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REVIEW

Dermatotoxicity of Immune Checkpoint Inhibitors in Advanced Non-Small Cell Lung Cancer: Current Advances in Mechanistic Insights and Predictive Biomarker Identification

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Abstract: Immune checkpoint inhibitors (ICIs) have substantially improved clinical outcomes in patients with advanced non-small cell lung cancer (NSCLC). However, the cutaneous immune-related adverse events (cirAEs) they elicit—being the most frequent and earliest-emerging toxicities—not only compromise treatment adherence but also exhibit a distinct positive association with systemic immune activation and antitumor efficacy. Given these characteristics, elucidating the pathogenic mechanisms of cirAEs and identifying predictive biomarkers are critical for the early detection and intervention of cirAEs, as well as for forecasting the onset of other immune-related adverse events (irAEs) and assessing ICI therapeutic prognosis. This review systematically summarizes recent advances in the pathological mechanisms of cirAEs and predictive biomarkers. Mechanistically, cirAEs result from multifactorial interplay, including genetic predisposition, shared antigen-driven cross-reactivity, and breakdown of cutaneous immune tolerance. For predictive biomarkers, strategies span traditional predictors (eg, demographic and immunological features) and their clinical translation challenges to emerging methods leveraging multi-omics integration and radiomics. Finally, this review addresses future challenges and directions in cirAEs research: Specifically, the positive association between cirAEs and efficacy demands accurate differentiation of "manageable toxicities" from "high-risk toxicities"; furthermore, future studies must validate causal biomarkers via prospective multi-omics cohorts and develop AI-driven dynamic prediction models to enable toxicity-stratified management and optimization of personalized immunotherapy.

Keywords: non-small cell lung cancer, immune checkpoint inhibitors, cutaneous immune-related adverse events, immunotherapy, predictive biomarkers

Introduction

Lung cancer remains a leading cause of global cancer-related incidence and mortality.[1] Over the past decade, immune checkpoint inhibitors (ICIs) have substantially reshaped the treatment paradigm for advanced and metastatic non-small cell lung cancer (NSCLC).[2] These agents, notably monoclonal antibodies targeting programmed death-1/programmed death-ligand 1 (PD-1/PD-L1) and cytotoxic T-lymphocyte-associated protein-4 (CTLA-4), counteract tumor cell-mediated suppression of T-cell activation (eg, via PD-L1 overexpression), consequently reinstating anti-tumor immunity.[3–6] However, this therapeutic immune reactivation can concurrently trigger immune-related adverse events (irAEs) involving multiple organ systems.[7] Among these toxicities, cutaneous immune-related adverse events (cirAEs) are the most frequent and earliest-emerging, posing significant clinical challenges. Importantly, grade

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≥3 cirAEs (such as severe rash or bullous dermatitis) occur in a notable subset of patients, frequently necessitating treatment delays or cessation and consequently elevating the risk of disease progression.[8–10]

CirAEs represent the most prevalent and frequently earliest-onset irAEs during ICI therapy, occurring in 30–50% of patients.[11] They generally emerge at ~4 weeks post-treatment initiation, which is markedly earlier than endocrine irAEs (~12 weeks) and gastrointestinal irAEs (~22.2 weeks).[12–14] While most cirAEs are non-life-threatening, severe manifestations —including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), extensive/severe bullous pemphigoid, and grade 4 rash (>30% body surface area with severe symptoms or infection)—may occur and warrant treatment interruption or discontinuation.[15] Furthermore, cirAEs demonstrate significant ICI class differences: CTLA-4 inhibitors typically induce a higher incidence and severity of cirAEs compared to PD-1/PD-L1 inhibitors, with an earlier onset.[16–18] This incidence further exhibits variability across cancer types, histological subtypes, and disease stages, suggesting underlying mechanistic complexity.[19]

The onset of cirAEs demonstrates a significant positive correlation with subsequent multi-organ irAEs; specifically, in patients with multi-organ irAEs, cirAEs incidence is substantially higher than in those with isolated irAEs, indicating their potential role as sentinel biomarkers for predicting broader immune toxicities.[20] Notably, patients experiencing cirAEs typically demonstrate superior objective response rates (ORR), prolonged progression-free survival (PFS) and overall survival (OS), along with reduced mortality risk compared to non-affected individuals.[12,21–24] Furthermore, in patients with multi-organ irAEs, the number of irAEs positively correlates with both PFS and OS.[25] Mechanistically, cirAEs fundamentally reflect direct cutaneous manifestations of systemic immune activation, offering unique insights into ICI mechanisms and toxicity profiles. As a visible manifestation window for localized immune events, skin pathologies (eg, vitiligo and dermatitis) exhibit consistent and significant correlations with systemic ICI-induced immune responses and clinical efficacy—making it the clinically best-established organ for such associations.[25] Given their early emergence, high incidence, and unique associations with systemic immune activation and efficacy, elucidating the pathophysiology of cirAEs is therefore critical for deciphering ICI mechanisms of action and toxicity heterogeneity.

