Checking autoimmune genetic risk to stratify immune checkpoint inhibitor responders

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The development of immune checkpoint inhibitors (ICIs) in recent years has been one of the most significant advances in the treatment of cancer. However, even among tumors where ICIs have shown the most promise, they are not effective in all patients, and there are no clearly defined molecular or cellular markers to identify patient subgroups most likely to benefit from these agents.

Building on the intriguing observation that the development of cutaneous immune-related adverse events (irAEs) is associated with a longer overall survival (OS) in patients treated with PD-1 targeting checkpoint inhibitors, Khan et al. (1) in PNAS investigated whether there could be a genetic explanation. Indeed, they report that patients with metastatic urothelial carcinoma (mUC) who carry high genetic risk profiles for two dermatologic autoimmune diseases, psoriasis and vitiligo, are more likely to achieve longer survival rates, marking a genetic basis for ICI response and revealing a screening tool to select patients most likely to have treatment success.

To achieve self/nonself discrimination, our immune system has incorporated delicately balanced mechanisms involving costimulatory and inhibitory signals to coordinate immune activation and inactivation to control and calibrate the specificity and amplitude of immune responses. Immune checkpoints regulate this balance. These are molecules that need to be activated (or inactivated) to initiate or block immune responses. Their primary function is to prevent an overrun response that may then be misdirected to destroy healthy cells in the body (“self”). Immune checkpoints engage when bound by specific partner proteins on the surface of T lymphocytes, sending “off” signals to the T cells, whose normal role is to monitor for and direct a cell-mediated response toward “altered self,” including tumor cells.

Two checkpoint proteins are central to the regulation of this process: cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death 1 (PD-1). The PD-1 molecule is expressed on T cells and binds to programmed cell death ligand 1 (PD-L1) or PD-L2, molecules that are expressed on various cell types, resulting in an interaction that produces a signal to inhibit T cell proliferation, resulting in T cell anergy, or nonresponsiveness. This process is part of the normal immunoregulation that is baked into functional responses that occur after infection to limit the destruction of bystander healthy host cells and prevent autoimmunity.

In a clever mechanism to avoid immune detection and destruction, many tumors are able to express immune checkpoint molecules on their surface, rendering them inappropriately recognized as self-tissues. In this way, tumors can “hijack” the normal physiological role of immune checkpoint proteins in a form of “identity theft” to disable an effective T cell attack. The inhibition of checkpoints therefore unmasks

Fig. 1. Checkpoint inhibition mechanisms. (A) Engagement of PD-1 and PD-L1 immune checkpoint molecules inhibits antitumor T cell response. (B) Checkpoint blockade of PD-1 and PD-L1 engagement by anti-PD-L1 antibodies releases antitumor T cell response. (C) Local and systemic factors that can impact treatment success of checkpoint blockade.
tumor cells to be correctly recognized as foreign, removing the “brakes” applied to tumor antigen-specific T cells by the engagement of checkpoint proteins inappropriately expressed on the tumor surface and allowing tumor-specific responses to be generated.

ICI drugs, typically monoclonal antibodies directed against checkpoint proteins, have scored some impressive results in several cancers and continue to show promise in ongoing clinical trials. There are now numerous approved inhibitors, including those that target PD-1 (CD279) and its ligand PD-L1 (CD274), which is expressed on the surface of multiple tissue types, including kidneys and lungs. Well over 500 clinical trials have been conducted involving PD-1 and PD-L1 inhibitors (2–6). OS rates with checkpoint-based immunotherapy have been demonstrated to surpass chemotherapy in many instances. PD-1/PD-L1 inhibitors have been approved as frontline therapy and in some cases the standard of care for several tumor types, including melanoma, Merkel cell cancer, non–small-cell lung cancer, renal cancer, bladder cancer, head and neck cancer, and Hodgkin’s lymphoma (3). These clinical data bring to light the fact that a significant proportion of cancer patients possess the capacity for antitumor T cell reactivity if tumor-associated immunosuppression is mitigated, allowing for costimulatory signals to be properly delivered.

Although checkpoint blockade has shown that reactivating antitumor immune responses can regress tumors, there remain a significant proportion of patients who do not respond to ICIs and retain a poor prognosis (7, 8). The widespread utilization of immune checkpoint inhibition therapy is hampered by low response rates as well as the severity of irAEs in some fraction of patients. There are likely a number of molecular determinants of checkpoint blockade clinical response. High tumor burden or size, low level of tumor immunogenicity linked to lower levels of neo-antigen expression and lower mutational load, low levels of infiltrating immune cells, and low levels of PD-L1 expression have all been associated with poor outcomes (9, 10). These measures predominantly capture local factors. There is now substantial evidence in mice supporting a role for factors that impact host systemic immunity as well in determining tumor response to PD-L1 blockade (11).

Interestingly, dermatological irAEs have been associated with prolonged survival rates in patients receiving PD-1 checkpoint inhibitors (12). Skin-related irAEs are among the most commonly observed clinical findings during treatment, but contributing factors are unclear. The relative roles of local and systemic factors in a given tumor or patient, and the genetic underpinnings of treatment response and toxicities remain poorly understood.

