Understanding and Overcoming the Inflammatory Toxicities of Immunotherapy

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ABSTRACT

Checkpoint blockade immunotherapy has led to impressive therapeutic responses in a wide variety of tumors, but also leads to a spectrum of inflammatory toxicities that can involve any organ system in the body. Although most inflammatory toxicities resolve with systemic immune suppression, fatal toxicities can occur, and interruption and discontinuation of immunotherapy because of toxicity are common. In addition to their clinical impact, these inflammatory toxicities also provide a window into immune regulation in humans. By studying the cellular and molecular mechanisms that drive this inflammation, we have an opportunity to learn how the immune checkpoints, cytotoxic T lymphocyte antigen-4 and programmed death-1 and its ligand, maintain immune homeostasis throughout the body. Although we have an increasingly detailed understanding of the mechanisms that drive effective antitumor immunity, we have a rudimentary picture of the mechanisms of toxicity. Most toxicities involve barrier organs, suggesting an important role for interactions with the environment, including the microbiome. Early analyses have implicated cytotoxic T cells, although the antigens recognized by these cells, and the pathways activated by and around them are still unknown. By gaining a detailed understanding of the immune mechanisms of toxicity, we have the potential to develop novel interventions for them. These treatments should take advantage of differences between effective antitumor immunity and the principal drivers of organ inflammation. By targeting these mechanistic differences, we can develop therapies that can be used alongside immunotherapy, blocking inflammatory toxicity while preserving or even enhancing the response to cancer.

Introduction

Immunotherapy toxicities as a model to understand immune regulation

Immunotherapy has transformed the treatment landscape for cancer, producing durable remissions in tumors that were previously almost uniformly fatal. MAbs that block the regulatory immune checkpoints, cytotoxic T lymphocyte antigen-4 (CTLA-4) and programmed death-1 (PD-1) and its ligand (PD-L1), have been the most broadly successful cancer immunotherapy to-date, although numerous other strategies are in development (1). Alongside its impressive success, immunotherapy has led to a diverse range of inflammatory side effects, collectively referred to as immune-related adverse events (irAE; ref. 2). Yet, irAEs are more than just toxicities from a drug, they are a window into immune regulation in humans. Checkpoint blockade interrupts immune regulatory pathways in an adult who, in most cases, had a relatively normal immune system prior to the start of therapy. From this perspective, the toxicities of checkpoint blockade are the phenotype of receptor loss. Thus, studying irAEs may provide insight into how CTLA-4, PD-1, and PD-L1 maintain immune homeostasis. Building upon these insights, the broad range of immunotherapies in clinical development (e.g., blockade of LAG3, TIGIT, and TIM3) offer a chance at a far deeper understanding of immune regulation (1).

Understanding checkpoint blockade toxicities may also provide key mechanistic information about the onset of autoimmune disease. Unlike for spontaneous autoimmune diseases, the timing and nature of the inciting immune perturbation are known. Organ inflammation can thus, be studied from preimmunotherapy through the initial symptoms of tissue damage, and ultimately into resolution. These toxicities can then serve as a human model of real disease, with the potential for insight into the earliest stages of autoimmunity where novel therapeutic targets may be identified.

The most common inflammatory toxicities of checkpoint blockade occur at barrier organs, including the skin, gastrointestinal mucosa, liver, and, to a lesser extent, respiratory epithelium. This distribution of toxicities suggests that both the CTLA-4 and PD-L1 pathways have an important function in limiting the responses to nonpathogenic foreign antigens such as commensal microbes (2). Endocrine glands are the other major class of organs affected by checkpoint blockade toxicities, although any organ system in the body, including joints, cardiac muscle, and the central nervous system, can be targeted (2).

Mechanism of Organ Injury From Checkpoint Blockade

Understanding immunotherapy toxicities in cellular and molecular detail will not only teach us important biology, but will also be an important step in developing targeted therapies. Currently, we have very little concrete information about the immune mechanisms driving checkpoint blockade toxicity (**Fig. 1**). Research thus far points to several interesting areas for further investigation.