Consequently, elucidating the pathophysiology of cirAEs and identifying robust predictive biomarkers will not only enable early diagnosis and intervention of cirAEs but also inform risk prediction for other irAEs. While cirAEs represent a pan-cancer phenomenon in ICI therapy, NSCLC—as one of the earliest breakthrough and most extensively treated solid tumors with ICIs—has generated the richest clinical experience and research data, thus providing a robust foundation for mechanistic understanding of cirAEs and discovery of predictive biomarkers. Here, focusing specifically on NSCLC patients, this review synthesizes and critically evaluates current mechanistic insights into cirAEs within this disease context alongside predictive biomarkers, aiming to advance safer and more effective personalized immunotherapy.

Pathogenic Mechanisms of cirAEs

ICIs augment anti-tumor immunity through blockade of key inhibitory immune checkpoints (eg, PD-1/PD-L1 and CTLA-4). Notably, CTLA-4 and PD-1 demonstrate fundamentally distinct immunoregulatory mechanisms.[26] Optimal T-cell activation necessitates two critical signals: 1) T-cell receptor (TCR) engagement with peptide-major histocompatibility complex (MHC) complexes on antigen-presenting cells (APCs); 2) CD28 molecule (CD28)-mediated co-stimulation via CD80/CD86 binding.[27,28] CTLA-4 predominantly suppresses early-phase immune responses through three key mechanisms (Figure 1): 1) Initiating inhibitory signaling: CTLA-4-CD80/CD86 engagement recruits Src homology 2 domain-containing tyrosine phosphatase (SHP-2) and protein phosphatase 2A (PP2A), consequently inhibiting phosphoinositide 3-kinase (PI3K) and protein kinase B (PKB) signaling;[29–31]2) Promoting ligand transendocytosis: CTLA-4 internalizes CD80/CD86 from APCs via transendocytosis, reducing APC surface expression and impairing T-cell co-stimulation;[32–34] 3) Inducing immunosuppressive cytokines: CTLA-4 signaling can induce the production of immunosuppressive cytokines such as transforming growth factor-β (TGF-β) and interleukin-10 (IL-10). Conversely, PD-1 is widely expressed on activated T cells, B cells, natural killer (NK) cells, and other immune subsets. It engages two ligands: PD-L1 and PD-L2. PD-L1 exhibits broad expression across immune cells (T/B cells, dendritic cells (DCs), macrophages) and non-immune cells, including tumor cells. PD-L2 expression is more restricted, predominantly localized to APCs (eg, dendritic cells and macrophages).[35,36] Critically, PD-1 engagement with its ligands elicits differential biological outcomes.[37] Specifically, PD-1:PD-L2 binding favors T helper 2 (Th2)-polarized responses,

