN, Wang H, Bartlett BR, Kemberling H, et al. (2015) PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med 372: 2509-2520.
16. Le DT, Durham JN, Smith KN, Wang H, Bartlett BR, et al. (2017) Mismatch-repair deficiency predicts response of solid tumors to PD-1 blockade. Science 357: 409-413.
17. McGranahan N, Furness AJ, Rosenthal R, Ramskov S, Lyngaa R, et al. (2016) Clonal neoantigens elicit T cell immunoreactivity and sensitivity to immune checkpoint blockade. Science 351: 1463-1469.
18. Peng W, Chen JQ, Liu C, Malu S, Creasy C, et al. (2016) Loss of PD-TEN promotes resistance to T cell-mediated immunotherapy. Cancer Discov 6: 202-216.
19. Van Allen EM, Golay HG, Liu Y, Koyama S, Wong K, et al. (2015) Long-term benefit of PD-L1 blockade in lung cancer associated with JAK3 activation. Cancer Immunol Res 3: 855-863.
20. Higuchi T, Files DB, Marjor NA, Mantia-Smaldone G, Ronner L, et al. (2015) CTLA-4 blockade synergizes therapeutically with parp inhibition in BRCA1-deficient ovarian cancer. Cancer Immunol Res 3: 1257-1268.
21. Kim ST, Tayar J, Trinh VA, Suarez-Almazor M, Garcia S, et al. (2017) Successful treatment of arthritis induced by checkpoint inhibitors with tocilizumab: A case series. Ann Rheum Dis 1: 2.
22. Stroud CRG, Cherry C, Hegde A, Walker P (2017) Tocilizumab for the management of immune mediated adverse events secondary to PD-1 blockade. J Clin Oncol 35: e21712-e21712.
23. Johnson DB, Ballo JM, Compton ML, Chalkias S, Gorham J, et al. (2016) Fulminant myocarditis with combination immune checkpoint blockade. N Engl J Med 375: 1749-1755.