HHS Public Access

Author manuscript

Immunol Rev. Author manuscript; available in PMC 2024 September 01.

Published in final edited form as:

Immunol Rev. 2023 September ; 318(1): 89–95. doi:10.1111/imr.13238.

Role of B cells in immune-related adverse events following checkpoint blockade

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Summary:

Blockade of immune checkpoints has transformed the therapy of several cancers. However immune-related adverse events (irAEs) have emerged as a major challenge limiting the clinical application of this approach. B cells are recognized as major players in the pathogenesis of human autoimmunity and have been successfully targeted to treat these disorders. While T cells have been extensively studied as therapeutic targets of immune checkpoint blockade (ICB), these checkpoints also impact B cell tolerance. Blockade of immune checkpoints in the clinic is associated with distinct changes in the B cell compartment that correlate with the development of irAEs. In this review, we focus on the possible role of humoral immunity, specifically human B cell subsets and autoantibodies in the pathogenesis of ICB-induced irAEs. There remains an unmet need to better understand the T:B cell cross-talk underlying the activation of pathogenic B cells and the development of ICB-induced irAEs. Such studies may identify new targets or approaches to prevent or treat irAEs and improve the application of ICB therapy in cancer.

Keywords

immune checkpoint blockade; adverse events; mechanism; autoimmunity; B cells; cancer

ICB-induced irAEs- lessons from the clinic relevant to possible mechanisms

Blockade of immune checkpoints such as programmed death-1 (PD-1), PD-ligand1 (PD-L1), or cytotoxic T lymphocyte-associated antigen4 (CTLA-4) has led to durable tumor regressions, particularly in patients with tumors such as melanoma[1]. However, the application of these transformative therapies has been commonly associated with the development of immune-related adverse events (irAEs)[2]. Clinically, these toxicities exhibit highly diverse presentations and can manifest with the involvement of several distinct

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Conflicts of interest: The authors have declared that no conflict of interest exists.

organs/systems[3–5]. Development of irAEs is common in patients receiving ICB, occurring in over 70–80% of patients and includes high-grade AEs in nearly 40–50% of patients receiving combination CTLA-4 and PD-1 checkpoint blockade (CCB)[4]. For example, a pooled evaluation of data from Checkmate 037, 067 and 069 trials involving patients receiving ipilimumab (anti-CTLA4), nivolumab (anti-PD-1) or combination described grade 3–4 irAEs in 8%, 19% and 40% of patients respectively[5]. The clinical details of irAEs observed following ICB therapy and their management has been reviewed in detail elsewhere[6]. However a few lessons from the clinic are relevant to the current review and understanding pathogenesis. First, while the development of specific irAEs may be unpredictable, most irAEs seem to develop within a few cycles of therapy, particularly exemplified by CCB, wherein irAEs occurred with a median time of onset of 14.5 days[7]. This suggests that pre-existing predisposition and early post-therapy changes may be key to understanding the pathogenesis of most irAEs. The impact of underlying predisposition is also illustrated by data from ICB therapy of patients with prior autoimmunity, which led to both higher incidence of irAEs as well as exacerbation of underlying autoimmunity[8–10]. Second, each of the ICB strategies has led to a distinct pattern of toxicities in the current trials[4]. For example, the most common ICB-induced grade 3 or 4 toxicities were colitis following anti-CTLA4, pneumonitis following anti-PD-1, hepatitis and colitis following CCB[5]. Therefore mechanistic studies of ICB-induced irAEs should include uniformly treated patients. This is also consistent with prior observations that each of the ICB strategies leads to distinct genomic signatures in immune cells of treated patients[11–13]. Third, inflammatory clinical phenotypes associated with most ICB-induced irAEs resolve following the cessation of ICB and often require only limited duration of immune-suppressive therapy, although organ damage such as that in the setting of endocrinopathies may require long-term hormone replacement therapy[6]. This suggests that the specific irAEs are likely the result of immune imbalance and acute loss of tolerance mechanisms transiently created by the specific ICB therapy. As discussed further below, similar mechanisms may also be phenocopied in humans with genetic loss of specific immune checkpoints (such as those with haploinsufficiency for CTLA4)[14] and again supporting the concept that immunoregulatory mechanisms of ICB-induced irAEs may be agent-specific. Fourth, while the irAE syndromes seem to bear some resemblances to naturally occurring autoimmunity (e.g. for endocrinopathies)[15], major human autoimmune conditions (such as lupus) are not common clinical manifestations of ICB-associated irAEs. While this may be in part related to under-representation of patients with known autoimmunity in ICB trials, it also suggests that there may be distinct differences with naturally occurring autoimmunity, for specific mechanisms and particularly autoantigenic targets. Emerging clinical patterns of irAE presentations also suggest that there may be shared mechanisms between toxicities that seem to occur together, as exemplified by some neuromuscular toxicities such as myositis and myasthenia gravis[16]. Finally, while there is some evidence that patients who experience irAEs in ICB responsive tumors may have higher likelihood of clinical response, this has not been consistent across all specific ICB therapies and trials[17]. Importantly, ICB therapy of patients with ICB-refractory tumors also led to similar patterns of irAEs as those observed in patients with ICB-responsive tumors[18]. In general, the pattern of irAEs seems to correlate more with the nature of specific ICB therapy than the underlying malignancy. As discussed further below, this suggests that while there may be some overlap in terms of

