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REVIEW

Biomarkers associated with immune-related adverse events induced by immune checkpoint inhibitors

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Abstract

Immune checkpoint inhibitors (ICIs) constitute a pivotal class of immunotherapeutic drugs in cancer treatment. However, their widespread clinical application has led to a notable surge in immune-related adverse events (irAEs), significantly affecting the efficacy and survival rates of patients undergoing ICI therapy. While conventional hematological and imaging tests are adept at detecting organ-specific toxicities, distinguishing adverse reactions from those induced by viruses, bacteria, or immune diseases remains a formidable challenge. Consequently, there exists an urgent imperative for reliable biomarkers capable of accurately predicting or diagnosing irAEs. Thus, a thorough review of existing studies on irAEs biomarkers is indispensable. Our review commences by providing a succinct over-view of major irAEs, followed by a comprehensive summary of irAEs biomarkers across various dimensions. Furthermore, we delve into innovative methodologies such as machine learning, single-cell RNA sequencing, multiomics analysis, and gut microbiota profiling to identify novel, robust biomarkers that can facilitate precise irAEs diagnosis or prediction. Lastly, this review furnishes a concise exposition of irAEs mechanisms to augment understanding of irAEs prediction, diagnosis, and treatment strategies.

Key Words: Immunotherapy; Immune checkpoint inhibitors; Immune-related adverse events; Biomarkers; Cancers

Core tip: The development of effective biomarkers for precise immune-related adverse events (irAEs) prediction and diagnosis is urgently needed. Therefore, a comprehensive review of current studies on irAEs biomarkers is essential. This review encompasses major irAEs and provides an overview of existing biomarkers for prediction, diagnosis, and prognosis. Additionally, it explores diverse approaches for identifying novel, reliable biomarkers, including machine learning, single-cell RNA sequencing, multiomics analysis, and gut microbiota assessment. Lastly, the review delves into the mechanisms underlying irAEs to enhance comprehension and guide the prediction, diagnosis, and management of these events.

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INTRODUCTION

Immunotherapy has revolutionized cancer treatment, exemplified by the 2011 approval of ipilimumab, catalyzing the development of diverse immune checkpoint inhibitors (ICIs) for malignancy[1]. ICs, crucial for immune tolerance and response modulation, regulate immune cell activation[1,2]. ICIs disrupt inhibitory signals within the tumor microenvironment, enhancing immune responses against tumor antigens[2]. However, ICI therapy often triggers immune-related adverse events (irAEs), affecting nearly all organs[3]. Notably, in melanoma studies, adverse events occurred in 86% of nivolumab-treated patients, 86% of ipilimumab-treated patients, and 96% of combination therapy recipients[4]. While rare, some irAEs can be fatal, particularly early in treatment with anti-CTLA-4 antibodies inducing colitis[5]. Understanding irAEs mechanisms and identifying biomarkers for prediction and management are critical.

Despite research progress, irAE mechanisms remain elusive[6]. Diagnosis and management depend on traditional tests, necessitating non-ICIs factor exclusion[7]. Reliable irAEs biomarkers for prediction, diagnosis, and severity assessment are urgently needed. Recent studies have identified potential biomarkers, but a comprehensive summary and novel biomarker discovery methods are lacking. This review provides an overview of irAEs biomarkers – blood cells, cytokines/chemokines, proteins, and immunogenetics – and explores emerging biomarker identification methodologies. Additionally, it offers a brief overview of irAEs types and mechanisms to inform future biomarker investigations.

irAEs

Understanding irAEs characteristics, symptoms, and incidence across organs is crucial for biomarker discovery, offering physiological parameters and dynamic indicators of irAE incidence and location, varying with tumor and ICI types. Common irAEs include cutaneous and gastrointestinal (GI) toxicity, hepatotoxicity, renal toxicity, endocrine toxicity, hematotoxicity, joint toxicity, neurotoxicity, cardiotoxicity, and pulmonary toxicity. Here, we summarize irAEs and specific organ symptoms (Figure 1).

GI toxicity

irAEs affecting the GI tract are both common and severe[8]. Notably, anti-CTLA-4 agents are associated with higher rates of GI toxicity than are anti-PD-1/PD-L1 antibodies[9]. Colitis is the predominant manifestation, with PD-1 inhibitors reported to cause adverse effects such as diarrhea, abdominal pain, nausea, vomiting, ileus, and hematochezia, indicative of various GI diseases[10]. Conversely, GI irAEs with anti-CTLA-4 agents mainly present as colitis, characterized by symptoms like diarrhea, abdominal pain, rectal bleeding, nausea, and fever[11]. Despite these apparent symptoms, reliable biomarkers are essential to differentiate GI irAEs from other GI lesions caused by factors such as bacterial infections.

Hepatotoxicity

Hepatotoxicity, although rare with ICI clinical use, poses challenges in diagnosis and management due to variable symptoms and severity[12]. The incidence rates vary, with the lowest rates (0.7%–2.1%) observed with PD-1 inhibitors, intermediate rates (0.9%–12%) with PD-L1 or standard dose CTLA-4 inhibitors, and the highest rates (13% and 16%) with combined CTLA-4/PD-1 inhibitor therapy and high-dose CTLA-4 inhibitors[13]. Hepatitis associated with ICIs is generally nonfatal, with chronic diseases like viral hepatitis or nonalcoholic steatohepatitis considered risk factors[9]. For instance, a 2018 report by De Martin *et al*[14] described granulomatous hepatitis in users of CTLA-4 inhibitors, while lobular hepatitis was associated with PD-1/PD-L1 inhibitor use[14].

Nephrotoxicity

Renal injury in the context of ICIs treatment is identified by markers such as serum creatinine, cystatin C, and presence of hematuria. Acute interstitial nephritis is the most common renal-related immunotoxicity, with other forms including membranous nephropathy, minimal change disease, and thrombotic microangiopathy. The incidence of acute kidney

