

Regulatory T cells in lung adenocarcinoma: Mechanisms of immune escape, prognostic significance and therapeutic opportunities (Review)

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Abstract. Lung adenocarcinoma (LUAD) represents the most prevalent type of lung cancer, accounting for 35-40% of all lung cancer cases. Regulatory T cells (Tregs), a CD4⁺ T cell subtype with immunosuppressive functions, play a pivotal role in maintaining self-tolerance under physiological conditions. Recent evidence has increasingly highlighted their involvement in various cancers. In LUAD, Treg infiltration into tissues undermines the immune anticancer response, correlating with disease stage, treatment efficacy and prognosis. By inhibiting robust anti-tumor immune mechanisms, Tregs facilitate tumor immune escape in LUAD. Furthermore, elevated Treg cell accumulation in LUAD has been linked to reduced overall survival rates. Tregs serve as independent predictors for LUAD diagnosis in patients at high risk of recurrence. Systematic depletion of all Tregs to enhance anticancer efficacy poses risks of inducing severe autoimmune pathologies. Consequently, understanding the precise structure of tumor-infiltrating Tregs is essential for effective targeting of these cells in tumors. Additionally, identifying candidate targets or methods for the specific elimination of tumor-infiltrating Tregs is necessary for developing efficient and safe combination immunotherapy strategies for LUAD. The present study focuses on the regulatory role of Tregs in LUAD prognosis, immune escape and targeted therapies, elucidating the molecular mechanisms of Treg involvement and presenting associated therapeutic targets.

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1. Introduction

Lung cancer has the highest morbidity and mortality rates among malignant tumors worldwide, primarily comprising non-small cell lung cancer (NSCLC) and small cell lung cancer (1). Lung adenocarcinoma (LUAD) serves as the most prevalent histological type of NSCLC (2). For decades, surgery, radiotherapy and chemotherapy have remained the principal treatment strategies for lung cancer. Nevertheless, the median overall survival for this disease remains disappointingly low, often limited to a few months. LUAD progresses through stages, starting from atypical adenomatous hyperplasia to adenocarcinoma *in situ*, then to minimally invasive adenocarcinoma, ultimately leading to dominant invasive adenocarcinoma (3). Attention to early surgical intervention for lung cancer has improved survival outcomes in patients diagnosed at early stages (4). Despite advances in understanding LUAD, its aggressive nature and associated risks continue to impact patient survival and prognosis. Recent years have witnessed promising results from targeted therapies based on biomarkers, markedly enhancing survival rates among LUAD patients (5). However, LUAD remains one of the most invasive and lethal tumor types, often diagnosed at advanced stages involving metastatic tumors. This is primarily due to the challenge of distinguishing benign from malignant solid lung nodules at an early stage, resulting in a 5-year survival rate of <20% (6,7). The rapid progress in targeted therapy for advanced LUAD has paved the way for personalized treatment approaches (8). Most LUAD patients present with advanced stages at diagnosis due to inadequate screening and the late onset of symptoms (9). Immunotherapy has emerged

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as a key strategy for treating advanced LUAD, primarily relying on immune checkpoint inhibitors (ICIs), which have demonstrated substantial antitumor activity across a number of solid tumors (10-12). However, despite the introduction of immunotherapy, the 5-year overall survival (OS) rate for LUAD remains only 25% (13). Current precision medicine initiatives emphasize LUAD targeted therapies and immunotherapies informed by a spectrum of biomarkers, including genetic alterations and changes at the transcriptional or protein levels. The development of stratified biomarkers has markedly enhanced the implementation of personalized treatment strategies in clinical settings. Studies have underscored the critical role of the immune microenvironment in tumor progression, highlighting its potential as a predictor of cancer prognosis and treatment response. Thus, a comprehensive understanding of the characteristics and regulatory mechanisms of the LUAD immune microenvironment is essential for the development of novel immunotherapy strategies.

2. Immunological features and immunotherapy of LUAD

The tumor microenvironment (TME) represents a multicellular community composed of malignant epithelial cells, infiltrating immune cells, stromal cells and various other cell types, which collectively influence disease progression (PD) and treatment response (14). Immune cells present in the TME include macrophages, mast cells, natural killer (NK) cells, dendritic cells (DCs) and T and B lymphocytes. Recruitment of different immune cell subsets to the TME occurs through interactions between chemokines and their receptors, shaping the TME specific to LUAD (15,16). The immune system can establish immunosuppressive conditions within the TME, facilitating tumor growth (17,18). Considerable attention has been directed toward the TME and its implications for prognosis and treatment response of lung cancer patients, marking a significant focus in cancer research in recent years. Interactions between tumor cells, immune cells and various regulatory factors are considered to collectively influence lung cancer development and treatment outcomes (19). Targeted therapy and immunotherapy have both demonstrated promising efficacy in selected patients with advanced or locally advanced lung cancer (20). However, the combination of targeted therapy and immunotherapy has not exhibited synergistic antitumor effects *in vitro* or in clinical trials (8). Further characterization of the TME in oncogene-driven LUAD has revealed generally weak immunogenicity. Moreover, dynamic interactions among multiple immune cells regulate the TME; thus, evaluating the effects of ICIs requires consideration beyond just interactions between T cells and tumor cells (21,22).