Distinct roles for the CTLA-4 and PD-1/PD-L1 pathways

CTLA-4 blockade and PD-1/PD-L1 blockade do not produce identical toxicities. CTLA-4 blockade leads to more inflammatory side effects than does either PD-1 or PD-L1 blockade, and in particular is more likely to produce treatment-limiting colitis (2, 3). PD-1 blockade is associated with a higher risk of thyroiditis and potentially

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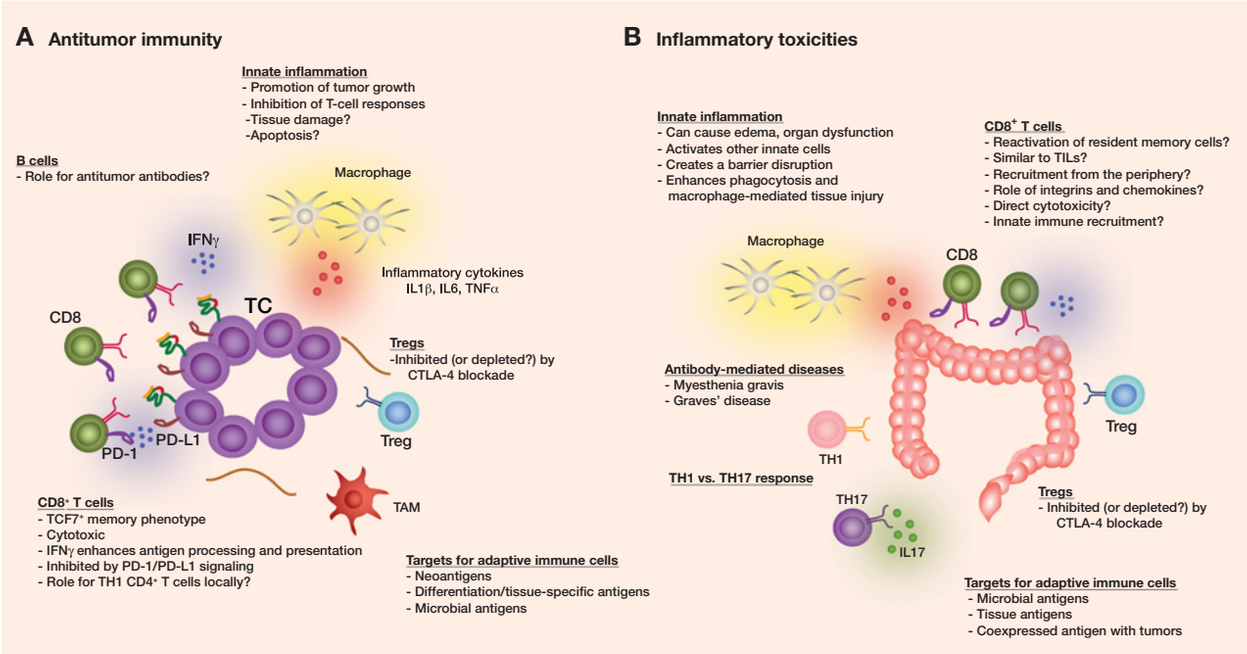

Figure 1.

Balancing inflammatory toxicities with antitumor immunity. **A,** Effective antitumor responses to checkpoint blockade are driven by reactivation of exhausted effector memory $CD8^+$ T cells recognizing MHC class I–presented tumor neoantigens. These responses may be limited by innate inflammatory cytokines such as TNFα. **B,** The inflammatory toxicities of checkpoint blockade may also be driven by reactivation of $CD8^+$ T cells, but with potentially distinct trafficking patterns, antigenic targets, and pathogenic cytokines. Question marks indicate current areas of uncertainty in the field. TAM, tumor-associated macrophage; TC, tumor cell; TIL, tumor-infiltrating lymphocyte.