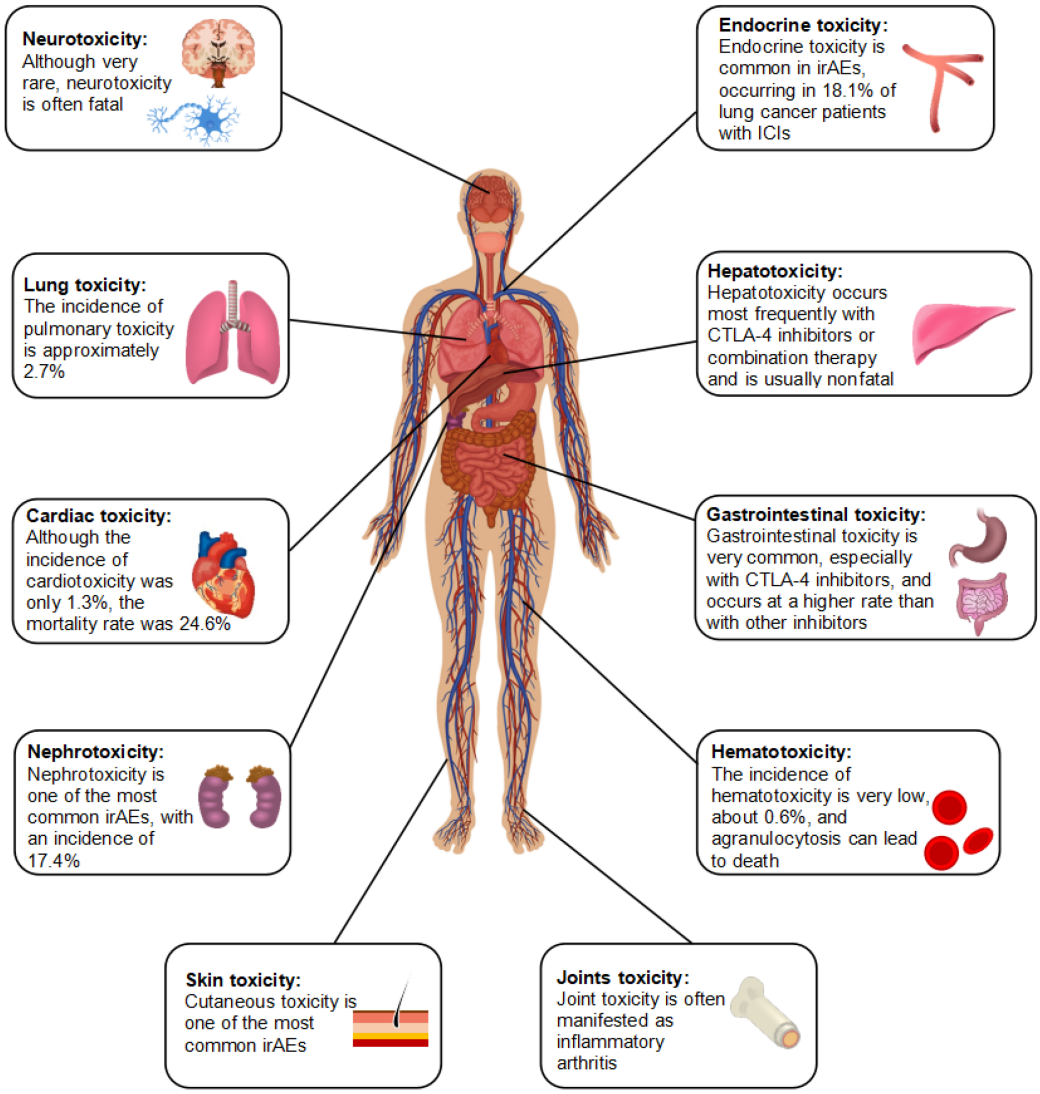

Figure 1 Immune-related adverse events in different organs. Immune checkpoint inhibitors therapy causes immune-related adverse events primarily in the brain, lungs, heart, kidneys, skin, joints, endocrine system, liver, intestines, and blood. irAEs: Immune-related adverse events.

injury (AKI) in ICI treatment is ~17.4%, often associated with irAEs, hypertension, and cerebrovascular disease[15]. A 2019 case reported by Shingarev *et al*[16] revealed extensive interstitial inflammation, tubulitis, and severe tubular damage on renal biopsy[16].

Endocrine toxicity

Endocrine toxicity, a prevalent immune-related adverse effect, primarily affects the thyroid gland and is characterized by glandular or tissue damage leading to hormone imbalance[17]. Hypophysitis, type 1 diabetes, and adrenal dysfunction are also frequently observed, with thyroid dysfunction (indolent thyroiditis, hypothyroidism, thyrotoxicosis, or thyroid storm) more common in PD-1 inhibitor therapy and hypophysitis in CTLA-4 inhibitor therapy[18]. In lung cancer treatment, endocrine toxicity has an incidence of 18.1%[17], often causing irreversible disruptions[19]. Hormones can serve as biomarkers for assessing endocrine toxicity due to their aberrant levels resulting from damage to the endocrine system.

Hematotoxicity

Hematotoxicity is a rare critical concern due to its challenging treatment and high mortality rate[20]. Neutropenia, in particular, is associated with increased morbidity and mortality from infectious complications, with severe agranulocytosis often proving fatal[21]. In a 2021 study by Kramer *et al*[20], the incidence of hematological toxicity was ~0.6%. Thrombocytopenia and leukopenia were the most prevalent, at 34% each, followed by anemia at 28%. Other less common manifestations included hemophagocytic lymphohistiocytosis at 4%, and aplastic anemia, acquired hemophilia A, and coagulopathy at 2% each. Additionally, two patients had both thrombocytopenia and neutropenia, one patient had both anemia and thrombocytopenia, and one patient died (2%, agranulocytosis)[20].

Joint toxicity

Arthritis is a common rheumatic condition in ICI treatment, occurring in ~3% of cases[22]. Patients undergoing combination therapy are more prone to knee arthritis, often presenting with one or both knees initially affected. Conversely, those on ICI monotherapy tend to have small joint involvement initially. Patients receiving combination therapy involving PD-1/PD-L1 and CTLA-4 may present with knee involvement without initial small joint symptoms, significantly increased C-reactive protein (CRP) levels, and have a reactive arthritis-like phenotype[23].

Skin toxicity

Skin toxicity is one of the most common adverse events, seen in 90% of patients treated with CTLA-4 inhibitors, 70% of those treated with PD-1/PD-L1 inhibitors, and almost all of those receiving combination therapy[24]. The common symptoms comprise maculopapular, pruritic, psoriasiform, and lichenoid rashes, accompanied by other conditions like acneiform rashes, vitiligo-like lesions, autoimmune skin conditions, sarcoidosis, or nail and oral mucosal changes[25,26]. Furthermore, maculopapular symptoms were observed in 60% of patients receiving CTLA-4 inhibitors; histopathology findings comprise superficial perivascular dermatitis, perivascular dermatitis, and lichenoid dermatitis. Psoriasis may arise when using PD-1/PD-L1 inhibitors[27].

Neurotoxicity

Neurotoxicity associated with ICI therapy is rare yet potentially fatal. In 2020, Duong *et al*[28] investigated 18 patients with neurotoxicity. Their symptoms included central demyelinating disease (28%), autoimmune encephalitis with large grey matter involvement (17%), aseptic meningitis (6%), myasthenia gravis (17%) with myositis (6%), sensorimotor polyneuropathy (11%), and hypophysitis (17%). Unfortunately, six patients died[28]. Diagnosing neurotoxic events during ICIs treatment remains challenging due to the clinical diversity of irAEs, emphasizing the critical need for accurate diagnostic modalities for brain irAEs[29].

Cardiac toxicity

Cardiac toxicity is rare but poses a significant threat due to its potential lethality. The most common manifestation is myocarditis, often resulting in arrhythmias. Additionally, cardiotoxicity encompasses pericardial disease, vasculitis, and arrhythmias unrelated to myocarditis[30]. In a report by Rubio-Infante *et al*[31], cardiotoxicity was documented in 1.3% of cases, with myocarditis accounting for 50.8% of incidents and a mortality rate of 24.6%[31].

Lung toxicity

Pulmonary toxicity occurs in ~2.7% of cases, influenced by tumor type and the specific ICIs used. Patients with lung or kidney cancer face a heightened risk, with PD-1 inhibitors more likely to induce pulmonary toxicity compared to PD-L1 inhibitors. Symptoms, such as dyspnea, reduced exercise tolerance, and cough, may also include fever and chest pain. Identifying the causative agent and excluding inflammatory symptoms from viruses, bacteria, or fungi is crucial. Imaging techniques and biomarkers aid in this process, with computed tomography being valuable for excluding infectious pneumonia during pulmonary toxicity screening[32,33].

BIOMARKERS FOR irAEs

Current research attempts to identify biomarkers for predicting, diagnosing, assessing severity, and prognosticating irAEs, categorized into four groups: blood cell-based, cytokine/chemokine, immunoglobulin/other secreted proteins, and immunogenetic biomarkers (Figure 2). Blood cell counts, easily obtained from patients, reflect immune system status and show promise as irAEs biomarkers. Serum-derived cytokines/chemokines, integral to inflammation, provide insights into irAEs progression through continuous monitoring. Autoantibodies and abnormal cellular secretions detectable *via* biochemical assays indicate irAEs development. Immunogenetics, assessing patient-specific genetic single nucleotide polymorphisms (SNPs), human leukocyte antigen (HLA), and pre-existing autoimmune diseases, may predispose individuals to irAEs, enabling susceptibility screening.

Blood-cell-based biomarkers

Blood cells play critical roles in the immune response and likely contribute to irAE development. During ICI treatment, patients undergo routine monitoring of various blood markers, yielding extensive clinical data on the correlation between blood cell counts and irAEs. Various studies have investigated this relationship, focusing on changes in leukocyte types and numbers. Table 1 summarizes several blood markers for irAEs, underscoring the importance of analyzing different immune cells to understand immune dynamics and identify irAEs.