Khan et al. (1) set out to investigate the relationship between safety and efficacy through analyses of bladder cancer patients enrolled in the recent IMvigor211 phase 3 randomized controlled trial comparing monotherapy with the PD-L1 inhibitor atezolizumab vs. chemotherapy, along with some analysis using data from the phase 2 IMvigor210 study. Consistent with existing literature (12), the authors confirmed that OS was associated with low-grade skin irAEs in trial patients.

To test the hypothesis that genetic markers linked to the development of autoimmunity in the skin are associated with PD-L1 treatment response and side effects, the authors used publicly available genome-wide association study data for two autoimmune skin diseases, psoriasis and vitiligo, as well as atopic dermatitis, a condition not considered to be primarily autoimmune in nature, and germline whole-sequencing data from study trial patients to compute polygenic risk scores (PRSs) for each condition in study subjects.

The authors report that genetic profiles that increase risk for autoimmunity in the skin impact patient survival rates in PD-L1–treated patients and risk of skin toxicity during treatment. Specifically, high vitiligo, high psoriasis, and low atopic dermatitis PRSs were associated with and predictive of longer OS under anti–PD-L1 monotherapy. High atopic dermatitis risk scores were inversely correlated with OS under checkpoint blockade. Effector T cell gene signature, a measure of CD8 T cell function, was positively correlated with a longer OS, but on an independent basis from the PRSs. PRSs did not correlate with tumor mutation burden or PD-L1 expression on tumor immune cells or cell type enrichment scores. However, high psoriasis PRS did confer a stronger benefit to patients with high value staining of PD-L1 on tumor immune cells and high gene expression of CD8 T effector cell-associated genes. An extended analysis of PRSs for 10 other autoimmune conditions and for Alzheimer’s disease did not reveal any correlations. No correlation was found in the chemotherapy arm of the study.

Positive correlation with psoriasis and vitiligo may reflect the high Th17 pathway polarization of these diseases, in contrast with the directionality of the immune response in atopic dermatitis (low Th17 polarization). In fact, the survival benefit observed with high psoriasis PRS was strongest in patients with tumors expressing high levels of IL23A protein, a cytokine important with the Th17 pathway, along with high effector T cell scores. Conversely, the opposite pattern was seen between psoriasis PRS and the expression IL-12 subunits A and B, consistent with the divergent roles played by IL-12 and IL-23 in autoimmunity. High transcription expression determined by RNA-seq analysis of genes relevant to TH17 function (IL23A, CXCL2, and CCL20) in combination with the psoriasis PRS formed another subgroup that benefited from anti–PD-L1 therapy. These data support the notion that local and systemic factors including polygenic risk for dermatologic autoimmunity impacts patient survival by influencing the immune set point of the tumor microenvironment (Fig. 1).

This study gives emphasis to the importance of conducting detailed genetic and immunologic analyses in parallel with clinical trials. Investment into the biology behind treatment response should be considered in every case. Trials that focus solely on clinical safety and efficacy without concurrent or planned ancillary studies forfeit the one-chance opportunity to collect valuable data in real time to reveal mechanistic insights. Such expanded study designs have the potential to confirm or refute conventional wisdom regarding the mechanistic action of drugs, reveal new and unexpected pathways relevant to therapeutic response and adverse reactions, and potentially identify novel or improved targets for future therapeutic consideration.

Piggybacking on a major cancer therapeutic trial, Khan et al. leveraged an innovative search linking known genetic variants for immune-mediated skin conditions to side effect profiles as a window into improved response to therapy with PD-L1 blockade.
window into improved response to therapy with PD-L1 blockade. Confirmatory studies could lead to the delineation of defined subgroups of patients carrying malignancies (not limited to bladder cancer) who are inherently predisposed to a favorable response to PD-L1 therapy based on genetic factors and thus significantly improve outcomes in cancer therapy. Such studies could illuminate previously unknown therapeutic mechanisms, as well as foster the development of tools with clinical utility to guide therapeutic decision-making. In fact, the three corresponding authors identified in Khan et al. have a patent pending through Genentech/Roche on the use of PRSs for dermatological autoimmune diseases as methods for patient selection for treatment with ICIs. These studies help to buttress the potential of genomic medicine and provide another step forward toward the promised land of personalized care.

Still, a number of outstanding questions remain that are both specific to this study and more general: 1) Are the results of this study transferable to other PD-1/PD-L1 blockers and checkpoint blockers overall? 2) Can genetic risk profiles be broadened beyond autoimmune-associated genetic variations to suggest previously unrecognized sentinels of improved outcomes? 3) Does susceptibility to other/all Th17 pathway prominent disease processes confer similar therapeutic response benefit? 4) What mechanisms link genetic risk profiles for cutaneous autoimmunity to checkpoint inhibition-related dermatologic irAEs such as skin rash, pruritus, and bullous lesions? 5) What are the exact molecular and cellular factors impacted by dermatologic risk alleles that increase the immunogenicity of tumors and promote intrinsic T cell responses? 6) Can local and systemic factors be combined into a qualitative score predictive of response rates across tumor type and checkpoint blockers? 7) Can boosting these factors directly in patients without advantageous genetic risk profiles work to enhance treatment response?

The discovery of ICIs represents a major milestone for immuno-oncology. Numerous studies support the assertion that immunotherapy can durably control advanced cancer in many cases. Continued research aimed at comprehensively determining reliable and predictive biomarkers of treatment response can be expected to further advance the development of patient stratification algorithms useful for clinical decision support and point the way to new avenues for future work to deepen our understanding of cancer.