Review Article

Asia Pacific Allergy

OPEN

From tumor to tolerance: A comprehensive review of immune checkpoint inhibitors and immune-related adverse events

Henry Sutanto[†,1,2], Ardea Safira[†,1,2], and Deasy Fetarayani[1,2,3,*]

ABSTRACT

The advent of immune checkpoint inhibitors (ICIs) has revolutionized the treatment landscape for various malignancies by harnessing the body's immune system to target cancer cells. However, their widespread use has unveiled a spectrum of immune-related adverse events, highlighting a critical balance between antitumor immunity and autoimmunity. This review article delves into the molecular immunology of ICIs, mapping the journey from their therapeutic action to the unintended induction of immune-related adverse events. We provide a comprehensive overview of all available ICIs, including cytotoxic T-lymphocyte-associated protein 4, programmed cell death protein 1, programmed death-ligand 1 inhibitors, and emerging targets, discussing their mechanisms of action, clinical applications, and the molecular underpinnings of associated immune-related adverse events. Special attention is given to the activation of autoreactive T cells, B cells, cytokine release, and the inflammatory cascade, which together contribute to the development of immune-related adverse events. Through a molecular lens, we explore the clinical manifestations of immune-related adverse events across organ systems, offering insights into diagnosis, management, and strategies to mitigate these adverse effects. The review underscores the importance of understanding the delicate interplay between enhancing antitumor responses and minimizing immune-related adverse events, aiming to guide future research and the development of next-generation ICIs with improved drug safety profiles.

Keywords: Cancer; immune checkpoint inhibitors; immune-related adverse events; immunology

1. Introduction

The immune system's role in cancer surveillance is a crucial aspect of our body's defense mechanism against the development and progression of malignancies. The concept of immune surveillance suggests that the immune system can identify and destroy nascent tumor cells, thereby preventing cancer formation and progression. This theory has been supported by various studies demonstrating the immune system's ability to recognize tumor-associated antigens and eliminate cancer cells before they can establish a significant tumor mass [1-3]. Immune checkpoints are crucial regulators of immune responses, acting as "brakes" to prevent the immune system from attacking normal cells while enabling it to fight infections or diseases. These checkpoints include molecules such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed cell death protein 1 (PD-1), and programmed death-ligand 1 (PD-L1), which can inhibit T-cell function when engaged [4-6]. The rationale for targeting immune checkpoints in cancer therapy stems from their role in cancer cells' ability to evade immune surveillance. By inhibiting these checkpoints, immune checkpoint inhibitors (ICIs) can re-activate T cells, enabling them to recognize and destroy cancer cells. This approach has led to significant advancements in cancer treatment, particularly for malignancies previously considered resistant to conventional therapies [7, 8]. However, the use of ICIs has also led to the emergence of autoimmune diseases as a significant side effect. These diseases occur when the unleashed immune response begins to attack normal tissues, leading to a range of immune-related adverse events (irAEs). The development of autoimmune diseases following ICI therapy underscores the delicate balance between enhancing antitumor immunity and maintaining self-tolerance. Understanding the mechanisms behind these adverse effects is crucial for developing strategies to mitigate them and improve patient outcomes [9, 10].

The incidence of irAEs induced by ICIs can vary by region, potentially due to differences in genetic backgrounds, environmental factors, and medical practice patterns. For instance, a study from the United States has documented the incidence and risk factors associated with irAEs requiring hospitalization. It noted an irAE incidence requiring hospitalization of 3.5% among patients initiating ICI therapy, with variations observed across different cancer types and ICI combinations [11]. Another study investigated the safety profile and outcomes of 90 patients with renal cell carcinoma treated with ICIs at 2 United States medical centers, examining the incidence of treatment-related adverse events and the specific irAEs encountered. IrAEs were seen in

[1]Internal Medicine Study Program, Department of Internal Medicine, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia, [2]Department of Internal Medicine, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, [3]Division of Allergy and Clinical Immunology, Department of Internal Medicine, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

*Correspondence to Deasy Fetarayani Division of Allergy and Clinical Immunology, Department of Internal Medicine, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.

Email: deasy-f@fk.unair.ac.id

†Henry Sutanto and Ardea Safira contributed equally to this article.

Received: 6 March 2024; Accepted: 2 May 2024

Published online 30 May 2024

http://dx.doi.org/10.5415/apallergy.0000000000000146

42.2% of individuals, with the most common irAEs involving the skin (15.6%), gastrointestinal tract (14%), endocrine organs (11%), and lungs (7.8%). There were 16.7% grade III/IV irAEs, resulting in cessation of therapy for 13.3% of patients [12]. Meanwhile, a Japanese study analyzed 533 cases treated with ICIs for various malignancies, investigating irAEs and their predictors. They found that 27.0% developed irAEs of all grades, with 10.7% being grade ≥3. Anti-CTLA-4 therapy was associated with a higher likelihood of irAEs compared to anti-PD-1 or anti-PD-L1 monotherapy. Liver injury was the most common irAE, with combination therapy of PD-1 and CTLA-4 antibodies and baseline eosinophil count ≥130/μL identified as independent risk factors for immune-related liver injury. Remarkably, patients experiencing irAEs showed higher disease control and overall survival rates compared to those without. Thus, irAE occurrence might indicate increased efficacy and longer survival with ICI therapy [13]. Similar findings were reported by another study, showing that the median overall survival was 35.9 and 26.5 months for patients with and without irAEs [12].

This review aims to dissect the intricate balance between the immune system's role in cancer surveillance and the emergence of irAEs following ICI therapy. By delving into the molecular and cellular mechanisms of ICIs targeting CTLA-4, PD-1, and PD-L1 (Fig. 1), it seeks to elucidate how these therapies enhance immune responses against cancer while also predisposing patients to irAEs. The review will summarize the clinical applications and efficacy of ICIs across various cancers, assess strategies for mitigating irAEs, and highlight future directions in ICI research, including novel agents and personalized medicine approaches. Ultimately, this comprehensive analysis aims to evaluate the transformative impact of ICIs on cancer immunotherapy and explore the dual challenge of maximizing antitumor activity while minimizing autoimmune risks, thus guiding future advancements in the field.

2. Overview of immune checkpoint inhibitors

2.1. CTLA-4 inhibitors

CTLA-4 inhibitors operate by obstructing the CTLA-4 checkpoint molecule on T cells, thereby preventing its binding with B7 molecules (CD80/CD86) on antigen-presenting cells (APCs; Fig. 1) [14]. This blockade enhances T-cell activation and proliferation, augmenting the immune system's ability to attack cancer cells. CTLA-4 inhibition can also modulate regulatory T cells (Tregs), which are essential for maintaining immune tolerance. Studies have elucidated that beyond merely blocking