pneumonitis, although the increased incidence of pneumonitis is confounded by the use of PD-1/PD-L1–targeting therapies in patients with underlying lung disease (2, 3). CTLA-4 and PD-1/PD-L1 have distinct functions in immune regulation, which likely underlie the spectrum of toxicities seen with their inhibition (4–6). CTLA-4 is a high-affinity decoy receptor for the B7 costimulatory ligands that prevents binding to CD28 on naïve T cells and is expressed at low levels on naïve cells, but is upregulated upon activation (7–9). In the absence of CTLA-4, the threshold for T-cell activation decreases and the magnitude and breadth of naïve T-cell activation increases, leading to enhanced repertoire diversity (7–10). However, a broadened repertoire may increase the frequency of self-reactive T cells, increasing the risk for autoimmunity (10).

Regulatory T cells (Treg) are the highest expressers of CTLA-4, where it mediates immune suppression by sequestering and even removing B7 from the surface of activated antigen-presenting cells (11, 12). The importance of CTLA-4 on Tregs is underscored by the Treg-specific CTLA-4 knockout, which phenocopies both Treg deficiency and CTLA-4 deficiency, although in both cases, the disease is somewhat less severe (11, 13, 14). Animal studies have demonstrated a role for Fc-dependent Treg depletion in the antitumor mechanism of CTLA-4–targeting antibodies (15, 16). Whether similar Treg depletion occurs in human tumors has remained unclear, but this mechanism could explain the sudden onset of severe inflammation in multiple organs following anti–CTLA-4 therapies (**Fig. 1A**; ref. 17). In patients who develop colitis after CTLA-4 blockade, Treg numbers are preserved or expanded, even when biopsies are taken on the day of symptom onset, indicating that at least for this toxicity, Treg depletion is not the major mechanism driving inflammation (**Fig. 1B**; ref. 18). Even if CTLA-4–targeting antibodies do not deplete human Tregs, blockade of Treg-expressed CTLA-4 may still play an important part in driving immunotherapy toxicities.

In humans, CTLA-4 haploinsufficiency is a severe inflammatory disease with variable penetrance, showing many phenotypic similarities to CTLA-4 blockade (19). Toxicities from ipilimumab, the only clinically approved CTLA-4–blocking antibody, are dose dependent, suggesting that toxicities may arise after a threshold level of CTLA-4 is inhibited and that the degree of receptor occupancy may be what distinguishes patients who develop toxicities from those who do not (20, 21), possibly explaining why toxicities from CTLA-4 inhibition typically arise in the setting of a recent infusion, and often rapidly progress after initiation.

Similar to CTLA-4, PD-1 expression is controlled by T-cell stimulation, although the highest expression is on T cells that have received repeated stimulation (22). Unlike the restricted expression of the B7s, PD-L1 can be expressed on a variety of cell types in response to IFNγ and other inflammatory signals, whereas the second ligand for PD-1, PD-L2, has a more narrow tissue distribution, largely expressed on myeloid cells and B cells (22). Ligation of PD-1 sends a direct inhibitory signal to T cells through activation of the tyrosine phosphatase, SHP2 (22). The regulation of PD-L1 by IFNγ leads to an important role in suppressing chronic inflammatory responses through PD-1–mediated T-cell inhibition and eventually exhaustion. Reactivation of previously exhausted T cells, particularly $CD8^+$ T cells, appears to be critical for the antitumor activity of PD-1/PD-L1 blockade (5, 6). Inflammatory toxicities may similarly result from reactivation of exhausted T cells held in-check within organs by interactions with PD-L1, mimicking the response in tumors. In the setting of a

preexisting, self-reactive, exhausted T-cell pool, we may expect rapid development of toxicity. This occurs with many of the life-threatening toxicities that have been observed and in some patients with underlying autoimmune disease who are treated with immunotherapy (23, 24). Another possibility is that, an infectious trigger may lead to inflammatory toxicities when tissues are unable to downregulate T-cell responses through PD-1/PD-L1. Potential infectious triggering of immunotherapy toxicities has been observed anecdotally and is consistent with the late-onset inflammation that can happen with PD-1 inhibitors.