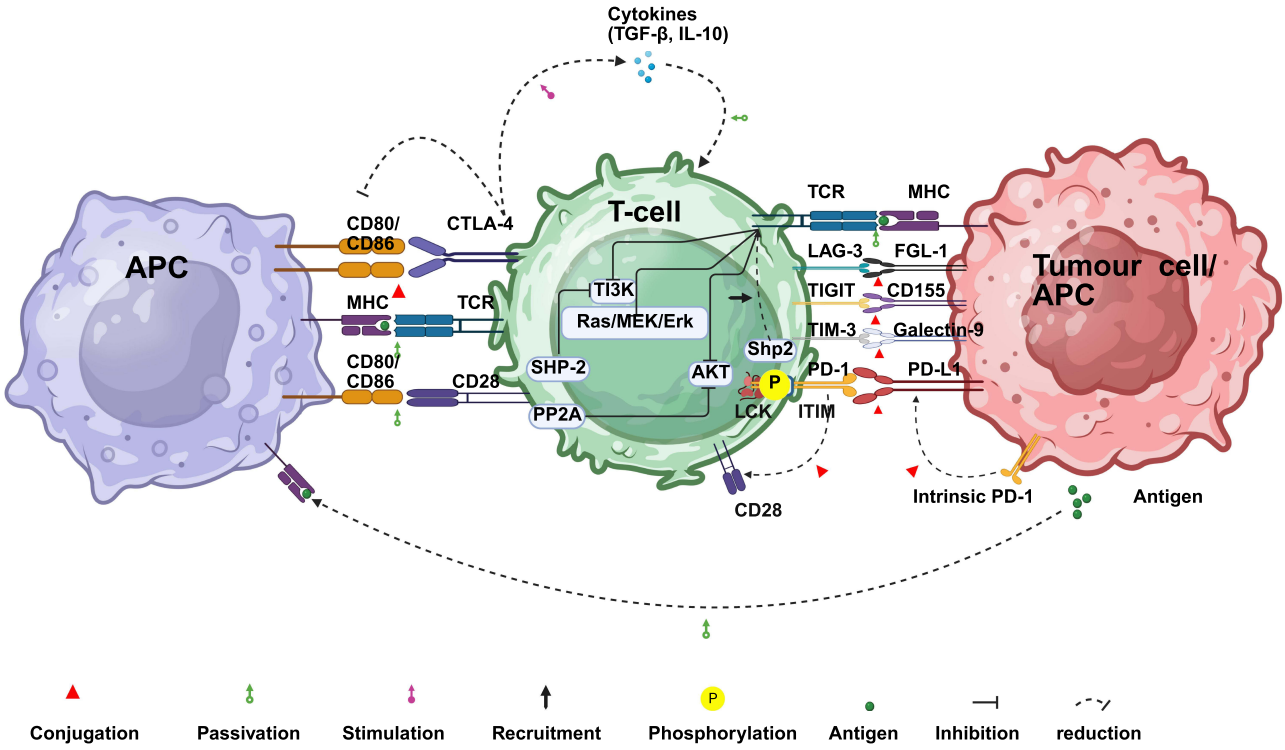

Figure 1 Mechanism of Immune Checkpoint Regulation in T-cell Responses.

while PD-1:PD-L1 engagement predominantly inhibits T-cell-mediated immunity.[38,39] PD-1 functions predominantly during the effector and exhaustion phases, mediating broader immune regulation.[40] Its core inhibitory mechanisms involve (Figure 1): 1) Attenuating TCR signaling: PD-1:PD-L1 binding phosphorylates intracellular immunoreceptor tyrosine-based inhibitory motif (ITIM) and immunoreceptor tyrosine-based switch motif (ITSM) motifs (mainly via lymphocyte-specific protein tyrosine kinase (Lck)), recruiting SHP-2. Activated SHP-2 dephosphorylates proximal TCR components and suppresses PI3K/Akt and Ras/MEK/Erk cascades, inhibiting T-cell activation, proliferation, and effector functions;[41–48] 2) Disrupting CD28 co-stimulation: PD-1 directly impedes CD28 signaling, further constraining T-cell activity.[41] Importantly, functional crosstalk exists between CTLA-4 and PD-1 pathways in regulating T-cell activation.[49,50] Significantly, recent studies have identified PD-1 expression on select tumor cells themselves.[51,52] Thus, PD-1 inhibitors can also restrain tumor growth by disrupting these tumor-intrinsic PD-1:ligand (eg, PD-L1) interactions.

Beyond classical checkpoints, next-generation inhibitors targeting Lymphocyte Activation Gene-3 (LAG-3), T cell immunoreceptor with Ig and ITIM domains (TIGIT), and T cell immunoglobulin and mucin domain-containing protein-3 (TIM-3) are in clinical development, driven by growing interest in their distinct immunoregulatory mechanisms.[53] LAG-3—expressed predominantly on activated/exhausted T cells and regulatory T cells (Tregs)—binds ligands (eg, major histocompatibility complex class II molecules, MHC-II) to attenuate TCR signaling, suppress $CD8^+$ T-cell function/proliferation, and potentiate Treg-mediated suppression;[54–57] TIGIT—expressed on T/NK cells—directly inhibits cytotoxic activity and cytokine production in effector T/NK cells via high-affinity binding to CD155 while concurrently inducing APCs such as DCs to secrete immunosuppressive cytokines and repress pro-inflammatory factors (eg, IL-12), thereby fostering an immunosuppressive milieu;[58,59] TIM-3—expressed broadly on immune cells—induces T-cell exhaustion, apoptosis, or functional impairment upon engagement with ligands.[60,61]

Having outlined ICI immunomodulation, we now focus on cirAEs pathogenesis. Notably, cirAEs demonstrate heterogeneous clinical presentations, with underlying molecular mechanisms and drivers varying considerably among patients of divergent genetic/immunological profiles. Therefore, elucidating the complex mechanisms underlying NSCLC-associated cirAEs is critical for developing effective predictive and management strategies. The central

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mechanism for general irAEs involves ICI-induced disruption of peripheral tolerance mechanisms, which suppresses autoreactive T cells, thereby disrupting tissue homeostasis. However, the early emergence and high frequency of cirAEs strongly suggest unique contributing factors distinct from these generic irAEs mechanisms. Current evidence supports three principal mechanistic hypotheses specific to cirAEs: 1) genetic predisposition, 2) shared antigen-driven cross-reactivity, and 3) cutaneous immune tolerance breakdown.

Genetic Predisposition: Contributions of Human Leukocyte Antigen (HLA), Autoimmunity Genes and Deoxyribonucleic Acid (DNA) Methylation