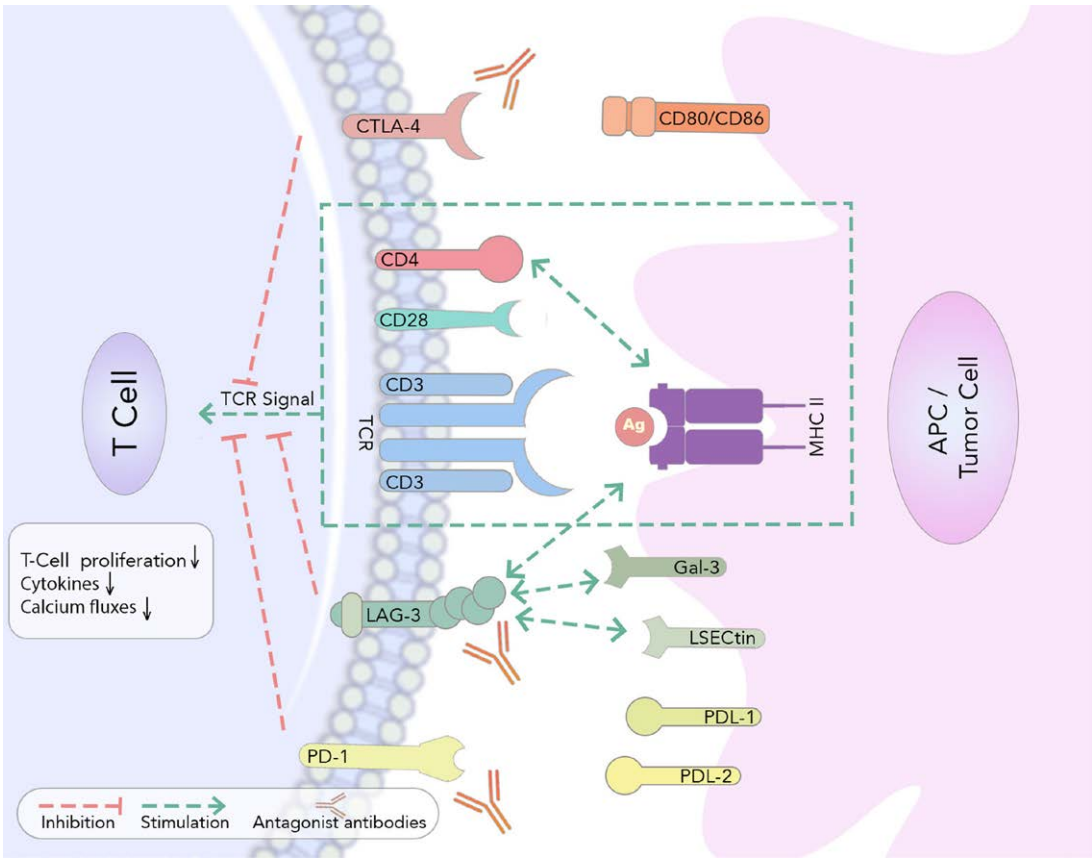

Figure 1. Immune checkpoint interactions in T cell regulation. The diagram illustrates the interaction between a T cell and an antigen-presenting cell (APC) or tumor cell, highlighting the major molecular components involved. The T cell receptor (TCR) complex, with CD3 and ζ-chain (CD247), recognizes the antigen (Ag) presented by the MHC II complex on the APC. Co-stimulatory signals are provided by the interaction between CD28 on the T cell and CD80/CD86 on the APC. Inhibitory pathways include CTLA-4 competing with CD28 for CD80/CD86, PD-1 interacting with PDL-1 and PDL-2, and LAG-3 binding to MHC II. Additional interactions are shown by Galectin-3 (Gal-3) and LSECtin on the APC side. The arrows indicate stimulation (green) or inhibition (red) of T cell responses, while the "Y" represents antagonist antibodies that block these interactions. The overall effect of these interactions is summarized at the bottom left, with the resulting decrease in T cell proliferation, cytokine production, and calcium fluxes. Ag, antigen; APCs, antigen-presenting cells; CD80/CD86, cluster of differentiation 80/86; CD4, cluster of differentiation 4; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; Gal-3, galectin-3; LAG-3, lymphocyte-activation gene 3; LSECtin, liver and lymph node sinusoidal endothelial cell C-type lectin; MHC-II, major histocompatibility complex class II; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; PD-L2, programmed death-ligand 2; TCR, T cell receptor [14].

CTLA-4's inhibitory signal, these inhibitors may also facilitate the depletion of Tregs within the tumor microenvironment, potentially enhancing their antitumor efficacy [15, 16]. CTLA-4 inhibitors, such as ipilimumab, have been approved for treating metastatic melanoma and have shown promise in other cancers. Their usage marks a significant advancement in cancer immunotherapy, offering new hope for patients with advanced or treatment-resistant cancers. The clinical efficacy of CTLA-4 blockade has paved the way for exploring combination therapies, including with other checkpoint inhibitors, for enhanced therapeutic outcomes [17]. Interestingly, the activation of the immune system by CTLA-4 inhibitors can lead to autoimmune reactions characterized by irAEs. These irAEs may affect various organs and systems, including the skin, gastrointestinal tract, liver, and endocrine systems. Managing these adverse effects is critical for maintaining the quality of life for patients undergoing CTLA-4 inhibitor therapy. Strategies for managing irAEs include corticosteroids and other immunosuppressive agents, depending on the severity of the symptoms [15].

2.2. PD-1 inhibitors

PD-1 inhibitors target the PD-1 receptor on T cells, preventing its interaction with PD-L1 and PD-L2 ligands on cancer cells and other cells in the tumor microenvironment (Fig. 1). This blockade releases the PD-1-mediated inhibition of T cells, enhancing the immune system's ability to fight cancer. PD-1 inhibitors thus reinvigorate exhausted T cells, promoting antitumor activity [18, 19]. T cell exhaustion refers to a state of dysfunction that T cells can enter when they are chronically stimulated by antigens, as commonly seen in cancer. This condition is characterized by the loss of effector functions, such as cytotoxic activity and cytokine production, and the upregulation of inhibitory receptors (eg, PD-1), which dampen immune responses [20]. Over time, when exposed to antigens for an extended period, some exhausted CD8+ T cells differentiate into stem cell-like or progenitor-like T cells expressing both transcription factor T cell factor-1 (TCF1) and PD-1 [21]. Recent findings have highlighted the significant roles of TCF1+ stem-like progenitor cells within the subset of exhausted T cells in cancer. These cells, marked by their expression of the transcription factor TCF1, exhibit stem cell-like properties that enhance their longevity and functionality, making them essential for sustained immune responses in the tumor microenvironment. Studies have shown that these progenitor cells are associated with improved responses to ICI therapies, suggesting their potential as targets for enhancing cancer immunotherapy outcomes. Specifically, the presence of TCF1+ cells in tumors correlates with better antitumor immunity and an improved capacity to respond to therapies aimed at reversing T cell exhaustion [21-23].

The distinct mechanisms and sites of action for PD-1 compared to CTLA-4 suggest complementary roles in regulating the immune response to cancer [18]. PD-1 inhibitors, including pembrolizumab and nivolumab, have been approved for a variety of cancers, such as melanoma, nonsmall cell lung cancer, renal cell carcinoma, and more. Their application has significantly improved outcomes for patients with these cancers, offering durable responses and, in some cases, leading to long-term remissions. The use of PD-1 inhibitors is rapidly expanding, with ongoing trials investigating their efficacy in other cancer types and in combination with other treatments for synergistic effects [18, 24]. Similar to CTLA-4 inhibitors, PD-1 blockade can lead to irAEs due to enhanced immune activation. However, the spectrum and incidence of irAEs associated with PD-1 inhibitors are generally reported to be less severe than those associated with CTLA-4 blockade [25]. PD-1 inhibitors are generally considered less toxic compared to CTLA-4 blockades due to differences in their mechanisms of action and the extent of their immune system interactions. CTLA-4 inhibitors affect the activation phase of the immune response, which is a critical control point, leading to a broad activation of T cells that can result in more severe and widespread irAEs. On the other hand, PD-1 inhibitors act later in the immune response, primarily at the effector phase within tissues and tumors, leading to a more targeted effect and typically less severe toxicities. A meta-analysis examines irAEs associated with ICI. They analyzed data from 21 randomized phase II/III immunotherapy trials conducted between 1996 and 2016, totaling 11,454 patients. The results indicate that ICIs are linked to increased risks of certain all-grade and high-grade irAEs compared to non-ICI arms. Specifically, PD-1/PD-L1 inhibitors showed a lower risk of high-grade colitis and rash compared to the CTLA-4 inhibitor ipilimumab [26]. In a preclinical study involving co-cultures of human cardiomyocytes and lymphocytes, both ipilimumab and nivolumab demonstrated effective anticancer properties but also induced significant cardiotoxic effects. Despite a comparable increase in the expression of NOD-like receptor (NLR) family pyrin domain containing 3 (NLRP3), MyD88, and p65/nuclear factor kappa-light-chain-enhancer of activated B cells compared to untreated cells, ipilimumab showed more pronounced pro-inflammatory and cardiotoxic effects compared to nivolumab. Moreover, in mice treated with ipilimumab, significant decreases in fractional shortening and radial strain were observed, indicating impaired cardiac function. This was accompanied by increased expression of NLRP3, MyD88, and interleukins (ILs) in the myocardium [27]. Nonetheless, vigilance for irAEs induced by PD-1 inhibitors remains essential, and management strategies may include temporary discontinuation of therapy and the administration of immunosuppressive medications for severe reactions [25].

2.3. PD-L1 inhibitors

PD-L1 inhibitors function by specifically targeting the PD-L1, which is expressed in tumor cells and tumor-infiltrating immune cells (Fig. 1). This expression allows cancer cells to evade the immune system by interacting with the PD-1 receptor on activated T cells, leading to the inhibition of T-cell function and proliferation. PD-L1 inhibitors, such as durvalumab, atezolizumab, and avelumab, block this interaction, thereby enabling the immune system to detect and destroy cancer cells. These inhibitors are engineered to enhance the body's immune response against cancer by preventing the suppression of T-cell activity, allowing for a more robust attack on tumor cells [28]. PD-L1 inhibitors have shown significant promise in the treatment of various cancers, including nonsmall cell lung cancer, urothelial carcinoma, and melanoma, among others. Their application has led to improved survival rates and better disease outcomes in patients, especially those who have not responded well to traditional therapies. Clinical trials and United States Food and Drug Administration (FDA) approvals underscore their efficacy and expanding role in cancer treatment, positioning them as a cornerstone of modern oncology alongside or in combination with other therapeutic modalities [29]. While PD-L1 inhibitors have transformed cancer treatment, their immune-mediated mechanism of action can also lead to the development of irAEs. These irAEs can affect multiple organ systems, including the skin,

gastrointestinal tract, endocrine glands, and more, necessitating careful monitoring and management. The management strategies for these adverse effects include corticosteroids and other immunosuppressive agents to mitigate the severity of the reactions and improve patient quality of life during treatment [30].