underlying immunologic mechanisms that are shared between anti-tumor effects and irAEs, pathways and antigenic reactivities that determine susceptibility for irAEs and mediate tissue inflammation in autoimmune target tissues leading to irAEs may be distinct from those leading to anti-tumor effects.

Role of B cells and T:B crosstalk in human autoimmunity

Both B and T cells form the core of adaptive immunity. Over the past decade, success of B cell depletion therapies in human autoimmunity has led to renewed emphasis on B cells as active participants in the pathogenesis of autoimmunity. Major advances in B cell biology and T:B cross talk in the past decade has in turn provided new mechanistic insights into human autoimmunity. Below, we discuss some key players relevant to the current review. The germinal center (GC) is now well recognized as a critical environment for the interaction of antigen-specific T and B cells. In recent years, our understanding of how T follicular helper (T_{FH}) cells and regulatory T_{FH} cells interact with GC B cells has exploded[19]. However the GC is not the only tissue for B cell activation, and extra-follicular (EF) responses can also provide an early source of antibodies during infection[20]. Although initially thought to be T-independent, EF B cells also engage T cells and have been shown to be particularly important for driving tissue inflammation in several autoimmune states such as rheumatoid arthritis and Sjogren's syndrome[21,22]. Although multiple B cell subsets have been described, a distinct subset of T-bet+CD21^{lo} B cells also implicated in EF responses may play an outsized role in human autoimmunity. T-bet is well recognized in the context of subset of T helper-1 (Th1)+ T cells, but also marks a distinct subset of B cells[23]. Some of the T-bet^{hi} B cells have the capacity to rapidly differentiate into antibody secreting plasma cells in lupus patients and seem to be responsible for the surges of autoantibodies observed during lupus flares[24]. These B cells are increased in tissues with aging and autoimmunity and also enriched in autoreactive B cell receptors[25,26]. These features, along with early alterations in this specific B cell subset in patients developing irAEs following ICB[27] strongly support a role for these cells in the pathogenesis of irAEs. Although understudied, the proportion of these cells may also be impacted by underlying racial background, with higher proportion in Black patients[20,28].

The role of B cells in human autoimmunity has long been supported by the well documented correlation between organ/tissue-specific antibodies even in the preclinical phase and the development of specific clinical autoimmune states. In some instances, the detection of these antibodies forms a part of the diagnostic criteria for clinical autoimmunity. This may be particularly relevant for the concept of subclinical autoimmunity, as the detection of autoantibodies can precede the development of clinical autoimmunity and organ damage, as in the case of endocrinopathies[29].

Improved understanding of the role of B cells in autoimmunity has illustrated how they may contribute to autoimmunity and tissue inflammation, beyond as a source of antibodies. This was particularly appreciated with the realization that some autoimmunity patients that respond clinically to B cell depletion therapies do not necessarily show an improvement in autoantibody levels[30]. Pathogenic B cells can also serve as source of inflammatory cytokines (such as interferon-gamma)[31], act as antigen-presenting cells[32], and may also

play an important role in initiating or sustaining tertiary lymphoid structures (TLTs)[33] in inflamed tissues. Similar mechanisms may be operative in ICB-associated irAEs.

Another important insight from recent studies of human autoimmune tissues is the interaction between T and B cell subsets in situ within autoimmune tissues itself[34]. In this setting, T cells entering these lesions can provide directly interact with and provide help to autoreactive B cells in these tissues, outside the context of the classical GC reactions. In some settings, these cells can be detected within inflamed tissues and seem to differ from the classic TFH cells in terms of their phenotype and functional properties and have accordingly been termed as TPH cells[34].