Genetic predisposition significantly contributes to cirAEs development. Several cirAEs—including vitiligo, bullous pemphigoid, and psoriasiform eruptions—demonstrate clinical similarities to classical autoimmune disorders.[62,63] Notably, psoriasiform eruptions—frequent cirAEs post PD-1/PD-L1 inhibition—exhibit autoimmune-mediated pathogenesis;[64–67] this association is clinically significant, as approximately 86% of psoriasis patients develop psoriasiform eruptions following ICI therapy.[68] Since autoimmune disorders generally exhibit strong genetic foundations, they offer a conceptual framework for deciphering ICI-triggered cirAEs. Supporting this genetic link, carriers of psoriasis-risk alleles (eg, HLA-Cw6, IL12B, IL23R, LCE3B (late cornified envelope 3B)/LCE3C) with parental psoriasis history demonstrate elevated susceptibility to psoriasiform eruptions.[69,70] Similarly, genome-wide association studies (GWAS) have implicated genetic variants in CTLA-4 and PD-1/PD-L1 loci with autoimmune disease risks including Graves' disease and systemic lupus erythematosus (SLE).[63,71] Specific HLA alleles and subclinical autoimmunity markers (eg, elevated autoantibodies) may potentiate autoimmune responses.[72,73] Beyond classical genetics, epigenetic regulation (especially DNA methylation)—bridging genetic predisposition and environmental triggers to modulate gene expression and immunity—has emerged as pivotal in oncogenesis and immune responses and is thus relevant to cirAE mechanisms. For instance, tumor suppressor promoter hypermethylation in NSCLC correlates with transcriptional silencing, adverse prognosis, and potential immunomodulatory effects via altered immune cell crosstalk in the tumor microenvironment (TME).[74] Collectively, the above associations predominantly derive from parallels with autoimmune pathogenesis and phenotypic resemblances. It is important to note that direct evidence causally connecting specific genetic/epigenetic alterations to defined cirAEs risk in ICI-treated NSCLC patients is sparse. While such genetic/epigenetic perturbations may theoretically underpin ICI-triggered heterogeneous autoantibody/cytokine production,[75,76] robust prospective cohort studies and functional validation demonstrating these variants as direct causal risk factors for ICI-associated cirAEs in NSCLC are lacking. Thus, prospective genetic/epigenetic association studies in ICI-treated NSCLC cohorts—integrated with functional validation—are imperative to establish causality, effect magnitudes, and predictive utility of these candidate factors for specific ICI-triggered cirAEs.

Shared Antigen-Driven Cross-Reactivity

Beyond genetic predisposition, numerous irAEs are mechanistically linked to shared antigen-driven cross-reactivity. ICIs augment immune recognition and targeting of tumor antigens. However, imperfect immune recognition specificity enables cross-reactivity against normal tissues expressing epitopes resembling tumor antigens during tumor targeting, precipitating irAEs.[77–79] Critical evidence derives from melanoma studies: PD-1 blockade in melanoma patients induces tumor-targeting T cells to cross-react with melanocyte-shared antigens, driving vitiligo and other cirAEs. Crucially, shared T-cell receptor clonotypes detected in melanoma and autoimmune skin lesions directly demonstrate identical clones targeting both tumor and normal skin.[80] Similarly, elevated baseline autoantibodies in subclinical autoimmunity correlate with irAEs development.[81] Importantly, this paradigm extends to NSCLC. Clinical evidence supports the shared antigen hypothesis in NSCLC-associated cirAEs. NSCLC patients developing cirAEs demonstrate enhanced circulating TCR repertoire diversity.[82] T-cell infiltration is consistently observed in post-ICI skin biopsies of NSCLC patients with cirAEs.[80,83] While these findings offer strong clinical correlations, direct mechanistic validation (eg, demonstrating identical TCR clones targeting shared NSCLC tumor and skin antigens) is currently lacking. Thus, shared antigen-driven cross-reactivity provides a framework linking ICI efficacy and cirAEs in NSCLC: T-cell responses against epitopes shared between tumor and normal cutaneous tissues may simultaneously drive antitumor immunity and skin toxicity.[84] This mechanism directly explains the association between cirAEs and enhanced systemic immune activation/

improved clinical outcomes during ICI therapy.[62,85–88] Notably, structural similarity between tumor antigens and tolerance-inducing self-antigens may impair APCs efficiency in priming tumor-specific T-cell responses. This APC dysfunction contributes to acquired ICI resistance and interpatient heterogeneity in therapeutic responses and irAEs profiles.[89,90]

Breakdown of Skin Immune Tolerance

Beyond genetic predisposition and the shared antigen mechanism, a pivotal mechanism underlying cirAEs is the breakdown of local immune tolerance within the skin. Importantly, genetic background may predetermine immune tolerance stability—modulating autoreactive T-cell repertoire size and activity—as noted in Section 2.1. Such genetic determinants may increase susceptibility to profound tolerance disruption and autoimmune responses during ICI therapy. Functionally, as the frontline barrier persistently encountering environmental antigens, skin exhibits a distinctive immune microenvironment designed to safeguard internal homeostasis against direct physical, chemical, and biological insults. To balance this constant surveillance with the need to avoid excessive inflammation, skin maintains a dense network of resident immune cells—including Langerhans cells (LCs), tissue-resident memory T cells (TRM), keratinocytes, and cytokine-secreting melanocytes—that actively surveil the microenvironment.[91,92] Collectively, they constitute a hyper-vigilant "immune sentinel post" poised to mount rapid immune responses. However, given perpetual exposure to diverse (often benign) antigens (microbial/chemical/physical), skin must employ exquisite peripheral tolerance mechanisms to distinguish threats from innocuous signals, thereby preventing aberrant/autoimmune reactions. Central to the maintenance of this local tolerance is the persistent expression of immune checkpoint molecules on cutaneous immune cells. Notably, PD-1 is highly expressed on dermal DCs and LCs, serving as a crucial molecule for sustaining local immune tolerance.[84] These molecules are essential for curbing nonessential inflammation and enforcing regional self-tolerance.[93,94] Consequently, ICI-mediated blockade of these checkpoints prompts hyperactivation of resident/recruited immune cells, driving attacks against self-antigen-expressing cutaneous structures. This intrinsic reliance on checkpoint-dependent tolerogenic mechanisms explains skin's heightened vulnerability as an early and frequent target of ICI-driven immune dysregulation.[84,95–97] Although cutaneous tolerance breakdown offers a rational pathogenic framework, direct experimental evidence establishing causality in skin toxicity remains limited. Future studies must employ advanced approaches—such as single-cell sequencing of cutaneous infiltrates, spatial transcriptomics of key pathways, functional validation of checkpoint roles in tolerance—to establish direct causal evidence.