2.4. Emerging checkpoint inhibitors

Emerging checkpoint inhibitors target novel immune regulatory pathways beyond the well-characterized PD-1/PD-L1 and CTLA-4 pathways. These include lymphocyte activation gene-3 (LAG-3; Fig. 1), T-cell immunoglobulin and mucin-domain containing-3 (TIM-3; Table 1), and T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domains (TIGIT). These novel targets are involved in regulating the immune response and are being explored for their potential to overcome resistance to existing therapies and to provide additional options for patients who do not respond to current checkpoint inhibitors [14]. Their mechanisms of action involve modulation of different aspects of the immune response, including enhancing T-cell activity, reducing immunosuppression in the tumor microenvironment, and improving the effectiveness of antitumor immune responses. As with PD-1/PD-L1 and CTLA-4 inhibitors, the manipulation of novel immune checkpoints carries the risk of inducing autoimmune reactions by disrupting immune tolerance and promoting autoimmunity. The extent and severity of these potential autoimmune reactions are currently under investigation in clinical trials. Understanding the balance between effective tumor immunity and the risk of autoimmunity is crucial for the development of these novel therapies. Ongoing research aims to identify biomarkers that can predict the risk of autoimmune reactions and to develop strategies to minimize these risks while maximizing therapeutic efficacy.

3. Molecular mechanisms of autoimmunity induced by ICIs

3.1. Activation of autoreactive T cells

ICIs have revolutionized cancer therapy by targeting regulatory pathways in T cells to enhance the immune response against tumors. However, this therapeutic strategy can also disrupt self-tolerance, leading to the activation of autoreactive T cells. The blockade of CTLA-4, PD-1, and PD-L1 pathways can remove inhibitory signals that maintain T cell tolerance to self-antigens. Consequently, T cells previously unresponsive to self-antigens may become activated, initiating autoimmunity. CTLA-4 blockade increases costimulatory signaling by preventing CTLA-4 from outcompeting CD28 for B7 ligands on APCs, leading to enhanced T cell activation and IL-2 production, which is critical for T cell proliferation and further cytokine production. Meanwhile, PD-1 blockade prevents the interaction between PD-1 on T cells and PD-L1 on tumor cells or APCs, rescuing exhausted T cells and enhancing their proliferation and effector functions. This leads to increased secretion of cytokines such as interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α), which are key mediators of inflammatory responses [31]. Evidence suggests that individuals with certain human leukocyte antigen (HLA) alleles, which are associated with a higher risk for autoimmune diseases, may be predisposed to developing ICI-induced autoimmune diabetes and colitis, highlighting a genetic component to the risk of autoimmunity with ICI therapy [32]. While the specific HLA alleles involved can vary depending

Table 1.
Comparative analysis of immune checkpoint molecules and their inhibitors in cancer immunotherapy

Feature	CTLA-4	PD-1	PD-L1	LAG-3	TIM-3
Function	Inhibits early stages of T cell activation	Inhibits T cell activity in peripheral tissues	Ligand for PD-1, inhibits T cell activity	Regulates T cell proliferation and homeostasis	Regulates Th1 immune responses
Expression	T cells	T cells, B cells, and myeloid cells	Various, including tumor and immune cells	T cells, NK cells, and B cells	T cells, NK cells, dendritic cells
Role in cancer	Tumor immune evasion	Tumor immune evasion, associated with exhaustion	Helps tumors escape immune response	Associated with T cell exhaustion and immune escape	Marker of T cell exhaustion, associated with poor prognosis
Inhibitors	Ipilimumab (anti-CTLA-4)	Nivolumab, pembrolizumab (anti-PD-1)	Atezolizumab, durvalumab (anti-PD-L1)	Relatlimab (anti-LAG-3)	Various in clinical trials
Clinical significance	Approved for melanoma and other cancers	Approved for multiple cancers including melanoma, lung, and renal	Approved for urothelial carcinoma, NSCLC, and others	Investigated for melanoma, potential in combination therapies	Emerging target, potential in combination therapies
Combination therapy	Combined with PD-1 inhibitors for enhanced efficacy	Effective when combined with CTLA-4 or other checkpoint inhibitors	Combined with other therapies for enhanced antitumor activity	Shows promise in combination, especially with PD-1 blockade	Co-expression with PD-1 suggests benefit in dual blockade

CTLA-4, cytotoxic T-lymphocyte-associated protein 4; LAG-3, lymphocyte activation gene-3; NSCLC, nonsmall cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; TIM-3, T-cell immunoglobulin and mucin-domain containing-3

on the autoimmune condition, some alleles have been more frequently associated with these risks. For example, HLA-DR4 has been linked to an increased risk of rheumatoid arthritis. HLA-B27 is well-known for its association with ankylosing spondylitis. HLA-DRB1*04 and HLA-DQB1*0302 have been associated with type 1 diabetes. HLA-DRB111:01 has been linked to an increased risk of developing irAEs such as pruritus, while HLA-DQB103:01 has shown a nominally significant association with colitis in patients undergoing ICI therapy [32-35].

The activation of autoreactive T cells involves complex molecular pathways. For example, the inhibition of PD-1/PD-L1 interaction can enhance T cell receptor signaling and cytokine production, leading to the proliferation and activation of T cells, including those with specificity for self-antigens (Fig. 2) [36]. Furthermore, ICIs can also affect Tregs, which play a crucial role in maintaining immune tolerance. The reduction in Treg function or numbers can further promote the activation of autoreactive T cells. The involvement of cytokines, such as IL-17, and the role of the immunoproteasome in antigen processing within the context of autoimmunity have also been explored, indicating that changes in cytokine profiles and antigen presentation contribute to the autoimmune phenomena observed with ICI therapy [37].

3.2. The roles of B cell and humoral immunity

B cells and humoral immunity play significant roles in the pathogenesis of irAEs induced by ICIs. B cells, traditionally known for their roles in antibody production, also influence autoimmunity and have been implicated in the development of irAEs when ICIs disrupt immune tolerance mechanisms. For example, the blockade of immune checkpoints can lead to alterations in B cell populations and functions, which are associated with the development of irAEs. These changes include shifts in B cell subsets and increased production of autoantibodies, contributing to autoimmune responses observed in patients undergoing ICI therapy. The pathomechanisms by which B cells and humoral immunity contribute to irAEs are multifaceted and involve several key aspects of immune regulation and response. Under normal conditions, B cells undergo strict checks to prevent the production of autoantibodies that would target the body's own tissues. However, ICIs can disrupt these checks by blocking inhibitory pathways that regulate B cell tolerance. This disruption can lead to the activation of autoreactive B cells, which produce autoantibodies against self-antigens (Fig. 2). These autoantibodies can form immune complexes or bind directly to tissues, initiating inflammation and tissue damage typical of autoimmune diseases. Notably, B cells are not only producers of antibodies but also important sources of cytokines. ICIs can induce B cells to produce pro-inflammatory cytokines such as IL-6 and TNF-α, which can exacerbate inflammation and lead to tissue damage. These cytokines can also promote the activation and differentiation of other immune cells, further amplifying the immune response. Furthermore, ICIs can alter the distribution and function of various B cell subsets. For example, regulatory B cells (Bregs), which typically suppress immune responses and maintain tolerance, can be diminished in activity or number. On the other hand, effector B cells, which promote inflammatory responses, may become more active. This shift can lead to an overall increase in the inflammatory response, contributing to irAEs. B cells also act as APCs that can present antigens to T cells. ICI treatment can enhance the antigen-presenting capability of B cells, leading to increased activation of T cells. This heightened T cell activity can contribute to the development of irAEs, particularly when self-antigens are presented, leading to autoimmunity. In some cases, chronic inflammation driven by active B cells and T cells can lead to the formation of tertiary lymphoid structures (TLS) within tissues. These structures resemble lymph nodes and can perpetuate local immune responses against self-tissues, contributing to the chronicity and severity of irAEs [38-41].