Taken together, emerging evidence points to an important role for B cells and T:B crosstalk in not only initiating but also mediating and sustaining autoimmune inflammation within tissues. As discussed below, similar aspects of B cell biology may also be at play during ICB-induced irAEs when physiologic pathways are perturbed. The precise nature of T and B cell subsets that contribute to the pathogenesis of irAEs and the underlying mechanisms remain to be fully clarified.

Mechanisms of irAEs following immune checkpoint blockade

At present our understanding of mechanisms underlying irAEs following ICB therapy remains incomplete[35]. Several mechanisms have been implicated and they are not mutually exclusive[35]. Both autoreactive T and B cells likely play a central role in this process (Fig 1). Both CTLA4 and PD-1 have been implicated in maintaining immune tolerance impacting both B and T cells. CTLA4 deficient mice develop significant autoimmune lymphoproliferation[36], while PD-1 deficient mice develop lupus like autoimmune disease with cardiomyopathy and arthritis[37]. Interestingly, autoimmune complications were less evident in early preclinical studies of anti-tumor effects with antibody-mediated CTLA4 blockade[38] or PD-1 blockade[39], than subsequently seen in human trials with cancer patients. Several mechanisms have been implicated in the pathogenesis of ICB-induced irAEs. Aberrant activation of autoreactive T and B cells likely represents a prime factor for the pathogenesis of irAEs[40]. Given the prominent role for T cells in anti-tumor effects of ICB, most of the attention relating to irAEs has also focused on T cells. Our understanding of antigenic reactivities of pathogenic T cells in autoimmune tissues remains incomplete. In some cases, it has been proposed that tumor cell death can release self-antigens and elicit reactivities against both tumor and autoimmune tissues. In support of this model, shared TCRs between tumor and autoimmune tissue such as skin or cardiac muscle have been identified[41,42]. Others have suggested that a high proportion of T cells within colitis or dermatologic reactions represent tissue-resident memory (T_{RM}) T cells within the tissue itself[40,43,44]. As T_{RM} cells typically exhibit limited equilibration[45,46], this suggests that pathogenic autoimmune TCRs may differ from those mediating tumor regression. Characterizing the reactivities of pathogenic T cells in autoimmune tissues remains an area of active research[47]. Risk for irAEs have also been linked to germline variants in IL7, a cytokine intricately implicated in immune homeostasis[48]. Higher proportion of a distinct subset of CD4 effector cells at baseline correlated with the risk of development of severe irAEs in melanoma patients[49]. It should be noted that the patterns of tissue involvement in

irAE seems to be more agent specific and less impacted by the specific tumor type (which likely have distinct neoantigen or self-antigen reactivities), suggesting that this may be a feature of activation of pre-existing autoreactive cells, independent of the malignancy. In this review, we will focus mostly on the evidence as it pertains for the potential role of B cells and the role of T cells is considered in detail elsewhere[43].

Impact of immune checkpoints on B cells

Although both CTLA-4 and PD-1 have been extensively studied for their role as T cell checkpoints, they also play a critical role in B cell biology. Deletion of CTLA-4 by murine B-1a cells was shown to promote autoantibody formation[50]. CTLA-4 has also been implicated in regulating the function of TFH and T follicular regulatory (TFR) cells. Loss of CTLA-4 in murine TFH cells led to increased TFH cells and B cell responses, while loss of CTLA-4 in TFR cells further increased antibody responses by modulating TFR-mediated suppression[51,52]. Impact of CTLA-4 on human B cells is also illustrated by studies of humans with haploinsufficiency of CTLA-4. These individuals were found to have decline in circulating B cells, along with an increase in $CD21^{lo}$ subset of B cells, and increased risk of autoimmunity[14], thus phenocopying several of the changes observed in B cells from patients treated with combination checkpoint blockade. Early studies on PD-1 deficient mice had identified a role for PD-1 as a negative regulator of B cell function[53]. Inhibitory effects of PD-1 on B cells were later also demonstrated for human B cells[54]. Interestingly, the subset of human B cells that seem to express the highest levels of PD-1 are the T-bet+ B cells[27] discussed earlier to be implicated in autoimmunity.