In recent years, the advent of ICIs has revolutionized the treatment landscape for LUAD. Results from multiple clinical trials demonstrate that ICIs targeting programmed death-ligand 1 (PD-L1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) now constitute the first-line standard treatment for lung cancer, whether as monotherapy or in conjunction with platinum-based chemotherapy (10,23-26). Current targeted ICIs have shown encouraging therapeutic effects; for instance, durvalumab, an anti-PD-L1 antibody, has confirmed significant improvements in progression-free survival compared with placebo in patients with locally advanced unresectable

stage 3 lung cancer, with a sustained OS of 47.5 months in the treatment group vs. 29.1 months in the placebo group at the 5-year follow-up (27). Consequently, durvalumab received approval from the European Medicines Agency for patients with unresectable stage 3 PD-L1-positive lung cancer who do not experience PD after concurrent/sequential chemoradiotherapy. Recently, ICIs have also gained approval for use as adjuvant therapy following chemotherapy in specific patient populations. The Impower010 trial evaluated atezolizumab after adjuvant platinum-based chemotherapy in patients with completely resected stage IB-IIIA NSCLC, showing improved disease-free survival (DFS) compared with best supportive care in PD-L1 $\geq 1\%$ tumors. Notably, in the PD-L1 $\geq 50\%$ population, a 57% reduction in the risk of PD was observed (28). The improvements in DFS and early immune responses offer hope for improved treatment outcomes for patients. A meta-analysis by Guven *et al* (29) comparing neoadjuvant chemoimmunotherapy to standard neoadjuvant chemotherapy demonstrated a 41% reduction in the risk of PD or death. As ICIs become increasingly prevalent in lung cancer treatment, redefining the therapeutic approach for metastatic lung cancer recurrence becomes essential.

Despite significant advances in the treatment of lung cancer using ICIs, the OS rate remains low, with lung cancer continuing to be the leading cause of cancer-related mortality. Recent studies indicate that regulatory T cells (Tregs) serve as key regulators of immune function in lung cancer, capable of suppressing antitumor immunity and contributing to the clinical failure of ICIs (30). Evidence suggests that various resident immune cell subsets within the lung cancer TME may facilitate immune escape, thereby diminishing the efficacy of ICI-based immunotherapy (31). Among these, Tregs, a specialized subset of T cells, suppress antitumor immune responses and promote self-tolerance (32). The presence of Tregs may also act as a predictor of response to ICI immunotherapy. A study involving patients with NSCLC, gastric cancer and malignant melanoma treated with nivolumab, pembrolizumab, or the anti-PD-L1 antibody atezolizumab found elevated PD-1 levels on Treg surfaces in non-responders. Notably, the ratio of tumor-infiltrating PD-1⁺CD8⁺ T cells to Tregs proved to be a more reliable predictor of treatment response than other factors, including PD-L1 expression and tumor mutational burden. Consequently, the authors concluded that PD-1⁺ Tregs could serve as predictive biomarkers and should be targeted therapeutically to enhance the clinical efficacy of ICIs in lung cancer (33). These findings support the association between circulating and tumor-infiltrating Treg levels with lung cancer prognosis and underscore the immunosuppressive role of Tregs in this context. Thus, Tregs and their related cellular processes present a promising therapeutic target for lung cancer treatment, especially in conjunction with ICIs. However, despite the potential for targeting Tregs in lung cancer therapy, several limitations must be addressed before clinical implementation. While a number of studies support Tregs as potential prognostic biomarkers and/or predictors of treatment failure, their true utility as predictive biomarkers remains ambiguous. Additionally, targeting Tregs necessitates extreme caution. For instance, in a mouse model of pancreatic cancer, the genetic ablation of Tregs resulted in substantial remodeling of the TME and accelerated tumor formation (34). Therefore, the

combination of Treg-targeted therapies and ICIs warrants thorough investigation prior to clinical application.