3.3. Cytokine release and inflammatory cascade

The treatment with ICIs can lead to a significant alteration in cytokine profiles (Fig. 2), characterized by an increase in proinflammatory cytokines such as IFN-γ, TNF-α, IL-6, and IL-17 [36]. Initially, ICIs promote the activation and proliferation of T helper (Th) cells, particularly Th1 and Th17 subsets. Th1 cells are known to produce IFN-γ, which activates macrophages and is crucial for antitumor immunity but can also drive autoimmunity. Th17 cells produce IL-17, a cytokine that plays a role in inflammation and has been implicated in autoimmune diseases. The cytokine environment influenced by ICIs can skew T cell differentiation towards these proinflammatory subsets, contributing to the overall increase in IFN-γ and IL-17 [42]. Furthermore, the nonspecific activation of the immune system can lead to bystander activation of autoreactive T cells that were previously regulated by immune checkpoints. This can result in the production of autoantibodies and inflammatory cytokines, including IL-6, which plays a key role in promoting Th17 differentiation and sustaining inflammation. Thus, the initial increase in cytokines such as IFN-γ and TNF-α can create an inflammatory environment that promotes further immune cell recruitment and activation, leading to a positive feedback loop that amplifies cytokine production. The cytokine changes can disrupt immune homeostasis, leading to tissue damage and clinical manifestations of autoimmunity [43]. Additionally, cytokines such as IL-6 not only contribute to inflammation but also to the suppression of Treg function, which further exacerbates autoimmune responses.

The disruption of immune homeostasis by ICIs can manifest in various forms of autoimmunity, including but not limited to, inflammatory arthritis, thyroiditis, and type 1 diabetes (Fig. 3) [44]. The altered cytokine milieu not only promotes the activation and proliferation of autoreactive T cells but also impacts other immune cells, contributing to a self-perpetuating cycle of inflammation and autoimmunity. The chronic inflammatory state induced by the dysregulated cytokine production can lead to tissue damage and the clinical presentation of autoimmune diseases. Furthermore, the understanding of these processes is critical for developing strategies to mitigate the adverse effects of ICIs while preserving their antitumor efficacy [45].

3.4. Epitope spreading

Epitope spreading is the process by which the immune response, initially targeted at specific antigens, diversifies to recognize additional epitopes within the same antigen (intramolecular spreading) or on different antigens (intermolecular spreading). This phenomenon can exacerbate or perpetuate autoimmune diseases by broadening the immune attack against self-antigens, potentially leading to a more severe or widespread disease. In the context of ICI therapy, epitope spreading may occur as the enhanced immune response against tumor antigens leads to the unintentional targeting of related self-antigens. The inflammatory environment created by ICIs can expose previously hidden self-antigens to the immune system, promoting the activation

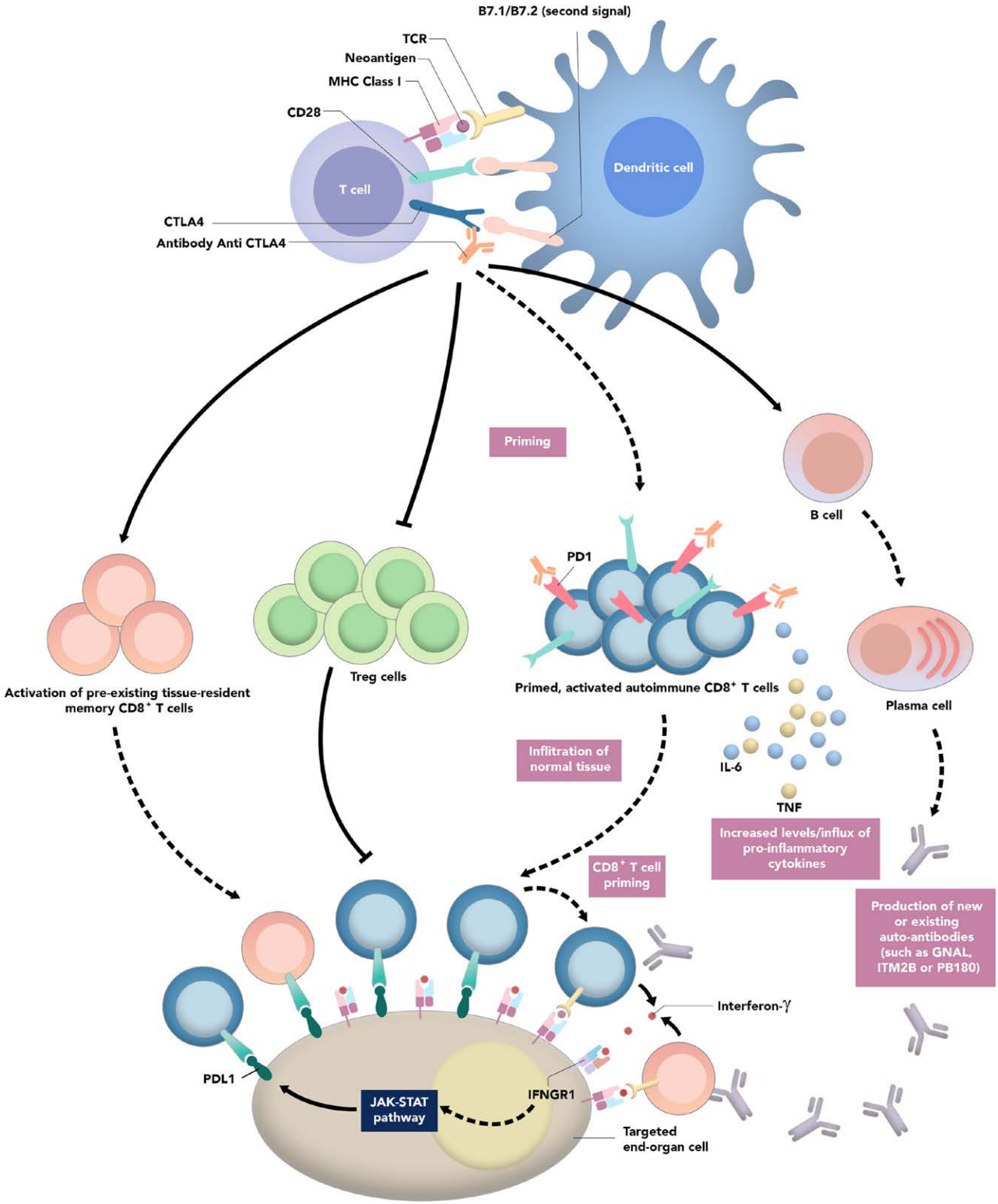

Figure 2. Cascades of autoimmunity induced by checkpoint inhibition. This diagram depicts the process of T cell activation, involving a T cell interacting with a dendritic cell presenting a neoantigen via MHC Class I. CD28 on the T cell provides a co-stimulatory signal upon binding with B7.1/B7.2 on the dendritic cell. The CTLA-4 pathway and its inhibition by an anti-CTLA-4 antibody are also shown. Following priming (initial activation of naive T cells by antigen-presenting cells), the activation of preexisting tissue-resident memory CD8+ T cells and the generation of primed, activated autoimmune CD8+ T cells are illustrated. These cells can infiltrate normal tissue and contribute to the immune response. The diagram also represents the PD-1 pathway on T cells, interaction with PDL1, and subsequent effects, such as cytokine production and signaling through the JAK-STAT pathway in targeted end-organ cells. The effects include increased levels/influx of pro-inflammatory cytokines like IL-6 and TNF, and the production of new or existing auto-antibodies. Interferon-gamma's role is also indicated. The loop involving B cells and plasma cells in the production of cytokines and auto-antibodies completes the depiction of the complex immune response. CD28, cluster of differentiation 28; CTLA4, cytotoxic T-lymphocyte associated protein 4; IFNGR1: interferon-gamma receptor 1; IL-6: interleukin 6; JAK-STAT, janus kinase-signal transducer and activator of transcription; MHC, major histocompatibility complex; PD1, programmed cell death protein 1; PDL1, programmed death-ligand 1; TCR, T cell receptor; TNF, tumor necrosis factor.