Predictive Biomarkers of cirAEs

The broad clinical adoption of ICIs underscores the critical need for accurate prediction and early recognition of cirAEs. Robust predictive biomarkers enable preemptive therapeutic planning for high-risk patients and comprehensive assessment of treatment benefit-risk profiles. Nevertheless, discovering biomarkers predictive of early therapeutic response and safety remains challenging. Current biomarkers for predicting ICI-associated cirAEs in NSCLC are broadly classified into multiple categories: traditional markers (eg, demographic/immunological features) and emerging approaches (eg, multi-omics integration and radiomics) (Figure 2). Therefore, critical evaluation of their predictive utility, limitations, and translational potential is essential for directing future research.

Conventional Biomarkers: Demographic/Immunological Features and Translational Challenges

While traditional biomarkers—primarily demographic and immunological features—have been more extensively studied than emerging multi-omics/radiomics approaches, their clinical translation presents substantial challenges. Current investigations largely rely on cross-sectional, cohort, or case–control designs to examine associations between demographic factors and cirAEs.[98–100] Reported associations include: Elevated body mass index (BMI) being implicated with heightened cirAE risk during pembrolizumab therapy in retrospective analyses;[101,102] Advanced NSCLC patients aged ≥71 years exhibiting higher irAE incidence post-ICI than those aged 65–70 years;[103–105] Elevated pretreatment geriatric nutritional risk index (GNRI) correlating with increased incidence of cirAEs (rash/pruritus).[106] Sex and comorbidities have also been suggested to modulate cirAE risk.[101,107] Despite these observed associations, these demographic factors typically function as risk modifiers rather