3. Overview of immunosuppression of regulatory T cells in the tumor microenvironment

Several resident immune cell types within the LUAD TME may contribute to immune escape, thus diminishing the effectiveness of immunotherapy based on ICIs. Among these cell types are Tregs, a specialized subset of T cells that suppress immune responses to promote self-tolerance (31). Tregs are a class of immunoregulatory suppressor cells characterized by the expression of CD4, CD25 and the transcription factor forkhead box protein P3 (Foxp3). They play a critical role in maintaining immune homeostasis and inducing immune tolerance (35). Initially identified for their function in sustaining autoimmune tolerance and homeostasis, tumor-infiltrating Tregs comprise 10-50% of tumor CD4⁺ T cells, compared with only 2-5% in the peripheral blood of healthy individuals. Notably, these Tregs demonstrate distinct immunological profiles and activation phenotypes (36,37). Accumulating evidence has further elucidated their roles in both autoimmune diseases and cancer (38-40).

Tregs can be classified based on their developmental origin into thymus-derived Tregs (tTregs), peripheral Tregs (pTregs) and *in vitro* induced Tregs (iTregs) (37,41,42). tTregs, generated in the thymus, are activated by autoantigens presented by thymic epithelial cells and subsequently migrate to the periphery, where they primarily inhibit specific antigens. Conversely, iTregs are differentiated from naïve CD4⁺ T cells in the thymus following TCR signaling, comprising various subsets such as Foxp3⁺ iTregs, type 1 Tregs (identified by the phenotype CD4⁺ CD25^{low} CD45RB^{low}) and Th3 cells (identified by the phenotype CD4⁺ CD25^{low}) (43). iTregs are marked by incomplete epigenetic regulation and functional instability, which have strong associations with autoimmune diseases, cancer and PD (44). Functionally and phenotypically, Tregs can be divided into naïve Tregs (or resting Tregs), effector Tregs (eTregs) and non-Tregs. Naïve Tregs are characterized as CD4⁺Foxp3^{low} CD25^{hi}, eTregs exhibit a CD4⁺Foxp3^{hi} CD25^{hi} phenotype, while non-Tregs are identified as CD4⁺Foxp3^{low} (45,46). Tregs possess a powerful capacity to suppress the host immune response, thereby preventing autoimmune diseases. However, tumor cells can recruit Tregs into the TME to inhibit antitumor immunity, thus diminishing the efficacy of tumor immunotherapy (47). Therefore, inhibiting the immunosuppressive function of Tregs represents a key strategy in contemporary immunotherapy. Additionally, Tregs not only regulate T cells but also modulate B cells, NK cells, DCs and macrophages through both humoral and cell-cell contact mechanisms (48). Multiple molecules are involved in the Treg-mediated inhibition mechanism, including CTLA-4, IL-2, IL-10, TGF- β , IL-35, glucocorticoid-induced TNF receptor, lymphocyte activation gene 3, granzyme B, adenosine and cAMP (47).

Considering the various Treg subsets with differing phenotypes and functions, the application of FoxP3 or other markers to distinguish these subsets may lead to confounding results due to the presence of non-Treg and other functional Treg subtypes (49). Single-cell RNA sequencing (scRNA-seq)

has gained prominence in immunological research, substantially advancing the understanding of different Treg subsets by analyzing the heterogeneity of immune cell subsets at the single-cell level (50). Moreover, the integration of spatial genomics offers a comprehensive perspective on the distribution of various Treg subsets within tumors. Combining single-cell sequencing data from patients at different tumor stages can further elucidate the spatiotemporal heterogeneity of Treg populations.

4. Research progress of Tregs in LUAD

The prognostic significance of Treg infiltration in LUAD

Treg infiltration and clinical outcomes in LUAD. Tregs play a pivotal role in shaping the immunosuppressive TME and are closely linked to tumor progression, metastasis, treatment response and clinical outcomes in LUAD (47). Tumor-associated Treg populations can be categorized into tumor-resident Tregs, tissue-resident Tregs and circulating-derived Treg subsets, each exhibiting distinct functional characteristics within the TME (51). Accumulating evidence indicates that Treg infiltration is typically increased in LUAD tissues, metastatic lymph nodes and peripheral blood and is associated with advanced disease stages, tumor recurrence and metastatic progression (52,53). Compared with normal lung tissues and peripheral blood, LUAD tumors demonstrate markedly higher Treg accumulation, suggesting that Treg recruitment and expansion contribute to the establishment of an immunosuppressive niche that facilitates tumor growth (54).

The association between Treg infiltration and clinical outcome has been extensively investigated, with most studies supporting an unfavorable prognostic association, particularly when Tregs are enriched within the tumor. Increased intratumoral Treg abundance has been associated with shorter OS and DFS, although the strength of this association varies according to tumor stage, Treg phenotype, tissue compartment and detection method (55). Xiong *et al* (55), for example, identified a close relationship between hypoxia-associated prognostic signatures and immune-cell infiltration, including Treg accumulation, suggesting that Treg-associated immune remodeling may contribute to adverse clinical outcomes. Xiao *et al* (56) provided more direct evidence linking a Treg-regulatory factor with patient survival by showing that Galectin-9 is upregulated in LUAD, suppresses CD8⁺ T-cell cytotoxicity, promotes Treg expansion and is associated with increased Treg infiltration and poor survival. Importantly, the latter findings support a biologically plausible link between Treg accumulation and unfavorable outcome rather than merely describing a statistical correlation.