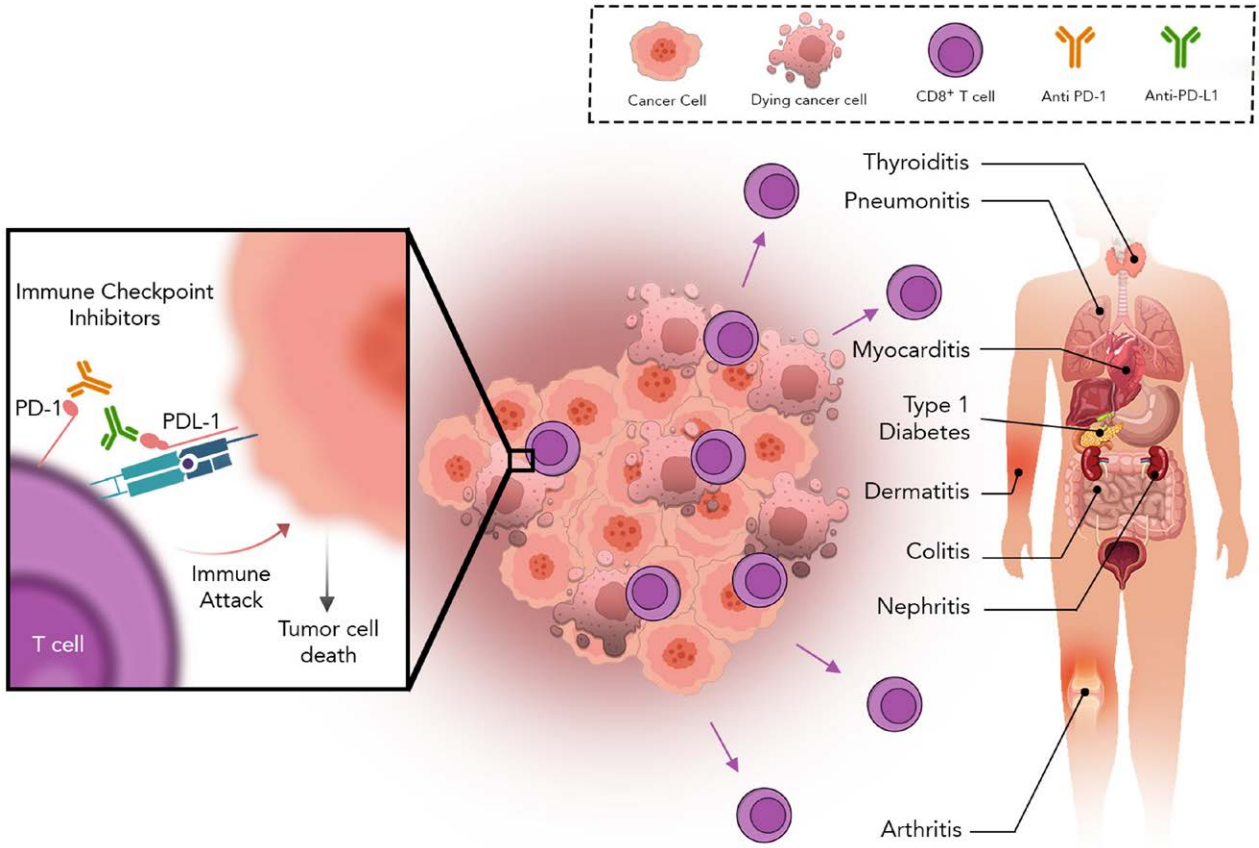

Figure 3. Mechanism of action and systemic adverse effects of immune checkpoint inhibitors. This figure illustrates the mechanism by which immune checkpoint inhibitors target the PD-1/PD-L1 pathway to induce tumor cell death, as well as the potential adverse effects of such treatments. The left side of the image shows a T cell being activated against a tumor cell due to the blockade of the PD-1/PD-L1 interaction by immune checkpoint inhibitors, leading to tumor cell death. The right side outlines various autoimmune-like side effects that can occur as a result of this immune activation, including thyroiditis, pneumonitis, myocarditis, type 1 diabetes, dermatitis, colitis, nephritis, and arthritis. PD1, programmed cell death protein 1; PDL1, programmed death-ligand 1 [44].

of autoreactive T and B cells against these new targets. Epitope spreading has been implicated in various autoimmune diseases, underscoring its significance in autoimmunity pathogenesis and its potential role in ICI-induced autoimmunity [46].

3.5. Genetic and environmental factors

The susceptibility to ICI-induced autoimmunity is influenced by a complex interplay of genetic and environmental factors. As previously described, genetic predispositions, such as specific HLA alleles, can increase the likelihood of developing autoimmune reactions by affecting immune response regulation and antigen presentation [32-35]. Apart from HLA genetic variants, several other genetic variants have been identified that can confer risks toward irAEs associated with cancer immunotherapies. For instance, several studies identified an IL-7 allelic variant rs16906115, an IL-22RA1 rs75824728, and rs113861051 on 4p15 as major risk factors for the development of ICI-associated irAEs. This finding underscores the impact of cytokine-related genetic variants on the risk of irAEs [47, 48]. Furthermore, a Japanese study involving 622 cancer patients aimed to identify variants predicting the risk of nivolumab-induced irAEs. While the study did not find significant associations, it identified single nucleotide polimorphism rs469490 among others as potentially associated, suggesting the need for further research in larger and diverse cohorts to confirm these findings [49]. Furthermore, genetic variations in immune checkpoint pathways may alter the efficacy and safety of ICI therapy, predisposing certain individuals to autoimmune side effects. Rare loss-of-function variants in genes involved in immune regulation can contribute to autoimmunity. For instance, mutations in the *SOCS1* gene, which encodes a suppressor of cytokine signaling, have been identified in patients with early-onset autoimmunity. *SOCS1* acts to inhibit the Janus kinase-signal transducer and activator of transcription pathway, and its haploinsufficiency can lead to increased cytokine signaling and autoimmune manifestations [50, 51]. Next, the expression quantitative trait loci (eQTLs) that affect the expression levels of immune-related genes can also play a role in autoimmunity. Single-cell eQTL mapping has identified cell type-specific genetic control of autoimmune disease, highlighting how genetic variation can impact the immune response at the cellular level and contribute to autoimmune disease susceptibility [52]. Genetic variants affecting pathways involved in T cell activation and differentiation, such as those regulating the balance between Th17 cells and Tregs, can also influence autoimmunity risk. For example, variants that enhance Th17 polarization may predispose individuals to autoimmune conditions due to the pro-inflammatory role of IL-17 [53].

Environmental factors, including prior infections, microbiome composition, and exposure to certain chemicals or drugs, can also modulate immune tolerance and trigger autoimmunity in genetically predisposed individuals. Infections, in particular,

have been shown to initiate autoimmunity through mechanisms such as molecular mimicry and bystander activation, which may be exacerbated by the immune dysregulation induced by ICIs [54]. Dysbiosis, or the imbalance in the microbial community, can lead to the activation of autoreactive T cells and the reduction of Treg functionality, thereby disrupting immune homeostasis. This disruption can promote the development of autoimmune diseases by facilitating the presentation of self-antigens and the production of proinflammatory cytokines. For instance, certain gut bacteria can produce metabolites that affect the differentiation of T cells into proinflammatory Th17 cells or promote the production of anti-inflammatory Tregs, thus influencing susceptibility to autoimmune conditions [55]. Additionally, molecular mimicry between microbial antigens and self-antigens can lead to cross-reactivity and the activation of autoreactive immune cells, further linking microbiome composition to autoimmunity [56]. Exposure to certain environmental chemicals or drugs can also modulate immune tolerance and trigger autoimmunity. These substances can act as adjuvants, stimulating the immune system and promoting the activation of autoreactive T cells. For example, drugs such as procainamide and hydralazine have been associated with drug-induced lupus, a condition where individuals develop autoantibodies and lupus-like symptoms following exposure to these medications. The mechanism behind this phenomenon involves the drugs' ability to induce epigenetic changes, such as DNA demethylation, leading to the overexpression of genes normally silenced in T cells, which in turn can trigger an autoimmune response [57, 58]. Environmental chemicals, including pollutants and endocrine-disrupting compounds, can also influence immune tolerance by affecting gene expression related to immune regulation or by directly stimulating immune cells, thereby increasing the risk of autoimmunity in genetically susceptible individuals [59].