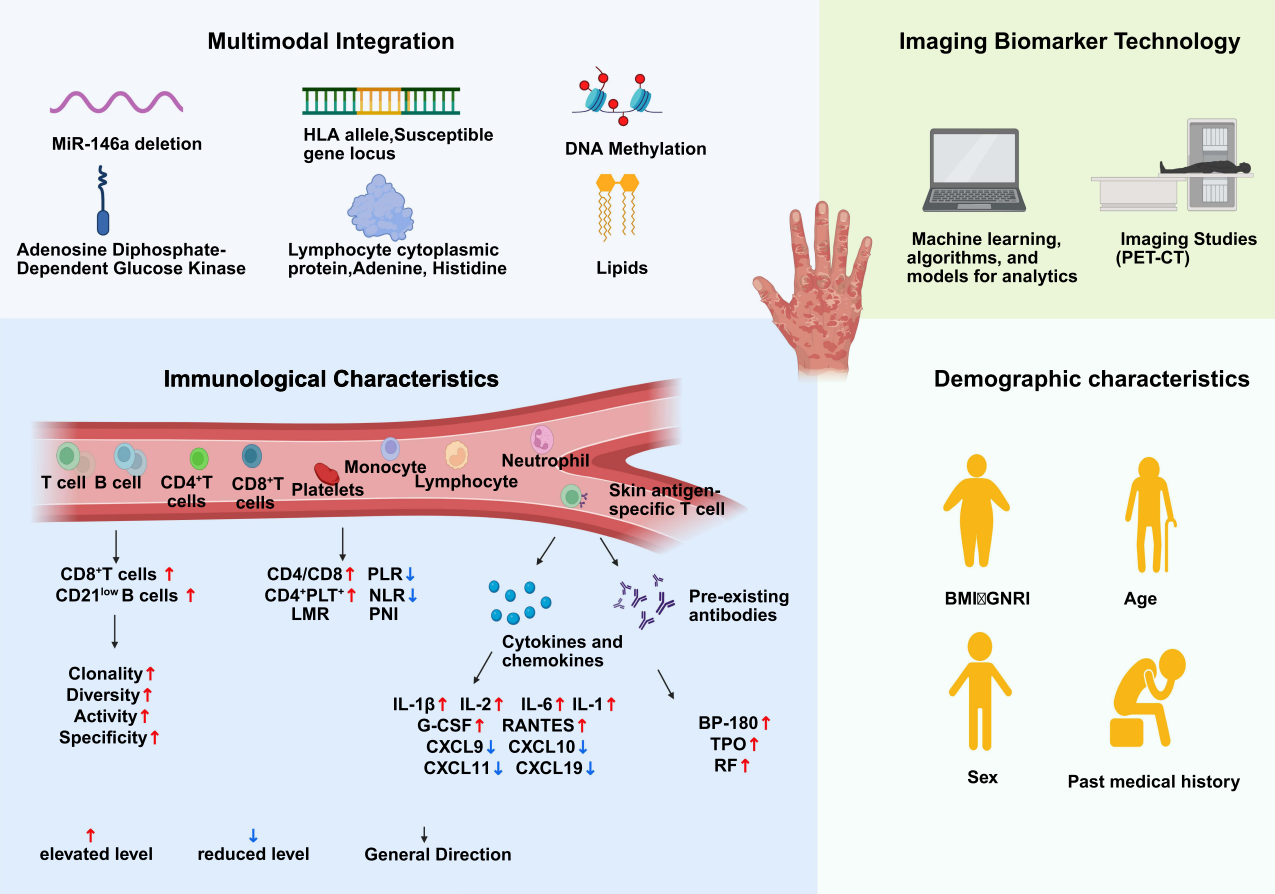

Figure 2 Predictive Biomarkers for cirAEs During ICI Treatment in NSCLC.

than direct etiological agents, resulting in limited predictive accuracy and specificity. Consequently, their independent predictive utility and clinical generalizability warrant rigorous validation in large prospective cohorts.

Peripheral blood immune signatures represent valuable potential biomarkers for ICI-associated cirAE prediction due to their minimal invasiveness and serial sampling feasibility. Studies demonstrate that early $CD8^+$ T-cell clonal expansion post-ICI correlates with severe irAEs;[108] Combined anti-PD-1/CTLA-4 therapy induces early PD-L1-high clonal $CD21^{low}$ B-cell expansion correlating with severe irAEs.[109] Regarding skin-specific toxicities, studies in NSCLC report that: Patients developing ICI-associated cirAEs exhibit early circulating TCR repertoire diversification and skin-antigen-specific T cells peripherally, indicating the predictive potential of these specific immune subsets.[80,82] Additional proposed blood-based predictors include: Inflammatory indices: elevated neutrophil-to-lymphocyte ratio (NLR), reduced lymphocyte-to-monocyte ratio (LMR), increased platelet-to-lymphocyte ratio (PLR), and decreased prognostic nutritional index (PNI); Immune cell-based markers: $CD4^+/CD8^+$ ratios and circulating $CD4^+$-platelet (PLT^+) complexes.[110,111]

Cytokine and chemokine dynamics represent additional potential predictors for cirAEs. Pro-inflammatory cytokines (eg, IL-2, IFN-γ, TNF-α, IL-1) may correlate with both treatment response and irAE risk.[112] Studies have identified several specific associations in NSCLC/lung cancer patients: Lower pretreatment serum levels of C-X-C motif chemokine ligand 9 (CXCL9), CXCL10, CXCL11, and CXCL19 are linked to irAE development;[113] Elevated post-treatment levels of granulocyte colony-stimulating factor (G-CSF) and regulated upon activation, normal T cell expressed and secreted (RANTES/CCL5) are associated with irAEs;[114] Increased serum levels of IL-1β, IL-2, IL-6, and IL-10 during immunotherapy correlate with irAEs.[115,116] Furthermore, baseline autoantibody levels constitute potential risk factors for post-ICI irAEs.[117] For example: Elevated baseline anti-BP180 antibodies increase the risk of cirAEs in PD-1/PD-L1-blockade-treated NSCLC patients;[118] Subclinical autoimmunity markers, such as anti-thyroid peroxidase antibody (anti-TPO),

correlate with irAEs in advanced NSCLC;[81] Elevated baseline rheumatoid factor (RF) independently predicts cutaneous reactions following ICI treatment.[22]

Despite extensive research on traditional biomarker-cirAE associations, their clinical predictive utility remains limited. Specifically, key limitations encompass: 1) Methodological constraints: Primarily retrospective designs with small cohorts; 2) Insufficient performance validation: Lack of rigorous evaluation of sensitivity/specificity (eg, ROC analysis, optimal cutoff identification); 3) Low mechanistic evidence: Predominantly observational associations without experimental validation of causality; 4) Heterogeneity and reproducibility issues: Significant inter-study variability with limited replicability across populations, hindering clinical translation.

Emerging Approaches: Multi-Omics Integration and Radiomics

Multi-omics integration (spanning genomics, transcriptomics, proteomics, and metabolomics) elucidates complex pathophysiological networks—from genetic alterations to immune-microbiome crosstalk—thereby surpassing traditional unidimensional approaches. This approach not only accelerates novel cirAE biomarker discovery but also addresses key limitations of conventional markers, such as sample heterogeneity and limited precision.