However, the prognostic role of Tregs should not be interpreted as uniformly detrimental in all LUAD patients. Tregs comprise functionally heterogeneous populations and their prognostic significance may depend on their phenotype, localization and interaction with other immune-cell populations. Spatial immune profiling has shown that the relative distribution of conventional CD4⁺ T cells, inducible Tregs, natural Tregs and CD8⁺ T cells can independently predict DFS, emphasizing that the composition and spatial organization of the T-cell compartment may provide more prognostic information than total Treg abundance alone (57). Thus, current

evidence supports Treg infiltration as an important component of the LUAD prognostic landscape, but does not establish a simple linear relationship in which increasing Treg numbers invariably predict poor outcome.

Molecular and cellular determinants associated with Treg-related prognosis. Beyond the direct assessment of Treg abundance, several studies have investigated tumor-associated molecules and cellular interactions that may influence Treg infiltration and thereby contribute to LUAD prognosis. These studies provide complementary evidence, but their ability to establish Tregs as the principal determinant of outcome varies considerably.

At the molecular level, GPD1L expression is reduced in LUAD and negatively correlates with Treg infiltration, while low GPD1L expression is associated with tumor progression and poor prognosis (58). Similarly, Zinc Finger CCCH-Type Containing 12D (ZC3H12D), a tumor suppressor involved in the regulation of inflammatory transcripts, is downregulated in LUAD and associated with shorter OS. Single-cell RNA sequencing further showed that ZC3H12D is highly expressed in immune-cell populations, including Tregs, suggesting a potential role in shaping the immune microenvironment (59-61). By contrast, SKA3 and TUBA1C are overexpressed in LUAD and associated with poor survival, together with increased infiltration of immunosuppressive populations including Tregs (61-63). Collectively, these findings support the existence of a Treg-associated molecular phenotype linked to unfavorable prognosis. Nevertheless, because these studies primarily establish associations among gene expression, Treg infiltration and survival, they do not by themselves demonstrate that altered Treg function is the causal mechanism through which these genes determine patient outcome.

The relationship between Tregs and the broader TME provides stronger biological context for these associations. The leukocyte-associated immunoglobulin-like receptor (LAIR) family functions as a collagen receptor and mediates interactions between immune cells and the extracellular matrix (64). LAIR2 expression is particularly enriched in FoxP3-expressing Tregs and the CD4+LAIR2+ Treg signature has prognostic significance in LUAD patients (65). Similarly, EPHA5 mutations are associated with increased CD8+ T-cell and M1 macrophage infiltration, reduced recruitment of immunosuppressive Tregs and prolonged survival in patients receiving immunotherapy (66). These findings suggest that the prognostic relevance of Tregs may depend not only on their absolute abundance but also on the balance between immunosuppressive and antitumor immune populations.

Other studies provide additional evidence that Tregs participate in a multicellular network within the LUAD TME. ILT4 is an immunosuppressive molecule predominantly expressed in myeloid innate cells and has been implicated in tumor proliferation, invasion and metastasis (67). Cancer-associated fibroblasts (CAFs) can cooperate with Tregs to establish an immunosuppressive niche and the coexistence of CAFs and FoxP3+ Tregs is associated with poor clinical outcomes in LUAD (68). In addition, immune regulatory molecules including ILT4, I κ B kinase α (IKK α), 5-hydroxytryptamine and GRP94 have been reported to promote Treg recruitment or activation, thereby contributing to immune escape and unfavorable prognosis (69-72).

Among these studies, the findings of Song *et al* (70) provide particularly important mechanistic support for the functional relevance of Tregs. Loss of IKK α in LUAD cells stimulates the production of Treg-inducing cytokines, thereby enhancing Treg recruitment and expansion within the TME. The resulting increase in Treg accumulation impairs antitumor immune responses and facilitates tumor immune escape. This study indicates that tumor-intrinsic alterations can actively reshape Treg-mediated immunosuppression through tumor-immune-cell communication. Therefore, Tregs may function not simply as a prognostic correlate, but as an intermediary linking tumor-cell alterations to immune suppression and disease progression.

Taken together, these molecular and cellular studies support a model in which Treg-associated prognosis is generated by interactions among tumor-intrinsic factors, stromal cells, immune regulatory molecules and effector immune populations rather than by Treg abundance alone. However, because a number of these studies rely on correlative analyses, their findings should be interpreted as evidence for a Treg-associated prognostic network rather than definitive evidence that Tregs independently determine patient survival. Biomarkers affecting Treg infiltration and LUAD prognosis are illustrated in Fig. 1 and summarized in Table I.