Lymphocytes, including T cells and B cells, are essential in specific immunity. Reschke *et al*[34] investigated T cell clusters, identifying increases in $CD4^+CD38^+HLA\text{-}DR^+$ T cells, $CD4^+$ effector memory T cells ($CD4^+CD45RA^-CD45RO^+CCR7^-$), $CD8^+CD38^+$ T cells, and CD8+ effector memory T cells ($CD8^+CD45RA^-CD45RO^+CCR7^-$) during irAEs occurrence, suggesting their potential as predictors[34]. Similarly, Nishimura *et al*[35] observed that low $CD21^{lo}$ B cell levels at baseline correlated with development in patients with renal cancer receiving combination therapy with anti-CTLA-4 and anti-PD-1 drugs[35].

Another study observed correlations between the severity of irAEs and changes in total white blood cell count and relative lymphocyte count, indicating a higher incidence of grade 3/4 lung/ GI irAEs with more pronounced alterations

Table 1 Blood cell biomarkers of immune-related adverse events

Biomarker	ICI type	Patients	Study cohort	irAE type	Judgment	Ref.
$CD4^+$ T cell	CTLA-4, PD-1	17	8/17 (47%) irAEs, among them, 4 multiple irAEs	NA	$CD4^+$ T cells increased during irAEs	[34]
$CD8^+$ T cell	CTLA-4, PD-1	17	8/17 (47%) irAEs, among them, 4 multiple irAEs	NA	$CD8^+$ T cells increased during irAEs	[34]
B cell	CTLA-4, PD-1	23	13/23 (57%) irAEs	NA	Low levels of CD21lo B cells at baseline in the irAE group, and significantly increase after the first cycle of combined CTLA-4 and PD-1 inhibitor treatment	[35]
White blood cell count and relative lymphocyte count	PD-1	101	38/101 (38%) irAEs. Among them, 6 multiple irAEs, 2 combined irAEs, 4 continuous irAEs	NA	An increase in white blood cell and a decrease in relative lymphocyte count were associated with the occurrence of G3/4 irAEs	[36]
Absolute eosinophil count	PD-1	321	18% ICI pneumonia in patients with an average age of 62.7 years	Lung irAEs	The absolute eosinophil count of patients with ICI-pneumonia was significantly higher than that of no ICI-pneumonia patients	[37]
Absolute lymphocyte count	PD-1	171	73/171 (42.7%) irAEs	NA	At 2 wk after initiation of treatment, an increase in absolute lymphocyte count was significantly associated with an increased risk of irAEs	[38]
Neutrophil/lymphocyte ratio	PD-1	275	121/275 (44.0%) irAEs, 86 with one irAEs, 26 with two irAEs, 9 with three or more irAEs, Severe irAEs (> grade 3) occurred in 29 (10.5%)	Lung irAEs	Increased neutrophil/lymphocyte ratio can predict the severity of subsequent irAEs pneumonia with high accuracy, and the higher the NLR value, the more severe irAEs occurs	[39]
	PD-1	92	45/92 (48.9%) irAEs	NA	Before treatment, neutrophil/lymphocyte ratio > 2.3 was significantly associated with an increased risk of irAEs	[40]
Lymphocyte/monocyte ratio	PD-1	92	45/92 (48.9%) irAEs	NA	Before treatment, lymphocyte/monocyte ratio > 1.6 significantly reduced the risk of irAEs	[40]
Absolute monocyte count	CTLA-4, PD-1, PD-L1	470	33% irAEs	NA	The incidence of irAEs was significantly associated with higher baseline absolute monocyte count	[41]
Platelet count	CTLA-4, PD-1, PD-L1	470	33% irAEs	NA	The incidence of irAEs was significantly associated with higher baseline platelet count	[41]
Platelet/lymphocyte ratio	CTLA-4, PD-1, PD-L1	470	33% irAEs	NA	The incidence of IrAEs was significantly associated with lower baseline platelet/lymphocyte ratio	[42]

irAEs: Immune-related adverse events; ICI: Immune checkpoint inhibitors.

[36]. Chu *et al*[37] identified a heightened risk of ICI pneumonia in patients with an elevated baseline absolute eosinophil count, establishing an optimal threshold for predicting pneumonia risk (0.125×10^9 cells/L)[37]. Elevated absolute lymphocyte count was also associated with an increased risk of irAEs[38]. Matsukane *et al*[39] reported a significant increase in the neutrophil/lymphocyte ratio (NLR) during occurrence of irAEs, particularly in pneumonia cases, corre-