B cell changes following checkpoint blockade and the risk of irAE

Several studies have now reported a correlation between therapy-induced changes in B cells or plasmablasts and increased risk for the development of irAEs[27,55–58]. One of the earliest studies in this regard was by Das et al, who studied patients with melanoma undergoing combination checkpoint blockade[27]. In this study, early B cell changes (defined as decline in circulating B cells, along with an increase in $CD21^{lo}$ B cells and plasmablasts correlated with the risk for development of severe irAEs following CCB. Phenotype and genomic signatures of $CD21^{lo}$ B cells in these studies resemble Tbet+ B cells implicated in autoimmunity and shown to be enriched to autoreactive BCRs. Importantly, the changes in B cells preceded the development of clinical complications suggesting that they may be useful biomarkers for the initiation of preventive intervention or closer monitoring. Other studies in patients with liver cancer, renal cell cancer or lung cancer patients have also described correlations between irAEs and similar changes in B cells including increase in $CD21^{lo}$ B cells and plasmablasts in patients undergoing PD1 blockade or combination CTLA4 and PD1 checkpoint blockade[55–58]. Together, these studies support a possible role for B cells and particularly the $CD21^{lo}$Tbet+ subset of human B cells in the pathogenesis of irAEs. Further studies are needed to dissect the properties of these B cells, their reactivities and elucidate the mechanisms by which they interact with T cells.

Autoantibodies and the development of irAEs

Autoantibodies can engage several potential mechanisms to mediate tissue injury and inflammation in the setting of autoimmunity as well as the development of irAEs. Antibodies against specific target organs can directly alter the function of specific receptors and mediate organ dysfunction. In some instances, autoantibodies can also engage other mechanisms such as complement or formation of immune complexes to initiate inflammation. Several studies have tried to analyze the presence of autoantibodies in patients developing irAEs and the presence of autoantibodies at baseline as potential biomarkers to predict the risk of irAEs[58–67]. Patients with melanoma or lung cancer with pre-existing autoantibodies were shown to be at a higher risk of development of irAEs, particularly those at higher grade[68,69]. The presence of autoantibodies is also a common feature of some autoimmune diseases such as rheumatoid arthritis and systemic lupus. Patients with prior autoimmune disease who receive ICB therapy are at an increased risk of worsening of underlying autoimmunity, development of new de-novo irAE or both[8–10]. This risk may be impacted both by the activity of the underlying autoimmune condition as well as its therapy. Thus patients undergoing active therapy for autoimmune disease at the time of initiation of ICB had fewer irAEs, presumably due to the suppression of irAEs by therapy[9]. Similarly, patients with active autoimmunity may be at higher risk of flares compared to those with inactive disease[70].

In spite of the general correlations between the presence of autoantibodies and irAE risk, correlations between organ-specific autoantibodies and irAEs involving the target organ has been limited to few syndromes, such as endocrinopathies[71] and myositis[72]. In some instances even when the clinical picture resembles a naturally occurring autoimmune disease, the prototypic target antibodies found in naturally occurring disease (for example acetylcholinesterase receptor antibodies in myasthenia gravis) may not be detected in the case of ICB-associated irAE[73]. In other words, while there is some overlap, the antigenic targets for autoreactive antibodies during the development of ICB-induced irAEs remain largely unknown and may well differ from naturally occurring autoimmunity.

B cell targeting therapies and irAEs

In most instances, the therapy for checkpoint blockade-induced irAEs involves the cessation of checkpoint blockade therapy and the introduction of steroids, which broadly impact several aspects of the immune system including B cells. However, there are some instances wherein B cells or antibodies have been more specifically targeted, therefore providing support for pathophysiologic role for B cells or antibodies in irAEs. Therapies such as intravenous immune globulin (IVIG) and Rituxan have been successfully utilized for hematologic toxicities such as immune thrombocytopenic purpura, analogous to their use in naturally occurring autoimmunity[74]. Plasmapheresis is currently recommended in therapeutic guidelines for specific neurologic irAEs, including for Guillain Barre-like syndromes, presumably with the hypothesis that the procedure leads to reduction in pathogenic autoantibodies[6]. In melanoma preclinical models, depletion of B cells did not adversely impact anti-tumor effects of PD-1 blockade[75]. The role of B cells within tumor tissue in enhancing T cell function and mediating protective immunity within tumors is an

area of active research, although the capacity of these therapies to deplete B cells within tumors is not known[76].

Role of T: B interactions and pathogenic inflammation

As discussed earlier, evidence in several autoimmune disorders (such as rheumatoid arthritis) points to a role for T:B interactions in driving pathogenic tissue inflammation. However the nature of specific B and T cell subsets that underlie the development of irAEs, and the nature of T:B interaction in the development of pathogenic tissue inflammation in ICB-associated irAEs remains to be fully understood. It is notable that specific human B cell subsets such as T-bet+ $CD21^{lo}$ B cells which have been implicated in ICB-associated irAEs have also been shown to exhibit propensity to migrate to tissue in the setting of tissue inflammation[23]. Studies that dissect the biology of the T:B interactions in patients experiencing irAEs may help the development of novel approaches to prevent or treat irAEs and thereby improve the application of immune checkpoint blockade in cancer. Such studies may also benefit from newer humanized models to study this cross-talk in-vivo in preclinical systems[77]. In recent studies, B cells have also been identified as important component of the tertiary lymphoid structures within tumors and implicated in mediating protective tumor immunity[76]. Therefore as with T cells, B cells infiltrating tumors versus those infiltrating autoimmune tissues could also play distinct roles, both in the context of tumor immunity as well as contributing to pathogenic inflammation within autoimmune tissues[76].