Treg-associated prognostic signatures and predictive models. Recent advances in transcriptomic analysis and computational biology have expanded the assessment of Treg-related prognostic features from single biomarkers to multidimensional molecular and immune signatures. Several studies have developed prognostic models incorporating immune infiltration, tumor metabolism, genetic alterations, or immune-related regulatory networks, consistently demonstrating that the composition of the LUAD immune microenvironment contains clinically relevant prognostic information. Shao *et al* (73) identified an alternative splicing-based prognostic signature associated with B-cell and immune infiltration, while Wang *et al* (74) developed an immune infiltration-related model that identified immune-cell populations associated with patient survival. Similarly, Li *et al* (75) established a mitochondrial-related gene signature associated with both immune infiltration and survival, suggesting an interplay between tumor metabolic status and immune regulation, whereas Gao *et al* (76) developed an immunophenotype-based risk score that effectively stratified patients according to distinct immune characteristics. Liu *et al* (77) further demonstrated that competing endogenous RNA networks interact with tumor-infiltrating immune cells to form prognostically relevant regulatory networks and Song *et al* (78) showed that an immune-related risk model incorporating TP53 status could predict both prognosis and immunotherapy response. Wu *et al* (79) likewise identified multi-gene immune-related signatures associated with prognosis and potential immunotherapy responsiveness. Fig. 2 and Table II show LUAD prognosis, survival and machine learning models derived from The Cancer Genome Atlas (TCGA; <https://portal.gdc.cancer.gov/>), Gene Expression Omnibus (GEO; <https://www.ncbi.nlm.nih.gov/geo/>), and Genotype-Tissue Expression (GTEx; <https://gtexportal.org/home/>) databases.

Taken together, these studies provide relatively consistent evidence that the immune landscape of LUAD, and the