Cell types mediating organ injury

The identity of the cells responsible for driving immunotherapy toxicities is presently unknown. In tumors, the presence of more stem-like effector memory cytotoxic $CD8^+$ T cells corresponds to effective antitumor responses (25). The ability to present on MHC class I and to respond to IFNγ also appears to be required for optimal responses (**Fig. 1A**; refs. 26, 27). However, whether these same pathways drive the inflammatory toxicities is unclear. $CD8^+$ T cells are found in many inflamed organs, and TH1-type immune responses may well be the predominant pathway causing organ damage, as they appear to be in tumors (17, 25–28). Indeed, in colitis from CTLA-4 blockade, cycling granzyme B^+ effector $CD8^+$ T cells and $IFN\gamma^+$ $CD4^+$ T cells are substantially expanded compared with normal colon and in biopsies from patients receiving CTLA-4 blockade who did not develop colitis (**Fig. 1B**; ref. 18). Nevertheless, TH17 cells or PD-1–regulated macrophages may also have an important role and could serve as distinct therapeutic targets (29, 30). The range of cytokine and chemokines produced in the inflamed tissues also may differ from that in the tumor, as might the consequences of these secreted factors on tissue function, although IFNγ is upregulated in both settings (5, 6, 1 8, 25, 31). These are questions that can be answered with current technology, but will require a dedicated effort to study the tissues affected by immunotherapy toxicities directly. The mechanisms of toxicity are likely to differ across organ systems, as they do across autoimmune diseases; although some similarities may exist, grouping toxicities together *a priori* may obscure important mechanistic information. Examination of peripheral blood is also likely insufficient, as blood integrates immune responses from across the body, including those against tumors. Local differentiation of cells upon arrival into tissues, or expansion of preexisting tissue resident cells, may also play significant roles in pathology. On the basis of a detailed clonal analysis in immunotherapy-induced colitis, both expansion of tissue resident $CD8^+$ T cells and influx of new T cells into the colon appears to occur (18). Once the immune response in inflamed organs is characterized, however, finding circulating cells or proteins that provide a window into tissue inflammation may be a more tractable problem.

Antigenic targets

The antigens recognized by adaptive immunity in checkpoint blockade toxicities are also of considerable interest. On the basis of the frequent involvement of barrier organs, microbial antigens are likely common targets (**Fig. 1B**). Consistent with this hypothesis, contents of the pretreatment microbiome modify risk for colitis from checkpoint blockade, and fecal microbiota transplant has been successful in treating a small number of patients with refractory disease (32, 33). In both cases, an indirect immune-modulating role for the microbiome cannot be excluded, particularly given the well-established correlation in both humans and mice between the microbiome and antitumor immunity (34–36). The expansion of $CD8^+$ T-cell clones in immunotherapy-induced colitis that overlap with the resident memory cells in the colon is also suggestive that at least some of the T-cell response is to microbial antigens, although this remains to be formally demonstrated (18).

In contrast to barrier organ inflammation, the endocrine toxicities of checkpoint blockade are likely driven by recognition of tissue-restricted autoantigens, although few have been specifically identified (37). Although the pattern of autoantigens identified thus far does not precisely mirror spontaneous autoimmune diseases, some overlap in targets has been observed, such as in Myasthenia Gravis and Graves' disease precipitated by immunotherapy (**Fig. 1B**; refs. 37, 38).