Summary

It is increasingly appreciated that immune checkpoint blockade not only leads to the activation of anti-tumor T and B cells within tumors that mediate tumor regression, but also activation of autoreactive T and B cells that lead to tissue inflammation and immune-related adverse events involving target organs (Fig 1). Risk of irAEs may be determined by preexisting susceptibilities in the host and manifest early during the course of therapy, before the onset of clinical symptoms. Improved understanding of this biology and underlying mechanisms may therefore not only allow for improved risk-stratification, but also yield new opportunities to prevent irAEs.

Acknowledgments:

KMD is supported in part by funds from NIH (CA238471 and AR077926). MVD is supported in part by funds from NIH (NIH R35CA197603. MVD and KMD are also supported in part by funds from Specialized Center for Research (SCOR) award from the Leukemia and Lymphoma Society.

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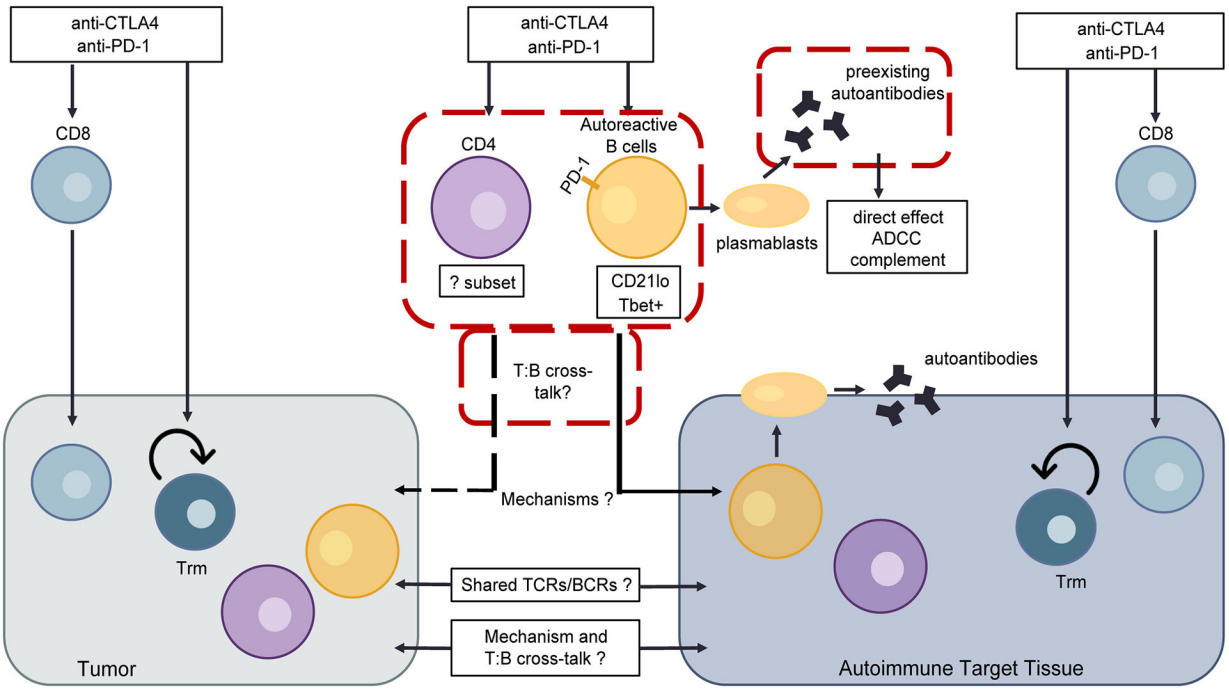

Figure 1. Role for B cells and T:B cross-talk in immune-related adverse events (irAEs) following immune-checkpoint blockade.

Activation of autoreactive B cells as well as T cells following checkpoint blockade contributes to irAEs. Baseline levels of CD4 cells as well as changes in $CD21^{lo}$T-bet+ B cells have been linked to the development of high-grade irAEs. Cross-talk between these cells may contribute to tissue inflammation in autoimmune tissues. Highlighted boxes represent some potential areas of intervention for preventing these irAEs.