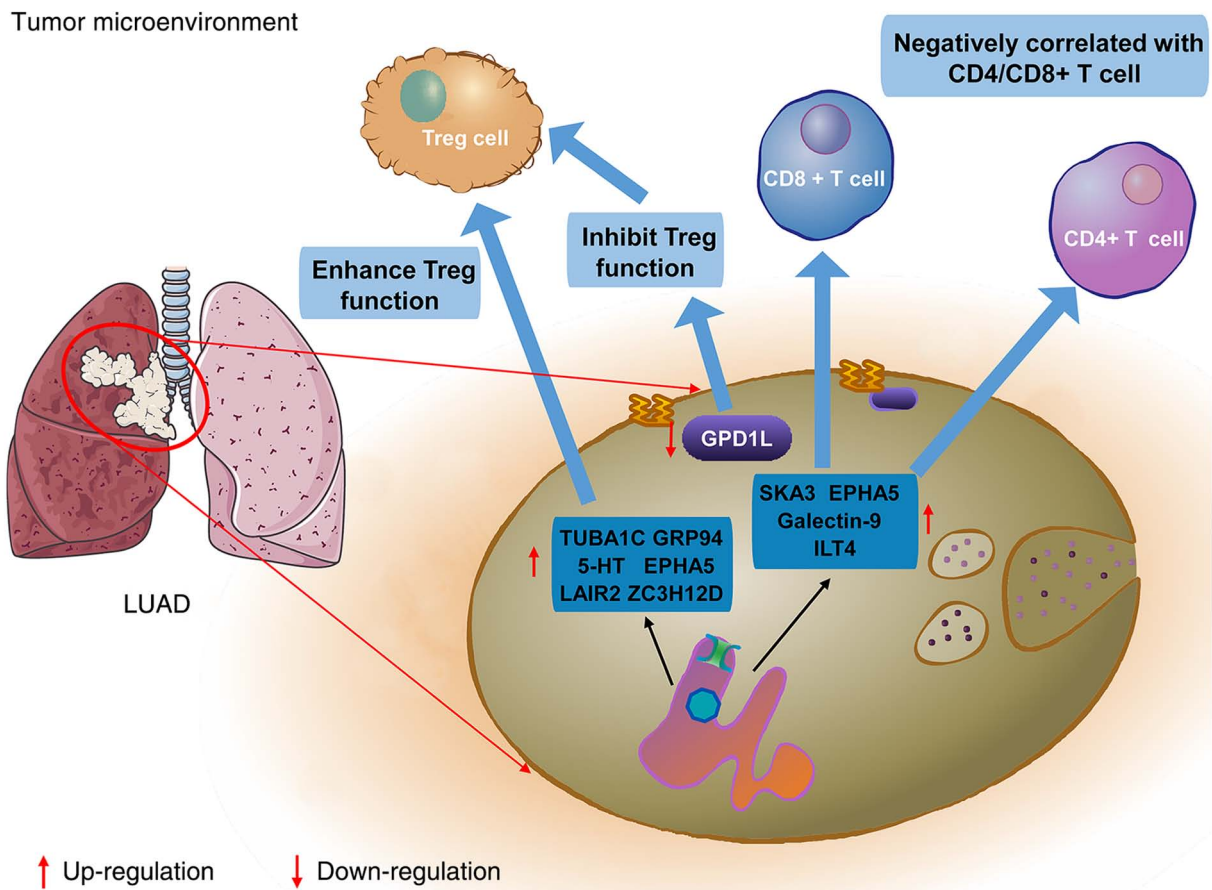


Figure 1. Biomarkers associated with Treg infiltration and prognosis in LUAD. This schematic summarizes key biomarkers involved in regulating Treg accumulation, activation and immunosuppressive function within the LUAD tumor microenvironment. It highlights their contributions to tumor immune regulation and clinical outcomes. Notably, Galectin-9, ZC3H12D, SKA3, LAIR2, TUBA1C, ILT4 and GRP94 are identified as dysregulated in LUAD, correlating with altered Treg infiltration and function. These molecules promote Treg proliferation and/or immunosuppressive activity while suppressing T cell-mediated antitumor immunity and are closely associated with unfavorable prognosis in LUAD patients. Treg, regulatory T cell; LUAD, lung adenocarcinoma; GRP94, glucose-regulated protein 94; ILT4, immunoglobulin-like transcript 4; LAIR2, leukocyte-associated immunoglobulin-like receptor 2; SKA3, spindle and kinetochore associated complex subunit 3; TUBA1C, tubulin alpha 1c; ZC3H12D, zinc finger CCCH-type containing 12D.

molecular programs associated with immune-cell infiltration, has substantial prognostic value. However, most of these models were not specifically designed around Tregs and their predictive performance reflects the combined contribution of multiple immune and tumor-related features. Therefore, they should be interpreted as indirect evidence supporting the prognostic relevance of Treg-associated immune states rather than as evidence that Tregs independently determine patient outcome. Among these studies, the work of Wang *et al* (80) provides more direct evidence for the clinical relevance of Treg biology, as a Treg-related prognostic nomogram was specifically developed for LUAD, demonstrating that Treg-associated genes can contribute to survival prediction. Nevertheless, even this Treg-focused model supports the prognostic utility of a Treg-associated molecular signature rather than establishing total Treg infiltration as a standalone biomarker. Thus, the current computational literature supports the concept that Treg-related molecular characteristics can improve prognostic risk stratification, but the incremental value of Treg-specific features over broader immune signatures remains to be systematically determined.

An important limitation is that most existing models are derived from bulk transcriptomic datasets, in which

Treg-associated signals may be confounded by other immune-cell populations, tumor purity, or differences in Treg abundance and phenotype. Moreover, the predictive performance of these models does not necessarily establish a biological or causal role for Tregs in determining survival. Future studies should therefore integrate Treg-specific single-cell and spatial features with clinical variables and longitudinal treatment information to determine whether specific tumor-promoting Treg subsets can provide more robust and reproducible prognostic information than bulk Treg-related signatures.

Tregs as prognostic biomarkers: Current evidence and future challenges. Overall, the available evidence supports several relatively robust conclusions. First, Tregs are consistently enriched in the LUAD TME and are associated with an immunosuppressive immune contexture (47,52-54). Second, a substantial proportion of clinical and molecular studies associate increased Treg infiltration or Treg-related signatures with advanced disease and unfavorable survival outcomes (55,56,58-65). Third, mechanistic studies such as the IKK α study provide biological support for the concept that tumor cells can actively promote Treg recruitment and expansion, thereby linking Treg accumulation to immune

Table I. Biomarkers for regulating Treg infiltration and LUAD prognosis.