4. Clinical manifestations of autoimmunity in ICI therapy

4.1. Organ-specific autoimmune reactions

ICIs can also initiate irAEs, including organ-specific autoimmune reactions. These manifestations reflect the broader immune activation against cancer cells but may also inadvertently target self-antigens, leading to autoimmunity. Cutaneous irAEs are among the most frequent, appearing as maculopapular rash, pruritus, vitiligo, and more severe conditions like bullous pemphigoid [60, 61]. Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare but severe mucocutaneous irAEs that can occur with ICI therapy. These conditions are characterized by extensive skin detachment and mucosal involvement, often triggered by an immune response that is excessively activated by ICIs. The severity of SJS and TEN can range from mild to life-threatening, with significant morbidity and mortality rates. Recent research has identified an increased risk of SJS and TEN in patients treated with ICIs. For instance, a systematic analysis and meta-analysis found a clear association between ICIs and an increased risk of developing these severe skin reactions. The study assessed SJS/TEN cases reported in clinical trials and the FDA Adverse Event Reporting System (FAERS), confirming a significant association with ICIs, with a median onset time of approximately 25.5 days from the start of therapy. The study also highlighted the severe outcomes associated with these conditions, including a high discontinuation rate of ICIs and a considerable mortality rate, especially for TEN [62]. Early intervention with topical steroids or systemic immunosuppression for severe cases can manage these cutaneous reactions effectively [60]. Historically, corticosteroids were administered with the aim of tempering the severe immune reaction characteristic of SJS/TEN [63, 64]. However, evidence regarding their effectiveness is mixed, and there is concern about potential adverse effects, such as increasing the risk of infections or delaying wound healing [65, 66]. Recently, the National Comprehensive Cancer Network (NCCN) guidelines for the management of immunotherapy-related toxicities suggested using prednisone or methylprednisolone at a dosage of 1 to 2 mg/kg/day along with intravenous immunoglobulin (IVIG) at a dosage of 1 g/kg/day, and possibly other immunosuppressive treatments like etanercept and cyclosporine for managing SJS/TEN, without distinguishing between true SJS/TEN and SJS/TEN-like rashes [61, 67].

Next, colitis is a notable irAE associated with ICIs, characterized by diarrhea, abdominal pain, and bloody stools. Management includes high-dose corticosteroids and, if refractory, drugs such as infliximab [68]. ICIs can also lead to thyroid dysfunction (hyperthyroidism followed by hypothyroidism), adrenal insufficiency, and hypophysitis. These conditions require hormonal replacement therapy and, in the case of hypophysitis, may necessitate lifelong hormonal supplementation [69]. Other reactions include hepatitis, pneumonitis, nephritis, hematological irAEs, and ocular irAEs. Hematological irAEs, including various cytopenias (reductions in the number of blood cells), anemias, and immune thrombocytopenia (ITP), reflect the broad impact of ICIs on the bone marrow and immune system's regulation of hematopoiesis. Meanwhile, ocular irAEs can manifest as uveitis, dry eye syndrome, or more severe conditions such as ocular myositis. Additionally, nephritis associated with ICIs often presents as an acute kidney injury requiring careful management to prevent long-term renal damage [70].

ICIs have also been associated with rare but potentially fatal cardiac autoimmune reactions. These cardiac irAEs can manifest as myocarditis, pericarditis, and arrhythmias, challenging clinicians due to their nonspecific symptoms and potential for rapid progression to severe outcomes. The exact mechanism of ICI-induced cardiac autoimmunity is not fully understood but is thought to involve T-cell-mediated attacks on cardiac tissue, possibly triggered by molecular mimicry or the expression of shared antigens between tumor cells and cardiac muscle. A study reported 2 rare cases of melanoma patients who developed fatal myocarditis after receiving a combination of ipilimumab and nivolumab. Both patients experienced myositis, cardiac electrical instability, and myocarditis with T-cell and macrophage infiltrates. Clonal T-cell populations found in the myocardium matched those in tumors and skeletal muscle [71]. A pharmacovigilance study further demonstrated that myocarditis "only" occurred in 0.27% of patients treated with the ipilimumab and nivolumab combination [71]. Overall, although the incidence of cardiac irAEs is low, the mortality rate among affected patients is notably high, underscoring the importance of early recognition and aggressive management.

Treatment typically involves high-dose corticosteroids and, in some cases, additional immunosuppressive agents such as mycophenolate mofetil (MMF) or tacrolimus. Recent studies also suggest that immunomodulatory drugs such as abatacept and ruxolitinib, when used either individually or in combination, can mitigate the severity of ICI-induced myocarditis and improve patient outcomes. Specifically, MMF, by inhibiting purine synthesis, and tacrolimus, by inhibiting calcineurin,

effectively suppress the immune response that contributes to myocarditis. Their role in this context is critical, especially in steroid-refractory cases, where conventional treatments fail to control inflammation and cardiac symptoms. Abatacept, a CTLA-4 fusion protein, acts by inhibiting T-cell activation. Meanwhile, ruxolitinib, a Janus kinase inhibitor, targets inflammatory pathways that are also implicated in the cardiac toxicity of ICIs. In a reported case, a patient with metastatic renal cell carcinoma developed severe ICI-induced myocarditis that was refractory to steroids. The introduction of MMF, in combination with abatacept, effectively managed the myocarditis and associated myasthenia gravis-like symptoms, leading to clinical improvement and eventual discharge from the hospital [72]. Another study reported a significant reduction in myotoxicity-related fatalities from 60% to 3.4% with the use of systematic screening for respiratory muscle involvement and combined treatment with abatacept and ruxolitinib in patients with severe ICI-induced myocarditis. This strategy involved dose adjustments of abatacept based on CD86-receptor occupancy, highlighting a personalized approach to treatment [73]. Another case report detailed the successful reversal of severe pembrolizumab-induced myocarditis in a young patient using a high dose of abatacept adjusted to ensure significant receptor occupancy, combined with ruxolitinib and corticosteroids, leading to rapid clinical improvement and hospital discharge [74]. Nevertheless, despite these interventions, the prognosis for patients with severe cardiac irAEs remains guarded, highlighting the need for further research into prevention, early detection, and management strategies for this serious complication of ICI therapy [75-78].

4.2. Systemic autoimmune reactions

Beyond organ-specific irAEs, ICIs can induce systemic autoimmune reactions, manifesting as a spectrum of symptoms affecting multiple organ systems simultaneously and often mimic classic autoimmune diseases in their clinical presentation. Unlike organ-specific irAEs, systemic irAEs can present a more complex diagnostic and management challenge due to their broader impact on patient health. Triple M syndrome, an overlapping condition of myositis, myocarditis, and myasthenia gravis, emerges due to the profound immune activation triggered by ICIs, leading to severe muscle and cardiac inflammation [79, 80]. Similarly, cytokine release syndrome (CRS) is a life-threatening condition precipitated by an overwhelming release of cytokines following ICI therapy, which can result in multi-organ dysfunction and shock. Severe cases of CRS have been reported in patients treated with ICIs for lung cancer, where patients experienced symptoms such as high fever, shock, and multi-organ failure. Treatment often requires intensive interventions, including steroids and tocilizumab, an anti-IL-6 receptor antibody [81].

Other systemic reactions include inflammatory arthritis, sicca syndrome, systemic lupus erythematosus-like syndromes, and vasculitis [82]. ICI therapy can induce inflammatory arthritis resembling rheumatoid arthritis or psoriatic arthritis. Patients typically present with joint pain, stiffness, and swelling. Inflammatory arthritis as an irAE is notable for its potential to persist even after discontinuation of ICI therapy, necessitating long-term management strategies. The use of systemic corticosteroids is the first line of treatment, with disease-modifying antirheumatic drugs such as methotrexate being considered for cases that are refractory to steroids or where steroid-sparing treatments are desired [83, 84]. ICIs can also induce symptoms resembling Sjögren's syndrome, characterized by dry mouth and dry eyes (sicca syndrome). This condition reflects underlying inflammation in the salivary and lacrimal glands. Management includes symptomatic relief with artificial tears and saliva substitutes, with more severe cases potentially requiring systemic immunosuppression [85]. Moreover, ICIs can trigger systemic reactions that mimic systemic lupus erythematosus, presenting with a range of symptoms including rash, arthritis, serositis, and hematological abnormalities. The presence of antinuclear antibodies and other autoantibodies can further complicate the clinical picture. Treatment involves systemic corticosteroids and, in cases of severe or refractory disease, the use of immunosuppressive agents such as mycophenolate mofetil [86]. Likewise, vasculitis induced by ICIs can range from localized cutaneous vasculitis to more severe systemic forms, such as granulomatosis with polyangiitis. Clinical manifestations depend on the vessels and organs involved but can include skin lesions, renal impairment, and pulmonary symptoms. Management typically involves corticosteroids, with cyclophosphamide or rituximab being options for severe or life-threatening cases [87].