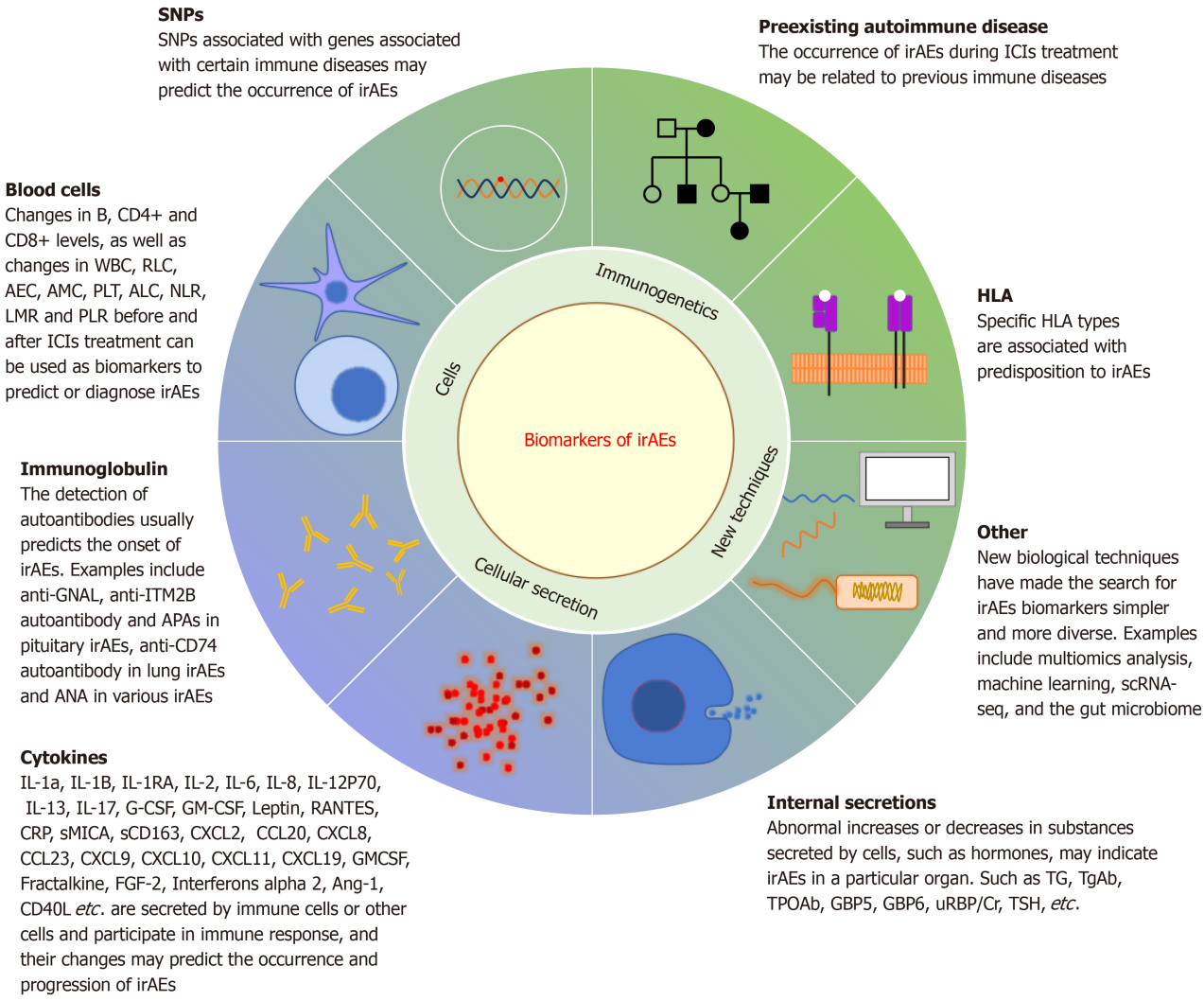

Figure 2 The biomarkers of immune-related adverse events. Biomarkers encompass cellular components, secretions, and immunogenetics, with emerging technologies poised to unveil novel biomarkers. Cellular biomarkers primarily entail variations in blood cell counts and ratios, while cellular secretions comprise cytokines, hormones, and antibodies. Immunogenetics focuses on identifying genetic predispositions to immune-related adverse events (irAE) from a genetic perspective. These categories collectively offer insights into potential biomarkers and genetic factors associated with irAE susceptibility. WBC: White blood cell count; RLC: Relative lymphocyte count; AEC: Absolute eosinophil count; AMC: Absolute monocyte count; PLT: Platelet count; ALC: Absolute lymphocyte count; NLR: Neutrophil/lymphocyte ratio; LMR: Lymphocyte/monocyte ratio; PLR: Platelet/lymphocyte ratio; CRP: C-reactive protein; sMICA: Soluble major histocompatibility complex class I chain-related protein A; TG: Thyroglobulin; GBP5: Guanylate binding protein 5; GBP6: Guanylate binding protein 6; uRBP/Cr: Urine retinol binding protein/urine creatinine; APAs: Anti-pituitary antibodies; TSH: Thyroid stimulating hormone; ANA: Antinuclear antibody; scRNA-seq: Single-cell RNA sequencing; irAEs: Immune-related adverse events; ICI: Immune checkpoint inhibitors; IL: Interleukin; GM-CSF: Granulocyte-macrophage colony-stimulating factor; RANTES: Regulated on activation, normal T cell expressed and secreted; sCD: Soluble CD; CXCL: C-X-C motif chemokine ligand; CCL: C motif chemokine ligand; FGF: Fibroblast growth factor; TgAb: Anti-thyroglobulin antibodies; TPOAb: Thyroid peroxidase antibodies; HLA: Human leukocyte antigen; SNPs: Single nucleotide polymorphisms.

lating with irAE severity[39]. Additionally, Egami *et al*[40] found that an NLR > 2.3 before treatment was a significant predictor of irAEs risk. Their study also highlighted the lymphocyte-to-monocyte ratio, with a high baseline level (lymphocyte-to-monocyte ratio > 1.6) predicting a lower risk of irAEs[40]. Elevated NLR was significantly associated with irAE development in both studies, suggesting its potential as a biomarker for irAEs in future research.

Further investigations by Michailidou *et al*[41] involving 470 patients revealed associations between several blood indicators and irAEs incidence. Parameters such as absolute monocyte count > 0.29 K/μL, platelet count > 145 K/μL, and platelet/lymphocyte ratio ≤ 534 at baseline were linked to a higher risk of irAEs[41].

Cytokines

Cytokines, pivotal in immune response modulation, have emerged as potential contributors to irAE development and severity. Their roles in inflammation and autoimmune disease underscore their relevance as predictive biomarkers[42] (Table 2). The study by Kurimoto *et al*[43] explored biomarkers of irAE-associated thyroid dysfunction, identifying elevated serum interleukin (IL)-1β, IL-2, and granulocyte-macrophage colony-stimulating factor (GM-CSF) levels at baseline in 26 patients. Reduced IL-8, G-CSF, and monocyte chemotactic protein-1 levels were significantly associated with irAE-related thyroid dysfunction during early ICI treatment[43]. IL-2 plays diverse roles in immunoregulation,

Table 2 Cytokines biomarkers of immune-related adverse events

Biomarker	ICI type	The number of patients	Study cohort	irAEs type	Judgment	Ref.
IL-1β, IL-2, GM-CSF	CTLA-4, PD-1	26	13/26 (50%) irAEs	Thyroid dysfunction	ICI-thyroid dysfunction patients had higher levels of serum IL-1β, IL-2 and GM-CSF at baseline	[43]
IL-8, G-CSF, MCP-1	CTLA-4, PD-1	26	13/26 (50%) irAEs	Thyroid dysfunction	The early decrease of IL-8, G-CSF and MCP-1 levels was significantly correlated with the occurrence of thyroid irAEs	[43]
G-CSF, Leptin and RANTES	PD-1	38	11/38 (29%) irAEs	NA	Serum G-CSF and RANTES levels were significantly increased and leptin levels were significantly decreased in irAE patients. RANTES was statistically correlated with irAE incidence	[48]
Il-6, CRP	CTLA-4, PD-1	16	13/16 (81%) irAEs	NA	In the early stages of irAEs, serum IL-6 and CRP levels were significantly higher than at baseline	[52]
CRP	CTLA-4, PD-1	37	100% irAEs, 25/37 (68%) two or more irAEs, 14/37 (38%) multiorgan irAEs	NA	CRP was significantly increased from baseline to the onset of irAEs	[53]
IL-6	CTLA-4, PD-1	17	12/17 (71%) irAEs	NA	The peak of IL-6 predicted the occurrence of irAEs	[54]
sMICA	CTLA-4	77	47% irAEs	NA	A high baseline serum level of sMICA predicted a low incidence of irAEs	[57]
sCD163	PD-1	1	The 58-year-old patient had metastatic melanoma	HLH	High levels of sCD163 were elevated during irAEs	[59]
IL-17, Ang-1, CD40L	CTLA-4, PD-1	52	28/52 (54%) grade 1 to 2 irAEs, 24/52 (46%) grade 3 to 4 irAEs	irAE-related dermatitis and pneumonia	Baseline plasma concentrations of Ang-1 and CD40L were significantly higher in patients with irAEs dermatitis; baseline IL-17 in patients with irAEs pneumonia was significantly different from that in non-irAE patients	[60]
IL-6, CXCL2, CCL20, CXCL8, CCL23	CTLA-4, PD-1, PD-L1	78	34% irAEs with receiving anti-PD1 /PDL1, 60% irAEs with receiving combination therapy. 1 irAEs with receiving anti-CTLA4 monotherapy	NA	At baseline, IL-6, CXCL2, CCL20, CXCL8 and CCL23 levels were significantly higher in the irAEs group	[63]
CXCL9, CXCL10, CXCL11 and CXCL19	CTLA-4, PD-1, PD-L1	78	34% irAEs with receiving anti-PD1 /PDL1, 60% irAEs with receiving combination therapy. 1 irAEs with receiving anti-CTLA4 monotherapy	NA	At baseline, patients with irAEs had lower levels of CXCL9, CXCL10, CXCL11, and CXCL19	[63]
CYTOX score (G-CSF, GMCSF, Fractalkine, FGF-2, IFNα2, IL-12p70, IL-1a, IL- 1B, IL-1RA, IL-2, IL-13)	CTLA-4, PD-1	98 + 49	98 patients were in the discovery cohort and 49 patients were in the validation cohort	NA	High expression of 11 cytokines in the CYTOX score was associated with severe irAEs	[64]

sMICA: Soluble major histocompatibility complex class I chain-related protein A; CRP: C-reactive protein; irAEs: Immune-related adverse events; ICI: Immune checkpoint inhibitors; IL: Interleukin; GM-CSF: Granulocyte-macrophage colony-stimulating factor; sCD: Soluble CD; HLH: Hemophagocytic lymphohistiocytosis; RANTES: Regulated on activation, normal T cell expressed and secreted; MCP-1: Monocyte chemotactic protein-1; CXCL: C-X-C motif chemokine ligand; C motif chemokine ligand; FGF-2: Fibroblast growth factor 2; IFNα 2: Interferon alpha 2.

including the stimulation of cytotoxic activity in $CD8^+$ T cells and NK cells, regulation of T-cell differentiation, and modulation of cytokine secretion of IL-1β, tumor necrosis factor-, and interferon- (IFN-γ)[44,45]. GM-CSF exhibits immunomodulatory effects in autoimmune diseases, demonstrating inhibitory properties against experimental autoi-

mmune thyroiditis in murine models[46]. Notably, early reduction of IL-8 was associated with improved prognosis in patients with malignant melanoma treated with anti-PD-1 therapy[47]. These findings highlight the potential of cytokines as valuable biomarkers for irAE prediction and monitoring.