In some cases, recognition of tumor antigens may lead to loss of self-tolerance and simultaneous targeting of host cells expressing the same proteins, mechanistically linking antitumor immunity to toxicity. This is most likely true for melanoma and vitiligo, where autoimmune destruction of normal melanocytes is clearly associated with favorable melanoma outcomes (**Fig. 1**; refs. 39, 40). The evidence that tumor type influences the spectrum of other toxicities is less well-established, and the differences observed may instead reflect common risk factors for both the cancer and the toxicity (3).

Detailed characterization of T-cell receptor clones in tumors and in inflamed organs, alongside information about the targets of those clones, will be critical for understanding the mechanistic relationship between antitumor responses and inflammatory toxicities. Identical expanded clones have been found in tumors and in inflamed myocardium in a patient with immunotherapy-induced myocarditis (28). Similarly, an exceptional responder to dual checkpoint blockade for uveal melanoma developed multisystem inflammation, which included an expanded clone found in the tumor and at multiple sites (41). The presence of identical clones at multiple sites is consistent with a broadly expressed antigenic target; however, an alternative explanation is that these clones are following inflammatory chemokine gradients and are present as bystanders rather than as locally activated effector cells. Consistent with this hypothesis, the chemokines, CXCL9 and CXCL10, are produced in both inflamed tumors and the inflamed colon, which could lead to recruitment of $CXCR3^+$ cells to both sites (18, 31). In addition to coexpression of a target antigen, some apparent toxicities could result from immune responses to occult metastases (42). In these settings, antitumor responses themselves could lead to bystander cell damage and organ dysfunction even if nonmalignant cells do not express the T-cell antigen.

Managing Toxicities to Improve Antitumor Immunity

A better understanding of immunotherapy toxicities is of conceptual interest, but also promises to improve our ability to manage these potentially life-threatening side effects. Most patients treated with PD-1– or PD-L1–blocking therapy are able to complete the therapy without developing a treatment-limiting toxicity, although toxicities that affect quality of life are common (3, 23). CTLA-4 blockade and combination CTLA-4 and PD-1 blockade commonly induce treatment-limiting toxicities, and although combination therapy may be more efficacious than single-agent PD-1 blockade, toxicity is the major reason this regimen is not used for all patients (3, 23). For approved adjuvant therapies and for neoadjuvant therapies that are under investigation, these toxicities take on further significance, as a large fraction of these patients would be expected to remain tumor-free even without systemic treatment.

Management of life-threatening toxicities

Although rare, several toxicities can be immediately life-threatening, including myocarditis, neurologic toxicities, and the most severe forms of pneumonitis and colitis, among others. Optimal management of these life-threatening toxicities remains unclear, although many respond to high-dose corticosteroids. In the absence of detailed mechanistic information, treatment has been guided by analogy to autoimmunity and to transplant rejection. For colitis, treatment often involves biologics that were initially approved for inflammatory bowel disease, whereas other toxicities have been managed with drugs such as tacrolimus, cyclosporin, mycophenolate mofetil, and antithymocyte globulin, with variable success (24, 43). Mechanistically, recombinant CTLA-4-Ig (e.g., abatacept) should act to reverse CTLA-4 blockade toxicities, and may also have a therapeutic benefit in PD-1 toxicities by interfering with costimulation (19). Interfering with cytokine signaling using JAK kinase inhibitors is another reasonable approach. Although both CTLA-4-Ig and JAK inhibitors are likely to block antitumor responses as well, this is certainly appropriate when toxicities are immediately life-threatening.

Preservation of antitumor activity in the setting of non–life-threating toxicities

Beyond life-threatening toxicities, one of the most important clinical questions in managing checkpoint blockade side effects is whether these organ-specific immune responses can be mechanistically separated from antitumor immunity. Systemic corticosteroids likely limit at least some antitumor responses through a variety of mechanisms, although the clinical data on this remains unresolved (44–46). Local steroids, in contrast, likely have minimal influence on antitumor responses, but can have powerful effects on toxicity (47). One of the reasons that determining the effect of steroids on antitumor immunity has been difficult is that many toxicities are correlated with improved antitumor responses. Thus, patients who receive steroids tend to do well compared with those who do not (45). Yet, analyses that include steroid dose suggest that patients whose toxicities are managed with lower doses have better outcomes than those managed with higher doses (46). All of the current data are, however, retrospective and subject to treatment bias. Resolving this controversy will require prospective trials, where patients are randomized to distinct treatment strategies, and both tumor and toxicity endpoints are assessed, which are now underway (NCT04305145).