4.3. Diagnosis, grading, and management

The diagnosis of irAEs requires a high index of suspicion, given their variable presentation and potential for overlap with symptoms of underlying malignancy or other treatment-related side effects. Early and accurate diagnosis is critical, involving clinical assessment, laboratory testing, imaging studies, and sometimes biopsy (Table 2). Regular monitoring of patients receiving ICIs for signs and symptoms of irAEs is essential. Laboratory tests including complete blood count, liver function tests, thyroid function tests, and inflammatory markers can help in early detection.

The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) provides a standardized classification for the severity of adverse events in clinical trials, including those related to cancer immunotherapy. CTCAE categorizes the severity of irAEs as follows: grade 1 (mild): asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. This level represents minimal discomfort and does not interfere with the patient's day-to-day activities. Grade 2 (moderate): minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL). These symptoms cause moderate discomfort and may limit some daily activities but do not require substantial or immediate treatment. Grade 3 (severe): severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL. At this level, the irAEs are sufficiently severe to require hospital intervention. This may include high-dose corticosteroids or other immunosuppressive medications. Grade 4 (life-threatening): life-threatening consequences; urgent intervention indicated. These adverse events require immediate and intensive treatment to prevent death. Finally, grade 5 (death): death related to adverse events [88]. The grading helps in guiding treatment decisions, such as whether to continue, withhold, or discontinue ICI therapy, and whether to initiate immunosuppressive treatments. For instance, mild irAEs (grade 1) may require close monitoring but no treatment alteration, whereas moderate (grade 2) irAEs might necessitate holding the ICI and initiating moderate immunosuppression. Severe (grade 3) and life-threatening (grade 4) irAEs generally require hospitalization,

Table 2.

Diagnostic modalities for detecting ICI-induced irAEs

Organ/system	Diagnostic modality	Description
General/systemic irAEs	Laboratory tests	Complete blood count, liver function tests, kidney function tests, electrolytes, inflammatory markers (e.g., CRP, ESR)
Dermatologic	Dermatological examination	Clinical assessment by a dermatologist
	Skin biopsy	Histopathological examination to confirm diagnosis like lichenoid dermatitis, bullous pemphigoid
Gastrointestinal	Endoscopy	Upper and lower endoscopy to visualize and biopsy the GI tract
	Laboratory tests	Fecal calprotectin, liver function tests, pancreatic enzymes
	Abdominal imaging	CT scan or MRI to assess for inflammation, obstruction, or other abnormalities
Hepatic	Laboratory tests	Liver function tests (ALT, AST, bilirubin, ALP)
	Abdominal ultrasound	To visualize liver for any structural changes
	Liver biopsy	To evaluate the extent of liver damage or inflammation
Endocrine	Laboratory tests	Hormone levels such as cortisol, thyroid function tests, sex hormones
	Imaging	Ultrasound of thyroid, CT or MRI for adrenal glands
Pulmonary	Pulmonary function tests	To assess lung function
	Chest X-ray	Initial assessment for pulmonary changes
	High-resolution CT (HRCT)	Detailed imaging to evaluate interstitial lung disease
	Bronchoscopy	With biopsy for histological examination
Cardiac	ECG	To detect arrhythmias or ischemic changes
	Echocardiogram	To assess cardiac function and structure
	Cardiac MRI	To evaluate myocarditis or other structural changes
	Troponin levels	Biomarkers of cardiac injury
Renal	Laboratory tests	Serum creatinine, urea, electrolytes, urine analysis for proteinuria and hematuria
	Renal ultrasound	To assess kidney size and rule out obstruction
	Kidney biopsy	To determine the specific type of nephritis or other pathology
Neurological	Neurological examination	Clinical assessment by a neurologist
	MRI of the brain and spine	To visualize lesions or areas of inflammation
	Lumbar puncture	Analysis of cerebrospinal fluid for inflammatory markers
	Electroencephalogram (EEG)	To assess for seizures or other electrical activity abnormalities
Musculoskeletal	X-ray	Basic imaging to assess joint structures
	MRI	Detailed imaging to assess soft tissue and joint integrity
	Laboratory tests	Muscle enzymes (e.g., CK), inflammatory markers
	Arthroscopy	Diagnostic and sometimes therapeutic intervention to assess joint health
Ophthalmic	Ophthalmological examination	Comprehensive eye examination by an ophthalmologist
	Fluorescein angiography	To assess retinal blood flow
	OCT (optical coherence tomography)	Detailed imaging of the retina

ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; CK, creatine kinase; CRP, C-reactive protein; CT, computed tomography; ECG, electrocardiogram; ESR, erythrocyte sedimentationrate; irAE, immune-related adverse events; MRI, magnetic resonance imaging; OCT, opticalcoherencetomography.

high-dose corticosteroids, and permanent discontinuation of the ICI [89].

The management of irAEs primarily involves the administration of corticosteroids to reduce inflammation (Table 3). The severity of irAEs dictates the dose and duration of corticosteroid therapy. For severe or corticosteroid-refractory irAEs, several alternative treatment modalities have been explored to manage these complex cases effectively. These include additional immunosuppressive agents such as TNF-α inhibitors, MMF, cyclophosphamide, or other immunomodulators. Additionally, IVIG, biologics (eg, tocilizumab and rituximab), and plasmapheresis could be useful. TNF-α inhibitors, such as infliximab, are particularly useful in managing severe cases of irAEs such as colitis, which are refractory to steroids [99]. TNF-α inhibitors have also been recommended for irAEs such as severe ICI-induced myocarditis and other critical conditions where swift control of inflammation is crucial. However, it is important to note that TNF-α inhibitors are contraindicated in patients with moderate to severe heart failure, indicating the need for careful patient selection and monitoring. While there is a concern that suppressing TNF-α might negatively impact the anticancer efficacy of ICIs, the majority of evidence suggests that at least short courses of TNF inhibitors do not compromise the anticancer effects. Preclinical studies suggest that TNF inhibition might even augment the antitumor effects of ICI therapy while ameliorating irAEs [100]. While, MMF inhibits lymphocyte proliferation and has been utilized as a second-line treatment for managing steroid-resistant irAEs, particularly in cases involving the gastrointestinal tract and liver [101, 102]. For more severe or life-threatening irAEs, such as severe pneumonitis or refractory rheumatological conditions, cyclophosphamide can be used [103]. It acts by suppressing the immune system and reducing inflammation. Tocilizumab, an IL-6 receptor antagonist, has been used successfully in managing irAEs, particularly those involving severe systemic symptoms such as CRS. It helps by directly inhibiting the pathways involved in inflammation [104]. Meanwhile, rituximab, a CD20 monoclonal antibody, targets B cells and has been used in cases of hematological irAEs, such as immune thrombocytopenia and autoimmune hemolytic anemia, as well as dermatological irAEs [105, 106]. Plasmapheresis can be used in life-threatening irAEs to rapidly remove circulating autoantibodies and immune complexes from the blood. It is particularly useful in neurologic and severe cutaneous irAEs where rapid reduction of autoantibodies is necessary [107]. IVIG is used as an immunomodulatory treatment for various autoimmune and inflammatory conditions. It has been shown to be effective in cases of irAEs that are refractory to corticosteroids, providing an alternative that can modulate the immune response without the side effects associated with prolonged corticosteroid use. For instance, IVIG has been successfully used in treating severe dermatological irAEs, offering both clinical remission and a favorable safety profile [105, 108]. The choice of intervention depends on the severity and nature of the autoimmune reaction [109]. Importantly, the treatment of irAEs does not necessarily require discontinuation of

Table 3.