In a separate study, serum levels were analyzed in 38 patients with advanced non-small-cell lung cancer undergoing treatment with PD-1 inhibitors. Patients experiencing irAEs showed significantly elevated G-CSF levels and regulated on activation, normal T cell expressed and secreted (RANTES), compared to those without irAEs. Conversely, leptin levels were significantly lower in patients with irAEs at week 4. Following multivariate analysis, only changes in RANTES levels correlated significantly with the incidence of irAEs[48]. Notably, the PD-1/PD-L1 pathway plays a crucial role in regulatory T-cell-mediated elimination of graft-versus-host disease (GVHD) in murine models. RANTES, known for its involvement in GVHD pathogenesis, acts as a chemokine for various immune cells, potentially mitigating GVHD severity in mice[49,50]. The role of RANTES in irAE development resulting from PD-1 inhibitors warrants further investigation.

CRP is a key component of the immune response, induced by IL-6 through the JAK/STAT3 pathway, thereby exacerbating inflammation[51]. A study by Husain *et al*[52] analyzed blood samples from 80 of 160 patients, revealing significantly elevated IL-6 and CRP levels in early irAEs compared with baseline[52]. Abolhassani *et al*[53] similarly found elevated CRP levels in 93% of patients at irAE onset compared with baseline, with CRP elevations preceding clinical symptoms in 42% of patients[53]. However, no significant changes in IL-6 levels were observed in their study. Wahl *et al*[54] noted peak IL-6 levels associated with irAEs in patients with melanoma, further emphasizing the role of IL-6 in irAE development[54]. Collectively, these findings highlight the potential of IL-6 and CRP as biomarkers for enhancing the diagnosis of irAEs when used in combination.

Major histocompatibility complex class I chain-related protein A (MICA), a ligand of *NKG2D*, is upregulated in stressed cells, including tumors, potentially reducing tumor immunogenicity by downregulating *NKG2D* expression, thereby dampening NK and T-cell activation[55,56]. Felix *et al*[57] found that higher baseline soluble MICA (sMICA) levels were associated with a lower incidence of irAEs in patients with melanoma treated with anti-CTLA-4 inhibitors. Elevated sMICA levels may suppress NK and T-cell activation, influencing the development of irAEs[57]. However, while high sMICA levels may predict a lower incidence of potential irAEs, they also have the potential to attenuate the response to ICI therapy. Further research is needed to elucidate the precise role of sMICA in irAEs and its impact on ICI therapy outcomes.

Soluble CD163 (sCD163) serves as an indicator of macrophage expansion and overactivation[58]. A study conducted by Sadaat *et al*[59] revealed elevated sCD163 levels (6384 ng/mL) in a patient undergoing treatment with a PD-1 inhibitor who subsequently developed hemophagocytic histiocytosis (HLH). HLH, although rare, poses significant risks and underscores the critical need for early diagnosis and intervention during ICI therapy. Further exploration with expanded study cohorts could yield valuable insights into the utility of sCD163 as a biomarker for HLH during ICIs treatment[59].

IL-17 plays a pivotal role in proinflammatory immune responses and has been implicated in dysregulation, acute respiratory distress syndrome, allergic pneumonia, and autoimmune diseases. Tyan *et al*[60] observed elevated baseline angiotensin-1 and CD40 ligand levels in patients with irAE dermatitis, as well as increased baseline IL-17 levels in patients with irAE pneumonia[60-62], suggesting its potential predictive value in irAEs, particularly those related to lung manifestations.

The combination of multiple cytokines as biomarkers holds promise for more accurate identification of irAEs. Khan *et al*[63] conducted an analysis of serum cytokine levels in 65 ICI patients and 13 controls before treatment, at 2–3 wk, and 6 wk post-treatment. They found that baseline IL-6, C-X-C motif chemokine ligand (CXCL) 2, C motif chemokine ligand (CCL) 20, CXCL8, and CCL23 levels were significantly higher in patients with irAEs, while CXCL9, CXCL10, CXCL11, and CXCL19 were lower. These findings suggest a potential link between increased cytokines associated with T-cell activation and autoimmune disease post-treatment, indicating susceptibility to irAEs in individuals with dysregulated immune systems[63]. Similarly, Lim *et al*[64] investigated cytokine combinations in predicting irAEs, reviewing serum cytokines across ICIs treatment stages in 147 patients. They identified 11 cytokines (G-CSF, GM-CSF, fractalkine, fibroblast growth factor 2, IFNα2, IL-12P70, IL-1A, IL-1B, IL-1RA, IL-2, and IL-13) that were significantly elevated in severe irAEs at baseline and early ICI treatment, forming the Cytokine Toxicity Score, which accurately predicted irAE severity[64].

Cytokines, as markers of inflammation, show promise as biomarkers for irAEs, supported by robust large-scale studies. Future research endeavors should consider additional factors such as viral inflammation to further refine cytokine accuracy in predicting irAEs.

Autoantibodies and metabolic abnormalities

Numerous studies have detected autoantibodies, typically targeting the organ where irAEs occur. The development of irAEs in an organ may lead to abnormal secretion and fluctuations in hormone or metabolite levels. Continuous monitoring for the presence of autoantibodies and changes in hormone or metabolite levels may offer valuable insights into diagnosing irAEs (Table 3).

In studies investigating irAEs affecting the thyroid, patients underwent testing to detect antithyroid autoantibodies. Notable observations included the extravasation of thyroglobulin during thyroid inflammation. Kurimoto *et al*[43] reported significant correlations between changes in thyroglobulin levels from baseline to early ICIs treatment and the occurrence of irAEs in patients with irAE-related thyroid dysfunction. During the early phase of ICI treatment, thyroid-stimulating hormone receptor antibodies and thyroid peroxidase autoantibodies were notably higher in the irAE group than non-irAE group[43]. Elevated baseline thyroid-stimulating hormone levels may also predict the development of irAEs, reflecting its regulatory role in the thyroid gland. Luongo *et al*[65] reported a higher risk of hypothyroidism when baseline thyroid-stimulating hormone exceeded 1.67 mIU/L[65]. Similarly, autoantibodies were detected in studies of pituitary irAEs involving 62 patients. Positive anti-pituitary autoantibodies were found in patients with ICI-induced

Table 3 Autoantibodies and metabolic abnormalities biomarkers of immune-related adverse events

Biomarker	ICI type	No. of patients	Study cohort	irAEs type	Judgment	Ref.
Thyroglobulin	CTLA-4, PD-1	26	13/26 (50%) irAEs	Thyroid dysfunction	The titers of TgAb and TPO in the irAE group were significantly higher after ICI treatment	[43]
TgAb, TPOAb	CTLA-4, PD-1	26	13/26 (50%) irAEs	Thyroid dysfunction	Serum Tg level in irAE group increased significantly before/after treatment	[43]
Thyroid-stimulating hormone	CTLA-4, PD-1	96	36/96 (37.5%) irAEs	Thyroid gland irAEs	High thyroid-stimulating hormone levels at baseline are associated with a higher risk of hypothyroidism	[65]
Anti-pituitary antibodies	CTLA-4, PD-1	62	17/62 (27%) ICI- ICI-induced isolated adrenocorticotropic hormone deficiency, 5/62 (8%) ICI-induced hypophysitis	Pituitary gland irAEs	Patients with ICI-induced isolated adrenocorticotropic hormone deficiency showed positive anti-pituitary antibodies at baseline and after treatment, and patients with ICI-induced hypophysitis showed positive anti-pituitary antibodies after treatment and before onset, and anti-pituitary antibodies can be used as biological predictors	[66]
Anti-GNAL and anti-ITM2B autoantibody		9 + 20	Study cohort: 3 hypophysitis, 6 non-hypophysitis; Confirmed cohort: 5 pituitaritis, 15 non-pituitaritis	Pituitary gland irAEs	Anti-GNAL and anti-ITM2B were associated with irAE hypophysitis	[67]
Anti-CD74 autoantibody		8 + 32	Study cohort: 2 pneumonia, 6 non-pneumonia; Confirmed cohort: 10 pneumonia, 22 non-pneumonia	Lung irAEs	Anti-CD74 autoantibody is associated with irAE pneumonia	[67]
Antinuclear antibody	PD-1	83	6/18 (33.3%) irAEs in antinuclear antibody positive group. 21/65 (32.3%) irAEs in antinuclear antibody negative group		The incidence of irAEs increased with antinuclear antibody titer	[68]
Urine retinol binding protein/urine creatinine	CTLA-4, PD-1, PD-L1	50	37/50 (74%) irAEs	Kidney irAEs	During the occurrence of ICI-induced acute kidney injury, the urine retinol binding protein/urine creatinine value of patients was significantly higher	[69]
Guanylate binding protein 5, Guanylate binding protein 6	CTLA-4, PD-1	19	All 19 patients were suspected of cardiac irAEs	Heart irAEs	Guanylate binding proteins 5 and 6 were significantly upregulated in ICI-induced myocarditis compared with dilated cardiomyopathy and virus-induced myocarditis	[70]