Multi-omics approaches have identified several promising biomarker candidates for irAEs and ICI response prediction. Through an integrated analysis of messenger RNA (mRNA), microRNA (miRNA), long non-coding RNA (lncRNA), proteins, and non-silent mutations across diverse cancer types, one study identified lymphocyte cytosolic protein 1 (LCP1) and ADP-dependent glucokinase (ADPGK)—both of which are intimately linked to T-cell activation—as candidate biomarkers for irAEs. A predictive model based on the combination of LCP1 and ADPGK showed superior predictive accuracy in linear regression models. In an initial validation cohort of 28 patients, LCP1/ADPGK expression was significantly higher in tissues from patients who experienced irAEs, with the cross-validated area under the curve (AUC) for the combined predictive metric achieving 0.80.[119] Nevertheless, these findings warrant confirmation in large-scale, prospective cohorts and independent validation sets, with careful control of potential confounders (eg, limited sample size, single-center bias, and tumor heterogeneity), to further assess their potential for clinical translation. High-resolution HLA-I typing in 179 PD-1/PD-L1-blockade NSCLC patients showed HLA-I homozygosity associated with reduced pruritus/rash risk.[120] Furthermore, HLA-DRB1*11:01 allele correlated with pruritus risk—aligning with its atopic dermatitis role—highlighting shared immunogenetics in cutaneous toxicity.[121] 16S rRNA sequencing implicates gut microbiome composition as a potential cirAE predictor.[122,123] MiR-146a deficiency correlates with severe irAEs in preclinical/clinical studies, enabling circulating miRNA-based noninvasive prediction.[124] Metabolomics identifies hypoxanthine, histidine,[125] indoleamine 2,3-dioxygenase (IDO) activity,[126] and very-long-chain fatty acid lipids[127] as potential ICI response predictors. Proteomics reveals leukemia inhibitory factor as a novel ICI resistance biomarker.[128] Functional proteomic analyses highlight the predictive value of detecting intact PD-1/PD-L1 complexes for ICI response in NSCLC.[126,127,129] Importantly, multi-omics biomarkers initially predictive of ICI efficacy may also forecast irAEs, warranting specific validation for toxicity prediction.

Radiomics noninvasively characterizes tumors and their microenvironment through high-throughput extraction of quantitative features from computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography-computed tomography (PET-CT) images. Current efforts leverage radiomics as imaging-based surrogates for the TME—particularly for quantifying tumor-infiltrating lymphocytes (TILs), which are established predictors of ICI response. Radiomics models derived from CT, PET-CT, or MRI features enable noninvasive TIL mapping, thereby indirectly informing efficacy and toxicity prediction.[130] Furthermore, radiomics-based models (with or without clinical features) can predict tumor PD-L1 expression—a key correlate of both efficacy and toxicity.[131–134] Though nascent in oncology, multi-omics-integrated radiomics represents a major frontier. Its noninvasive whole-lesion profiling captures spatial heterogeneity and enables longitudinal monitoring, offering powerful solutions for tumor heterogeneity assessment and dynamic monitoring. Robust radiomic models require validation in prospective trials—especially for organ-specific cirAEs—to achieve clinical utility.

Currently, most novel biomarkers are exploratory or derived from retrospective studies. Their predictive value and underlying causal mechanisms demand rigorous validation. Clinical translation faces challenges related to cost, throughput, and standardization. Future priorities include establishing prospective multi-omics cohorts analyzed

using advanced bioinformatics. Such cohorts must control for confounders and address heterogeneity to develop quantifiable predictive models. Ultimately, validation in independent cohorts and interventional trials is essential to guide personalized risk management.[135]

Conclusions and Future Directions

While ICIs substantially improve outcomes in advanced NSCLC, treatment-induced cirAEs pose significant clinical challenges yet offer unique mechanistic insights. Although current mechanistic frameworks for cirAEs include genetic predisposition, shared antigen-driven cross-reactivity, and cutaneous immune tolerance breakdown, robust direct experimental validation of these hypotheses is still needed. Furthermore, their applicability to non-cutaneous irAEs (eg, pneumonitis, colitis, endocrinopathies) remains unconfirmed. Consequently, future studies should investigate connections between irAEs and classical immune dermatoses, and class-specific mechanisms underlying organ-specific irAEs.

Predictive biomarker development for cirAEs confronts substantial challenges. Despite numerous candidate biomarkers (particularly blood-based immune signatures), limited sensitivity/specificity and significant inter-study heterogeneity constrain their clinical utility. Critically, most candidates remain exploratory—derived primarily from small cohorts—and lack validation in large, independent prospective studies; these are major translational barriers.

A key unresolved clinical dilemma stems from the cirAEs-efficacy association: distinguishing "manageable toxicities" (reflecting beneficial systemic immune activation) from "high-risk toxicities" (potentially severe or life-threatening). Currently, no reliable biomarkers exist to early predict cirAE progression trajectories or identify cases where toxicity dissociates from clinical benefit. Indiscriminate immunosuppression (eg, corticosteroids) may control toxicity but risk compromising antitumor immunity and therapeutic efficacy. Therefore, future biomarker research should prioritize predicting cirAEs progression dynamics and efficacy-decoupling risk over binary occurrence prediction.