First author/s, year	Number	Target genes	Expression level	Location	Function	Mechanism	(Refs.)
Xiao <i>et al.</i> , 2024	1	Galectin-9	Upregulation	LUAD	1. Inhibited CD8 ⁺ T cells 2. Induced Treg proliferation	Galectin-9 is regulated by NFATc2	(56)
Fan <i>et al.</i> , 2023	2	GPD1L	Downregulation	LUAD	1. Correlated with N stage and clinical stage 2. Negatively correlated with Treg and neutrophil infiltration 3. Inhibits the proliferation of LUAD	Not fully elucidated	(58)
Chen <i>et al.</i> , 2022	3	ZC3H12D	1. Downregulation in LUAD 2. Upregulation in Tregs	LUAD, Tregs and Immune cells	1. Negatively correlated with OS 2. Regulation of the ceRNA network	Regulates mRNA, miRNA, lncRNA, immune cells and immune molecules to affect the prognosis of LUAD	(60)
Lin <i>et al.</i> , 2022	4	SKA3	Upregulation	LUAD, Tregs and Immune cells	1. Correlated with poor survival 2. Negatively correlated with CD4/CD8 ⁺ T cells	SKA3 regulated the mitotic cell cycle, mitosis, chromosome segregation and cell division via pathways	(62)
Ly <i>et al.</i> , 2021	5	LAIR2	Upregulation	LUAD, Tregs and Immune cells	1. Correlated with poor survival 2. Enhanced <i>in vitro</i> tumor invasion into collagen	1. LAIR2 expression co-localized with Foxp3 2. LAIR2 was preferentially produced by activated CD4 ⁺ T cells	(65)
Bian <i>et al.</i> , 2021	6	TUBA1C	Upregulation	LUAD	1. Correlated with poor survival 2. Correlated with age, stage and lymph node metastasis 3. Activate and enhance the function of Tregs	TUBA1C regulated the cell cycle, p53 signaling pathway, glycolysis and gluconeogenesis	(63)
Chen <i>et al.</i> , 2020	7	EPHA5	EPHA5-mutant (Mut)	LUAD	1. Mut enhanced infiltration of CD8 ⁺ T cells and M1 macrophages 2. Mut decreased infiltration of Tregs	EPHA5 mutation cooccurred with homologous recombination (HR) or mismatch repair (MMR) gene mutations	(66)
Li <i>et al.</i> , 2020	8	ILT4	Upregulation	LUAD	1. Correlated with poor survival 2. Negatively correlated with CD8 ⁺ T cells 3. Enhance infiltration of Tregs	Not fully elucidated	(69)
Duan <i>et al.</i> , 2020	9	GRP94	Upregulation	LUAD	1. Correlated with poor survival 2. Enhance infiltration of Tregs	1. Inhibited the expression of caspase-7 and CHOP 2. Promoted the expression of TGF-beta and SMAD2	(71)

First author/s, year	Number	Target genes	Expression level	Location	Function	Mechanism	(Refs.)
Liu <i>et al</i> , 2019	10	5-HT	Upregulation	Serum	1. Correlated with poor survival 2. Enhance infiltration of Tregs 3. decreased the ratio of Th1/Th2 cells	5-HT1aR activates p-signal transducer and activator of transcription 3 (STAT3) and autophagy	(72)
Bahabayi <i>et al</i> , 2025	11	TCF1	Downregulation in Tregs	Tregs	TCF1-related indicators showed good auxiliary diagnostic significance for early LUAD	Downregulation of Notch signaling contributes to the decrease in TCF1 ⁺ Treg subsets	(127)
Wang <i>et al</i> , 2026	12	CCL20	Upregulation in Tregs	Tregs	1. High CCL20 expression correlated with increased Treg infiltration and served as an independent prognostic biomarker 2. CCL20 promoted the proliferation of LUAD	1. NF-κB/STAT signaling 2. CCL20-CCR6 ligand-receptor pair	(128)