irAEs: Immune-related adverse events; ICI: Immune checkpoint inhibitors; TgAb: Anti-thyroglobulin antibodies; TPOAb: Thyroid peroxidase antibodies.

isolated adrenocorticotropic hormone deficiency at baseline and post-treatment, and in those with ICI-induced hypophysitis post-treatment and pre-onset, suggesting a predictive biomarker for pituitary irAEs[66]. Tahir *et al*[67] showed an association between anti-GNAL and anti-ITM2B and ICIs hypophysitis and between anti-CD74 autoantibodies and ICIs pneumonia. An immunohistochemical analysis revealed *GNAL* and *ITM2B* expression in pituitary epithelium, and CD74 was moderately expressed in normal human lung tissues[67]. Moreover, autoantibodies with a broader activity, rather than targeting a specific organ, may serve as potential biomarkers of irAEs. In the safety research of PD-1 inhibitors in patients with advanced non-small-cell lung cancer, antinuclear antibody positivity showed no significant association with irAE occurrence, although irAE incidence tended to increase with rising antibody titer[68]. A significant increase in autoantibody presence or titer in patients undergoing ICI therapy should suggest the consideration of irAEs develop-

ment.

Organ metabolic dysregulation induced by irAEs can lead to changes in metabolite levels. Retinol-binding protein serves as a biomarker for renal proximal tubule dysfunction. Isik *et al*[69] demonstrated that in cases of AKI induced by ICIs, the urine retinol binding protein/creatinine ratio was significantly elevated in patients with ICI-induced AKI compared with those without, aiding in the clinical differentiation of ICI-induced AKI from other causes[69]. Similarly, alterations in cellular metabolism may indicate the onset of irAEs. The IFN-γ pathway, involving guanylate binding proteins 5 and 6, was investigated in ICI-associated myocarditis (ICIM). Transcriptome analysis revealed significant upregulation of guanylate binding proteins 5 and 6 in patients with ICIM, compared with those with dilated cardiomyopathy and virus-induced myocarditis. The involvement of the IFN-γ pathway in the pathogenesis of ICIM was highlighted, with IFN-γ pathway activation leading to upregulation of PD-L1 in mice, thereby dampening cytotoxic T cell immune responses in mouse models[70,71].

The detection of autoantibodies may serve as a precursor or indicator of impending irAEs, prompting the testing of patients with multiorgan irAEs for antibody presence to assess the potential of autoantibodies as biomarkers. Moreover, abnormal metabolic changes should be considered during ICIs treatment, as they may arise from organ damage due to irAEs.

Immunogenetics

Immunogenetics, at the intersection of immunology and genetics, delves into the genetic underpinnings of immune phenomena and gene regulation during immune responses. The emergence of genomics and high-throughput sequencing technologies has fortified the groundwork for exploring the genetic predisposition to immune diseases[72]. In investigations of irAEs, susceptibility to specific irAEs can be discerned through immunogenetic analysis and characterization of HLA. The insights from immunogenetic biomarkers, as outlined in Table 4, shed light on the intricate interplay between genetic factors and immune dysregulation in irAEs.

Previous studies have unveiled associations between certain HLA types and susceptibility to complex diseases. Similarly, HLA types warrant attention in inquiries into irAE susceptibility. In comprehensive research encompassing patients with pituitary irAEs, insulin-dependent diabetes mellitus, encephalitis, pruritus, and colitis, seven HLA blood types exhibited significant correlations with irAEs. Notably, Yano *et a*[73] observed markedly higher frequencies of the HLA-DR15, HLA-B52, and HLA-CW12 genes in the pituitary irAEs patient group compared to the healthy cohort in their exploration of pituitary irAEs. The linkage of HLA-DR15 to induced IL-17 production[73], alongside the association of elevated IL-17 levels with irAEs in cytokine biomarker investigations, hints at a potential predictive role in irAE development. Further exploration of HLA-DR15 and IL-17 promises insights into the underlying mechanisms of the irAEs that they mediate. Similarly, scrutiny of HLA-CW12 and HLA-DR15 in other studies has revealed elevated positive rates in patients with ICI-induced isolated adrenocorticotropic hormone deficiency and ICI-induced hypophysitis[66], underlining their relevance to pituitary irAE development. Stamatouli *et al*[74] identified a significant predominance of HLA-DR4 (76%) in patients with irAE-associated insulin-dependent diabetes mellitus, compared to American Gasol (17.3%) and spontaneous type 1 diabetes mellitus, offering a potential avenue for pre-emptive identification of high-risk populations for irAE-associated diabetes and exploration of underlying mechanisms[74]. Furthermore, *HLA-B*27:05* expression exhibited significant correlation with irAE-associated encephalitis[75], although validation with larger patient datasets is warranted[76]. Additionally, associations between *HLA-DRB1*11:01* expression and pruritus, and *HLA-DQB1*03:01* expression and colitis were observed by Hasan Ali *et al*[77] in a study involving 102 patients with metastatic tumors, with *HLA-DQB1*03:01* significantly associated with colitis development[77]. While several HLA studies have implicated certain types in triggering specific irAEs, the reliability of conclusions remains tempered by small sample sizes, necessitating further investigation with larger patient cohorts.

Pre-existing autoimmune disease emerges as a significant inducer of irAEs. Screening of 4438 patients revealed a correlation between the presence of autoimmune disease, defined by either strict or loose criteria, and the incidence and severity of irAEs following treatment[78]. Advancements in high-throughput sequencing technologies have significantly contributed to the understanding of SNPs in disease research, particularly in the context of irAEs associated with ICIs therapy. Recent evidence suggests that specific gene SNPs may play a role in predisposing individuals to irAEs[79-89].

Abdel-Wahab *et al*[87] conducted a study of the genomes of 44 patients with irAEs and 45 patients without, identifying 30 SNPs. Among these, 12 were associated with an increased risk of irAEs, while 18 were associated with a decreased risk. Notably, four genes in the increased risk group were linked to autoimmune disease and inflammation. Several SNPs in genes associated with autoimmune diseases have been identified. For example, SNPs in the *GABRP*, *DSC2*, *BAZ2B*, and *SEMA5A* genes have been linked to various autoimmune conditions[79-83]. Conversely, in the group with a reduced risk of irAEs, five SNPs were localized to four genes associated with inflammation or autoimmune disease, including *ANKRD42*, *PACRG*, *Robo1*, and *GLIS3*[84-89].

Furthermore, a study on *miRNA-146a*, known for its regulatory function in immune cells, found that knocking it out in a mouse model significantly increased the incidence of severe irAEs. The presence of the SNP rs2910164 located on this gene was associated with an elevated risk of irAEs, reduced progression-free survival, and increased neutrophil counts at baseline and during ICIs treatment[90].

The above-mentioned immunogenetic biomarker research represents a significant advancement in predicting irAEs. By conducting immunogenetic tests before treating patients with ICIs, it may be possible to anticipate the patient's susceptibility to certain irAEs.