Integrin inhibitors provide an alternative mechanism for organ-specific immune suppression by preventing trafficking of T cells into inflamed tissues. Vedolizumab inhibits trafficking to the gut by blocking $\alpha4\beta7$ integrin and appears to be effective in treating colitis from checkpoint blockade (48). Similarly, natalizumab, an $\alpha4$ integrin inhibitor, that blocks trafficking into both the brain and gut, may also have efficacy in neurologic toxicities. Provided that patients do not have primary tumors or metastases in these organs, use of integrin inhibitors is a conceptually attractive method for managing toxicities without having to discontinue immunotherapy.

Some immune mediators may interact differently with the tumor microenvironment and inflamed organs, providing targets that could dissociate antitumor immunity from toxicity. GM-CSF can have an important role in generating cross-presenting dendritic cells, but at the same time can promote the production of regulatory cells (49). When combined with ipilimumab, recombinant GM-CSF appears to improve antitumor responses, while at the same time, reducing the risk of colitis (50). The value of adding GM-CSF to ipilimumab and anti–PD-1 combination immunotherapy is now being assessed in a randomized multicenter clinical trial (NCT02339571).

The innate inflammatory cytokines TNFα, IL1β, and IL6, all have important roles in mediating tissue damage in autoimmunity, but have also been implicated in tumor promotion (1). Canakinumab, an antibody against IL1β, in particular led to a substantial decrease in new lung cancer diagnoses and deaths in a secondary analysis of the CANTOS trial for secondary prevention of cardiovascular disease (51). In animal models, inhibition of TNFα and IL6 improves antitumor immunity by enhancing T-cell responses (1, 52). TNFα inhibitors are effective at treating colitis from checkpoint blockade and also appear to be effective for several rheumatologic toxicities (2, 53). Thus, blockade of innate cytokines, such as TNFα, has the potential to treat certain toxicities, while enabling or even enhancing antitumor responses.

Conclusion

Immunotherapy toxicities offer an unprecedented opportunity to study immune regulation in humans. This work has the potential to teach us details about how each organ maintains immune homeostasis, as well as the numerous factors that combine to perturb that balance. But, understanding the immune mechanisms driving the inflammatory toxicities of immunotherapy is also more than an academic exercise. Every patient who receives these treatments for cancer has a potentially life-threatening disease, and pausing or discontinuing cancer therapy can have deadly consequences. Thus, a sophisticated understanding of the immune mechanisms that drive immunotherapy toxicities has the potential for substantial clinical impact. Identifying high-risk patients could lead to prophylactic treatments or more selective use of immunotherapy. Developing novel approaches that can be used alongside immunotherapy will also require a detailed immune analysis of the affected tissues and a direct comparison with the mechanisms of antitumor immunity. Mechanistic differences between these two types of immune responses should be the basis for identifying potential therapeutic targets. Such targets could dissociate toxicity from efficacy, improving the therapeutic window of immunotherapy and allowing a larger number of patients to benefit. As the scope of available immunotherapies widens and as combination treatments become more widespread, developing rational methods to manage their toxicities will only grow in importance.

Disclosure of Potential Conflicts of Interest

M. Dougan reports personal fees from ORIC Pharmaceuticals, Tillotts Pharma, Partner Therapeutics, and Genentech; grants from Novartis and Eli Lilly; and other from Neoleukin Therapeutics (stock options and consulting fees for scientific advisory board role) outside the submitted work. No other potential conflicts of interest were disclosed.

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Cancer Immunology Research

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