Proposed management of ICI-induced irAEs [90-98]

Organ/system	Specific irAE	CTCAE grade	Treatment options
General	Systemic inflammation	Grade 1	Observation, symptom management
		Grade 2	Corticosteroids, symptom-specific interventions
		Grade 3	High-dose corticosteroids, hospitalization
		Grade 4	Immunosuppressive agents, ICU care
		Grade 5	Supportive care, end-of-life considerations
Dermatologic	Rash, Bullous disease, Stevens-Johnson syndrome	Grade 1	Topical steroids, moisturizers
		Grade 2	Systemic steroids, topical immunomodulators
		Grade 3	Systemic immunosuppressants, TNF-α inhibitors
		Grade 4	Hospitalization, IV immunoglobulin
Gastrointestinal	Colitis	Grade 1	Symptomatic treatment (eg, loperamide for diarrhea)
		Grade 2	Oral steroids, dietary modifications
		Grade 3	IV steroids, infliximab
		Grade 4	Infliximab, vedolizumab, hospitalization
Hepatic	Hepatitis	Grade 1	Monitor LFTs, reduce dose of ICI
		Grade 2	Oral steroids
		Grade 3	High-dose IV steroids, mycophenolate mofetil
		Grade 4	Discontinue ICI, tacrolimus
Endocrine	Hypophysitis, primary adrenal insufficiency, thyroid dysfunction, hypoparathyroidism, type 1 diabetes	Grade 1	Monitor function, adjust hormone replacement
		Grade 2	Hormone replacement therapy (eg, thyroid hormones, insulin, hydrocortisone)
		Grade 3	Increase hormone doses, immunosuppression
		Grade 4	ICU care for crisis management
Pulmonary	Pneumonitis	Grade 1	Monitor symptoms, pulmonary function tests
		Grade 2	Oral steroids, bronchodilators
		Grade 3	High-dose corticosteroids, oxygen therapy
		Grade 4	Mechanical ventilation, cyclophosphamide, infliximab, mycophenolate mofetil
Renal	Nephritis, acute kidney injury	Grade 1	Monitor renal function, hydration
		Grade 2	Corticosteroids, hydration
		Grade 3	High-dose steroids, consider renal biopsy
		Grade 4	Dialysis, more aggressive immunosuppression
Neurologic	Neuropathies, meningitis	Grade 1	Symptomatic treatment, physical therapy
		Grade 2	Oral steroids, IVIG
		Grade 3	High-dose steroids, plasmapheresis
		Grade 4	ICU monitoring, aggressive immunosuppression
Ophthalmic	Uveitis, dry eye syndrome	Grade 1	Artificial tears, monitoring
		Grade 2	Topical corticosteroids, possible referral to ophthalmology
		Grade 3	Systemic corticosteroids, consultation with ophthalmology
		Grade 4	Aggressive immunosuppression, potential hospitalization
Cardiac	Myocarditis, arrhythmias	Grade 1	Monitor function, ECG
		Grade 2	Beta-blockers, ACE inhibitors
		Grade 3	High-dose corticosteroids, heart failure management
		Grade 4	Mechanical support, ICU care
Musculoskeletal	Arthritis, myositis	Grade 1	Analgesics, physical therapy
		Grade 2	NSAIDs, corticosteroids
		Grade 3	Immunosuppressants, referral to rheumatology
		Grade 4	Aggressive immunosuppression, joint surgeries if necessary
Hematological	Anemia, thrombocytopenia, neutropenia	Grade 1	Monitor blood counts, supportive care
		Grade 2	Growth factors, transfusions
		Grade 3	High-dose corticosteroids, IVIG
		Grade 4	Immunosuppressive therapy, plasmapheresis

ACE, angiotensin-converting enzyme; CTCAE, Common Terminology Criteria for Adverse Events; ECG, electrocardiogram; ICI, immune checkpoint inhibitors; ICU, intensive care unit; IVIG, intravenous immunoglobulin; LFTs, liver function tests; NSAIDs, nonsteroidal anti-inflammatory drugs; TNF-α, tumor necrosis factor-alpha.

ICI therapy, especially if the irAEs are mild to moderate and can be controlled with appropriate management. However, severe irAEs may necessitate pausing or discontinuing ICI treatment [110]. Collaborative care involving oncologists, immunologists, endocrinologists, and other specialists is vital for the optimal management of these complex patients.

5. Current strategies and future perspectives to mitigate autoimmune reactions

The advent of ICIs has underscored the need for comprehensive strategies aimed at identifying potential autoimmune risks. Genetic predispositions, such as specific HLA alleles, can influence the likelihood of developing autoimmune reactions to ICIs. Understanding the genetic underpinnings of autoimmunity can help identify individuals at higher risk and guide the development of personalized therapy approaches [111, 112]. Variations in HLA genes can predispose individuals to different immune reactions when exposed to certain drugs [113], including ICIs [114]. Moreover, research has shown that HLA-I homozygosity might serve as a protective biomarker for developing irAEs among patients with NSCLC treated with ICIs, suggesting that a deeper understanding of HLA typing could be crucial for both predicting irAE risk and tailoring ICI therapy to individual genetic profiles [115]. Next, continuous monitoring of immune responses in patients receiving ICIs is crucial for the early detection of autoimmune reactions. This involves regular assessment of clinical symptoms and laboratory markers indicative of immune activation or suppression [116]. Several biomarkers have been identified to potentially predict irAEs due to

ICI therapy. These biomarkers span a range of biological indicators, including blood cell counts, cytokines, autoantibodies, as well as microbiome compositions. Baseline absolute eosinophil counts (AEC) have been associated with the development of irAEs. Patients with higher baseline AECs are more likely to experience toxicities related to ICI therapy. This relationship has been validated across different types of cancers, suggesting that eosinophils could serve as a predictive biomarker for ICI-related toxicity [117]. Various cytokines and chemokines have also been investigated as biomarkers to predict irAEs. For instance, changes in levels of IL-6, IL-10, and TNF-α have been found to correlate with the onset and severity of irAEs. Furthermore, the composition of the gut microbiome has been explored as a potential predictor of irAEs. Specific microbial signatures may influence the immune system's response to ICIs and predict the likelihood of developing irAEs [112]. Several comprehensive review articles have discussed the potential of existing and novel biomarkers to predict irAEs [112, 118].

The evolution of personalized medicine has the potential to revolutionize ICI therapy by tailoring treatment to individual patient profiles. This approach leverages genomic, proteomic, and immunologic data to predict response to ICIs and the risk of developing autoimmunity. By integrating this comprehensive data, clinicians can make informed decisions about the use of ICIs, potentially selecting those with a lower risk of inducing autoimmunity in susceptible individuals [116]. Additionally, personalized medicine can guide the use of combination therapies, balancing efficacy with safety to optimize patient outcomes. Research into immunoproteasome, a variant of proteasome present in immune cells, has revealed its involvement in autoimmune pathology, including myocarditis associated with ICIs. Inhibitors of immunoproteasome have shown promise in mitigating autoimmune-related cardiac pathology in mouse models, suggesting a potential pathway for managing autoimmune myocarditis in humans, possibly including patients with ICI-related autoimmunity [37]. Next, the development of next-generation ICIs involves balancing efficacy with reduced autoimmunity risk. This includes enhancing selectivity, combination therapies, and personalized therapies. Research is ongoing to develop ICIs that more selectively target the immune checkpoints involved in tumor evasion while minimizing the impact on pathways critical for maintaining self-tolerance [119]. Another promising avenue is the use of nanotechnology to enhance the delivery of ICIs, potentially improving their specificity and reducing off-target effects [120-122]. Furthermore, combining ICIs with other therapeutic modalities, such as targeted therapy or chemotherapy, may enhance antitumor efficacy while potentially reducing the incidence or severity of autoimmune reactions [123]. At last, the search for novel therapeutic targets aims to expand the arsenal of ICIs by identifying new immune checkpoints that can be modulated to activate antitumor responses with a reduced risk of autoimmunity. Research has begun to explore beyond CTLA-4 and PD-1/PD-L1 to include targets such as LAG-3, TIM-3, and TIGIT, which may offer distinct advantages in terms of efficacy and safety [116].

6. Summary

The exploration of ICIs has underscored a complex interplay between the potentiation of antitumor immunity and the inadvertent induction of irAEs, presenting a dual-edged sword in cancer therapy. Critical insights have emerged, highlighting the delicate equilibrium required between activating the immune system to target malignancies and maintaining immune tolerance to prevent autoimmune diseases. The therapeutic efficacy of ICIs, while remarkable, is tempered by the risk of irAEs, underscoring the necessity of a balanced immune response for optimal treatment outcomes. This balance is not static but rather a dynamic interplay that can be influenced by genetic predispositions, environmental factors, and individual immune landscapes. The advancement of personalized medicine approaches offers promising avenues to tailor ICI therapy to individual risk profiles, potentially mitigating the risk of irAEs while preserving antitumor efficacy. Moreover, the identification of novel therapeutic targets and the development of next-generation ICIs aim to refine this balance further, enhancing the specificity and safety of these therapies. However, to fully realize the potential of ICIs and extend their benefits to a broader patient population, continued research is imperative. This research should focus on deepening our understanding of the mechanisms underlying ICI-induced autoimmunity, identifying predictive biomarkers for irAEs, and developing strategies to modulate the immune response more precisely. Through these endeavors, the goal is to expand the therapeutic window of ICIs, enabling more cancer patients to receive these life-saving therapies with minimized risk of irAEs.

Conflicts of interest

The authors have no financial conflicts of interest.

Author contributions

Sutanto: conception of study, writing of manuscript, revisions, and approval of final draft. Safira: writing of manuscript, revisions, visualization, and approval of final draft. Fetarayani: writing of manuscript, revisions, supervision, and approval of final draft.

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