Table 4 Immunogenetic biomarkers of immune-related adverse events

Biomarker	ICI type	No. of patients	Study cohort	irAEs type	Judgment	Ref.
HLA-DR15, HLA-B52, HLA-Cw12	CTLA-4, PD-1	11	9 HLA-DR15, 7 HLA-B52, 7 HLA-CW12	Pituitary irAEs	In 11 patients, gene frequencies of HLA-DR15, HLA-B52, and HLA-CW12 were significantly higher in the irAEs-developing group	[73]
HLA- Cw12, HLA- DR15, HLA- DQ7 and HLA-DPw9	CTLA-4, PD-1	62	17/62 (27%) ICI-induced isolated adrenocorticotropic hormone deficiency, 5/62 (8%) ICI-induced hypophysitis	Pituitary irAEs	The positive rates of HLA-CW12, HLA-DR15, HLA-DQ7, and HLA-DPW9 were significantly higher in patients with ICI-induced isolated adrenocorticotropic hormone deficiency, and the positive rates of HLA-CW12 and HLA-DR15 were significantly higher in patients with ICI-induced hypophysitis	[66]
HLA-DR4	PD-1, PD-L1	2960	27/2960 (0.9%) insulin dependent diabetes mellitus	Insulin-dependent diabetes mellitus	The expression of *HLA-DR4* gene is related to the incidence of insulin dependent diabetes mellitus	[74]
HLA-B*27:05	PD-L1	290	7/290 (2%) ICI-associated encephalitis	Encephalitis	The occurrence of irAEs encephalitis was significantly correlated with *HLA-B *27:05* expression	[75]
*HLA-DRB1*11:01, HLA-DQB1*03:01*	PD-1, PD-L1, CTLA-4	102	59/102 (58%) irAEs	Itching, colitis	The expression of *HLA-DRB1*11:01* was related to the occurrence of pruritus. The expression of *HLA-DQB1*03:01* was associated with colitis	[77]
Pre-existing autoimmune disease	CTLA-4, PD-1, PD-L1	4438	It was divided into strict criteria group for autoimmune diseases, lenient criteria group and control group		The prevalence of irAEs was higher in the strict criteria group and the loose criteria group than in the group without pre-existing autoimmune disease	[78]
Single nucleotide polymorphism (30 markers)	CTLA-4, PD-1, PD-L1	89	44/89 (49%) irAEs		A total of 30 variants or single nucleotide polymorphism were identified. Twelve of these were associated with an increased risk of irAEs and 18 with a reduced risk	[87]
MIR146A SNP rs2910164	PD-1, PD-L1	167	The study was conducted in mice and validated with data from cancer patients treated with ICI		MIR146A single nucleotide polymorphism rs2910164 can be used as a biomarker to predict severe irAEs in ICI patients	[90]

irAEs: Immune-related adverse events; ICI: Immune checkpoint inhibitors; HLA: Human leukocyte antigen.

NEW METHODS FOR BIOMARKER IDENTIFICATION

While extensive research has been dedicated to identifying biomarkers for irAEs, the current focus has predominantly been on blood biomarker titers, which limits the scope of biomarkers obtained through this method. Additionally, most studies to date have concentrated on singular aspects of assessment, lacking comprehensive, multifaceted analyses. However, new methodologies are emerging that enable the examination of irAE biomarkers from multiple perspectives. Utilizing innovative biological analysis techniques such as multiomics, single-cell RNA sequencing (scRNA-seq), machine learning, and gut microbiota analysis holds promise for identifying a broader array of biomarkers capable of predicting, diagnosing, and prognosticating irAEs (Figure 3). These advanced techniques offer a more comprehensive understanding of irAEs mechanisms and enable the development of more accurate predictive models for clinical application.

Integrated analysis of multiomics

To achieve a profound understanding of human diseases, it is imperative to delve into molecular mechanisms across

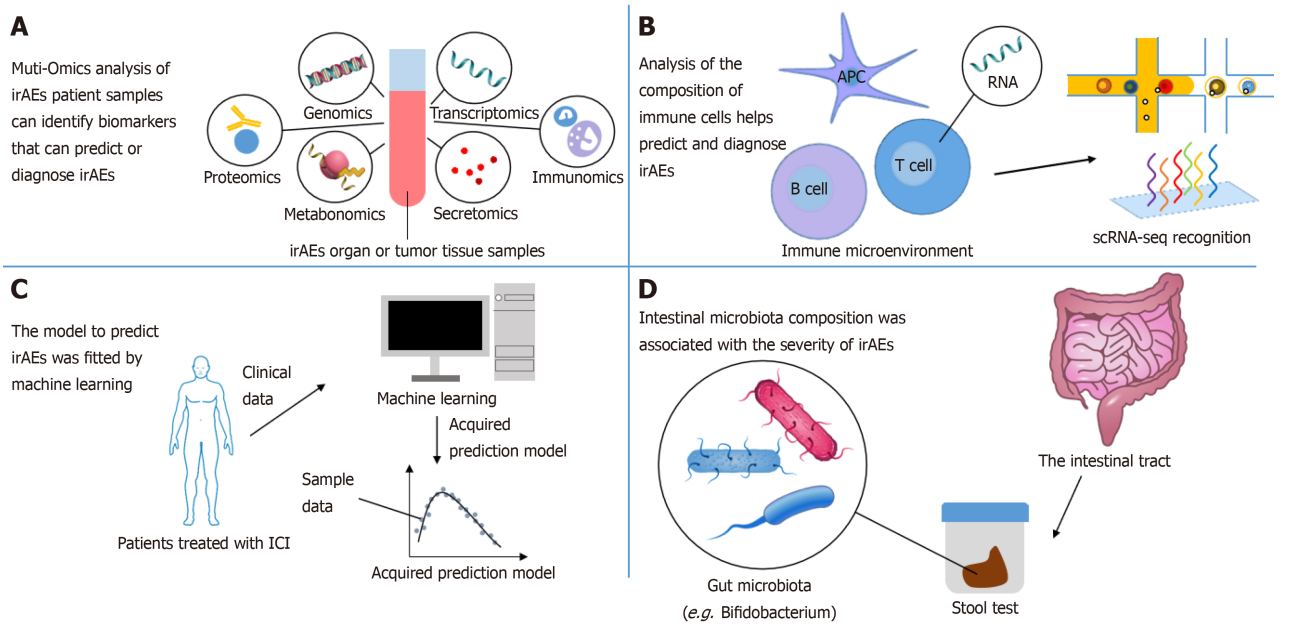

Figure 3 Methods that enable the discovery of new biomarkers. This includes multiomics analysis, single-cell RNA sequencing, machine learning, and gut microflora analysis. A: Integrated analysis of mutiomics; B: Single-cell RNA sequencing; C: Machine learning; D: Gut microbiota. scRNA-seq: Single-cell RNA sequencing; irAEs: Immune-related adverse events; ICI: Immune checkpoint inhibitors; APC: Antigen-presenting cells.

multiple levels, encompassing the genome, epigenome, transcriptome, proteome, and metabolome. The emergence of omics technologies has heralded an era of data proliferation across these diverse layers, collectively known as multiomics data[91]. Integrated analysis of such multiomics data furnishes a treasure trove of insights, facilitating systematic exploration of molecular intricacies. This methodology has been extensively harnessed in immunological research to decipher immune variability among populations and the underlying molecular cascades[92]. The copious volume of multiomics data generated annually lays the groundwork for exhaustive analysis[93].