A central clinical dilemma arises from the positive association of cirAEs with improved ICI efficacy: how to differentiate "manageable toxicities" indicative of productive anti-tumor immunity from "deleterious toxicities" that might evolve into severe, life-threatening events or substantially compromise quality of life? For this review, "manageable toxicities" are defined as Grade 1–2 adverse events (AEs) (eg, localized maculopapular rash or mild pruritus) that exhibit a good response to topical corticosteroids or systemic immunosuppression (eg, $\leq$0.5 mg/kg/day prednisone equivalent) and do not require permanent cessation of ICI therapy. Conversely, "high-risk toxicities" denote Grade 3–4 AEs that may progress to life-threatening severe cutaneous adverse reactions (eg, SJS, TEN) despite intensive immunosuppression, or that necessitate permanent discontinuation of ICIs. This distinction highlights a current critical gap: the absence of robust biomarkers capable of precisely predicting, at an early stage, which cirAEs will progress to severity or, conversely, which are associated with a lack of anti-tumor benefit. Indiscriminate use of immunosuppressive agents such as glucocorticoids to quell all inflammatory activity, albeit effective for toxicity management, risks concurrently blunting anti-tumor immune responses, potentially compromising treatment efficacy. Consequently, a paramount goal for future biomarker discovery should be the development of tools that forecast the trajectory of cirAEs severity and the risk of their dissociation from anti-tumor response, moving beyond mere prediction of incidence. Future studies must transcend static correlative analyses and prioritize creating dynamic, biomarker-informed risk stratification models. Such models ought to integrate multi-omics data to identify the critical transition point where toxicity escalates from low to high risk. Promising investigative avenues include, but are not limited to: (1) Baseline genetic risk (eg, specific HLA alleles); (2) Dynamic early serum cytokine/chemokine profiles (eg, rate of change [slope] for IL-6, CXCL9/CXCL10 levels early in treatment); (3) Expansion kinetics and evolutionary patterns of specific T-cell clones in skin biopsies or peripheral blood (informed by the conceptual framework of Subudhi[107] et al on the temporal dynamics of $CD8^+$ T-cell clonal expansion and irAEs); (4) Evolving features on serial non-invasive skin imaging. The overarching objective of these efforts should be the identification of early warning signals predictive of toxicity escalation (eg, from Grade 2 to Grade 3), rather than simply forecasting the onset of any-grade toxicity.

Despite these challenges, integrating multi-omics data with AI in prospective studies will accelerate the discovery of robust predictive biomarkers. This will facilitate precision risk stratification, early intervention, and personalized management—preventing unnecessary treatment discontinuation—while advancing mechanistic understanding to optimize the safety–efficacy balance and survival outcomes in advanced NSCLC immunotherapy.

Abbreviations

ICIs, Immune checkpoint inhibitors; NSCLC, non-small cell lung cancer; cirAEs, cutaneous immune-related adverse events; irAEs, immune-related adverse events; PD-1/PD-L1, programmed death-1/programmed death-ligand 1; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; DRESS, drug reaction with eosinophilia and systemic symptoms; ORR, objective response rates; PFS, progression-free survival; OS, overall survival; TCR, T-cell receptor; MHC, major histocompatibility complex; APCs, antigen-presenting cells; SHP-2, Src homology 2 domain-containing tyrosine phosphatase; PP2A, protein phosphatase 2A; PI3K, phosphoinositide 3-kinase; AKT, protein kinase A; TGF-β, transforming growth factor-β; IL-10, interleukin-10; NK, natural killer; DCs, Dendritic cells; APCs, antigen-presenting cells; Th2, T helper 2; ITIM, tyrosine-based inhibitory motif; Lck, lymphocyte-specific protein tyrosine kinase; LAG-3, Lymphocyte Activation Gene-3; TIGIT, T cell immunoreceptor with Ig and ITIM domains; TIM-3, T cell immunoglobulin and mucin domain-containing protein-3; Tregs, regulatory T cells; MHC-II, major histocompatibility complex class II molecules; DCs, dendritic cells; HLA, Human Leukocyte Antigen; DNA, deoxyribonucleic acid; LCE3B, Late cornified envelope 3B; GWAS, genome-wide association studies; SLE, systemic lupus erythematosus; TME, tumor microenvironment; LCs, Langerhans cells; TRM, tissue-resident memory T cells; BMI, body mass index; GNRI, geriatric nutritional risk index; NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutritional index; PLT, Platelet; CXCL9, C-X-C motif chemokine ligand 9; G-CSF, granulocyte colony-stimulating factor; RANTES/CCL5, regulated upon activation, normal T cell expressed and secreted; anti-TPO, anti-thyroid peroxidase antibody; RF, rheumatoid factor; mRNA, messenger RNA; LCP1, lymphocyte cytosolic protein 1; ADPGK, ADP-dependent glucokinase; AUC, area under the curve; IDO, indoleamine 2, 3-dioxygenase; CT, computed tomography; MRI, magnetic resonance imaging; PET-CT, positron emission tomography-computed tomography; TILs, tumor-infiltrating lymphocytes.

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