In a study by Jing *et al*[94], multiomics analysis was leveraged to scrutinize the correlation between the odds ratios of irAEs across various cancers and multiomics factors. They unveiled a binary linear-regression model involving LCP1 and ADPGK that proficiently predicted irAEs occurrence. Similarly, another inquiry by Jing *et al*[94] scrutinized the nexus between gender and irAEs using a diverse array of datasets, including clinical trials, pharmacovigilance data, and The Cancer Genome Atlas OMICS data. Their findings indicated no statistical discrepancy among results derived from different algorithms, suggesting no discernible sex linkage to the incidence of irAEs[95]. Multiomics analysis has been instrumental in appraising the effects of ICI treatment, carrying profound implications for irAE research. In a study by Huang *et al*[96] focusing on PD-L1 inhibitors, multiomics analysis was used to delineate distinct patterns of T cells expressing PD-L1 within the tumor microenvironment and identify factors prognosticating ICI efficacy. This approach presents a potent strategy for discerning patient cohorts poised to derive maximal benefits from ICIs therapy.

scRNA-seq

The advancement and refinement of scRNA-seq techniques have sparked a paradigm shift in our ability to comprehensively dissect the composition and dynamics of immune cells[97]. By harnessing scRNA-seq in irAE research, we unlock the potential to identify a spectrum of immune cell subsets intricately involved in irAE development and progression. In a recent groundbreaking study led by Lozano *et al*[98], peripheral blood samples from melanoma patients undergoing ICI treatment underwent rigorous analysis *via* single-cell sequencing, bulk RNA sequencing, and T-cell receptor sequencing. This integrative approach unveiled compelling associations between the abundance of CD4 memory T cells, T-cell receptor diversity, and the severity of irAEs[98]. While the utility of scRNA-seq in irAE research is still emerging, insights gleaned from studies focusing on ICI treatment efficacy hold promise. Pfister *et al*[99] delved into biomarkers for stratifying patients for optimal therapeutic response, utilizing scRNA-seq to scrutinize and categorize immune cells within the tumor microenvironment. Their findings suggested that patients with hepatocellular carcinoma, particularly those with nonviral hepatocellular carcinoma due to nonalcoholic steatohepatitis, might exhibit diminished responsiveness to immunotherapy, correlating with poorer outcomes with ICI therapy. This attenuated response was ascribed to aberrant T-cell activation culminating in tissue damage and compromised immune surveillance[99]. Similarly, a study on the benefits of ICI therapy unveiled PD-1hiCD8$^+$ T cells as predictive markers of ICI treatment response across diverse cancers[100]. In the realm of irAE research, leveraging scRNA-seq to scrutinize organ tissues impacted by irAEs promises to unravel changes in cellular composition and abundance, potentially unearthing novel cellular biomarkers.

Machine learning

Recent strides in artificial intelligence (AI) technology are reshaping the landscape of medicine, particularly in the realm of predicting immunotherapy responses[101]. Within this transformative domain, machine learning finds pervasive

application in biological research, encompassing tasks such as fitting data to predictive models or discerning intricate data patterns[102]. Serving as a potent ally in biomarker exploration, machine learning empowers researchers to analyze vast datasets derived from samples, crafting models adept at assessing a diverse array of irAEs. Through iterative refinement *via* continuous training, these models can achieve heightened accuracy. For example, Iivanainen *et al*[103] harnessed two electronic patient-reported outcome datasets as inputs for a machine-learning-based predictive model. This sophisticated model adeptly detected and predicted the occurrence of irAEs, emerging as a robust predictor of irAEs [103]. Similarly, machine learning methodologies used in studies on ICI efficacy offer profound insights for biomarker research in irAEs. Johannet *et al*[104] amalgamated deep learning analysis of histological samples with clinical data, culminating in the development and validation of a model predicting treatment outcomes in advanced melanoma patients. This model effectively stratified patients into high- and low-risk categories for disease progression, showing robust performance[104]. In another study focusing on biomarkers for ICI efficacy, tumor samples from patients with cancer treated with ICIs underwent sequencing targeting immuno-oncology genes. Machine learning algorithms were deployed to construct a predictive model for ICIs efficacy[105]. In this pioneering study, machine learning emerged as a pivotal tool for developing models to predict the efficacy of ICIs.

Gut microbiota

The gut microbiota's composition has emerged as a pivotal factor associated with the efficacy of ICIs[106]. Research conducted by Wang *et al*[107] demonstrated that vancomycin-pretreated mice exhibited exacerbated colitis when treated with CTLA-4 antibody, whereas pretreatment with *Bifidobacterium* significantly ameliorated immunopathology without compromising the ICI response[107]. Sakurai *et al*[108] observed a correlation between moderate GI irAEs and favorable ICI treatment outcomes. Their analysis identified Enterobacteriaceae as associated with effective ICI treatment and the management of GI irAEs, as demonstrated by a comprehensive analysis of microbial composition and transcriptional data from the host mucosa[108]. The profound impact of gut microbes on the immune system and the efficacy of immunotherapy underscores their potential as biomarkers for irAEs.

MECHANISM of irAEs

The intricate mechanism of irAEs is pivotal for optimizing treatment outcomes and mitigating their impact on cancer therapy. A deeper comprehension of these mechanisms not only aids in identifying biomarkers implicated in irAE pathogenesis and treatment response but also offers valuable insights for irAE management, thus minimizing treatment-related toxicity.

Research into the dynamics of the immune system unveils that irAEs originate from peripheral tolerance impairment beyond the tumor microenvironment. This leads to immune system activation and subsequent self-antigen attack[109], often resulting in organ-specific inflammatory symptoms. Key players in this process include antigen-specific T-cell responses, autoantibodies, B cells, and cytokines[110]. Histological analysis of inflammation sites indicates a notable infiltration of activated T cells during irAEs[111]. CTLA-4 blockers induce irAEs characterized by diverse T-cell receptor lineages and heightened $CD4^+$ and $CD8^+$ T-cell proliferation[112], while PD-1/PD-L1 blockers typically lead to activated T-cell infiltration into normal tissues[111]. Alterations in immune cell populations, activity, and types serve as crucial clues to irAE mediation. Emerging evidence suggests that some irAEs involve monocytes, with PD-1 inhibitors inducing cardiotoxicity through macrophage polarization[113]. The gut microbiome exerts a profound influence on irAEs and ICI efficacy[114]. Studies have demonstrated a correlation between the severity of irAEs and gut microbiota composition. For instance, research in a colitis mouse model showed that vancomycin pretreatment exacerbated irAE-associated colitis, while *Bifidobacterium* alleviated pathological effects without compromising ICI efficacy, possibly mediated by T regulatory cells[107].

Expression of ICI targets in nonhematopoietic cells may also contribute to irAEs, such as neurotoxicity associated with chimeric antigen receptor T-cell therapy[115]. Similarly, in ICI-induced pituitary inflammation, high CTLA-4 expression in pituitary endocrine cells, combined with CTLA-4 blockers, triggers immune responses resulting in extensive destruction of adenoid structures[116].

The diverse patterns of irAE progression underscore multifaceted mechanisms. Research from varied perspectives contributes to a comprehensive understanding of irAE occurrence and processes, providing valuable insights for clinical management and therapeutic interventions.

CONCLUSION

The quest for valuable biomarkers remains pivotal in predicting, diagnosing, and treating irAEs in ICI therapy. These biomarkers serve as crucial indicators for clinical management, enhancing efficacy, and ultimately improving survival rates for patients with cancer. Throughout this review, we explored major irAEs, potential biomarkers for prediction and diagnosis, methodologies for biomarker discovery, and underlying mechanisms of irAEs. While a range of biomarkers, including those from immunogenetics, blood cells, cytokines, and autogenic secretions, show promise, none have yet been identified for accurate prediction and diagnosis of irAEs. Further research is imperative to confirm these findings and establish robust biomarkers. Integrating multiple biomarkers into clinical practice can heighten predictive accuracy and refine diagnostic precision for irAEs. Despite the array of methodologies explored for uncovering novel biomarkers,

standard blood tests, and biochemical assays remain the cornerstone of clinical management. These tests yield crucial insights into blood cell composition, antibody titers, hormone levels, and other physiological parameters, complemented by organ-specific imaging modalities. Nonetheless, due to the intricate nature of irAEs and their diverse manifestations among different organs, discovering universally applicable biomarkers remains a challenge[117,118]. Despite the limited diversity in physiological data obtained from patients, the rapid advancements in AI technology and the accumulation of patient cases have generated a wealth of imaging and physiological information suitable for AI training and model development in irAE treatment. Consequently, we believe that harnessing machine learning methods for predicting and diagnosing irAEs holds significant promise[101,119].

FOOTNOTES

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