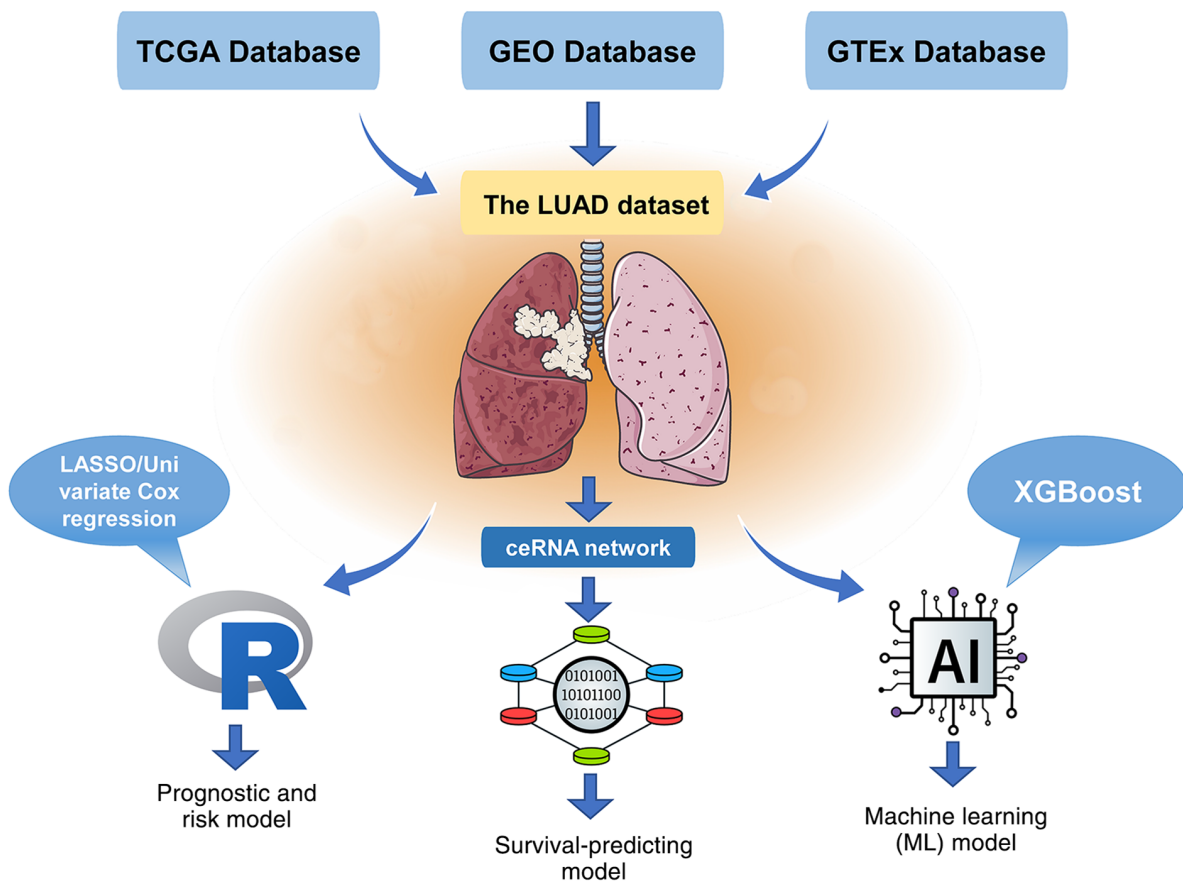


Figure 2. Prognostic prediction and immune infiltration models for LUAD based on TCGA, GEO and GTEx datasets. This figure presents machine learning-based prognostic models developed from extensive transcriptomic datasets, which offer potential approaches for predicting LUAD survival outcomes and immune infiltration characteristics. These models facilitate the identification of Treg-related prognostic biomarkers and immune signatures, providing insights into patient stratification and personalized immunotherapy strategies. However, further experimental validation is necessary to confirm the biological functions and clinical applicability of these predictive models. LUAD, lung adenocarcinoma; TCGA, The Cancer Genome Atlas; GEO, Gene Expression Omnibus; GTEx, Genotype-Tissue Expression; Treg, regulatory T cell.

suppression and tumor progression (70). Finally, computational studies indicate that Treg-associated molecular characteristics can contribute to prognostic risk stratification and may have potential value in predicting immunotherapy response (73-78).

Nevertheless, the current evidence does not justify concluding that Treg infiltration alone is a universally applicable or independent prognostic biomarker for LUAD. The prognostic effect may differ according to Treg subset, spatial localization, disease stage, detection methodology and the relative abundance of other immune populations. Furthermore, a number of molecular and machine-learning studies demonstrate associations rather than causality and their predictive performance may reflect the combined effects of multiple biological processes rather than Treg biology alone. Importantly, even when high Treg infiltration is associated with poor survival, this does not necessarily establish that Tregs are the primary drivers of tumor progression; Treg accumulation may also reflect an already established immunosuppressive or tumor-promoting microenvironment.

Therefore, the most appropriate interpretation of the current literature is that Treg infiltration and Treg-associated molecular signatures represent promising components of a multidimensional prognostic framework for LUAD, rather than definitive standalone biomarkers. Future studies should

determine whether specific tumor-promoting Treg subsets, rather than total Treg abundance, provide stronger and more reproducible prognostic information. Integrating single-cell sequencing, spatial transcriptomics, longitudinal clinical sampling and functional validation may help distinguish Tregs that actively drive tumor progression from those that primarily reflect the existing immune state of the tumor.

Mechanisms underlying Treg-mediated immune escape in LUAD. Tumor immune escape serves as a hallmark of cancer progression, with Tregs constituting one of the most significant immunosuppressive components within the LUAD TME. Unlike conventional immune cells that directly eliminate tumor cells, Tregs suppress antitumor immune responses through multiple mechanisms, including immune checkpoint regulation, secretion of inhibitory cytokines, metabolic remodeling and interactions with other stromal and immune populations. Increasing evidence indicates that Treg-mediated immune escape is not driven by a single pathway, but rather arises from coordinated regulation among tumor cells, immune cells and metabolic networks.

Immune inhibitory molecules mediated by Tregs. A primary mechanism through which Tregs facilitate immune escape is the expression of inhibitory receptors and immunosuppressive

Table II. Targeting Treg infiltration prognostic model of LUAD.

First author/s, year	Number	Prognostic model	Database	Model algorithm	Function	(Refs.)
Shao <i>et al</i> , 2023	1	Risk model (smRNA-seq)	TCGA	Cox regression analyses and LASSO regression	1. B cells were most markedly correlated with the risk score 2. Promotion of regulatory T cell differentiation	(73)
Wang <i>et al</i> , 2024	2	Machine learning (ML) model	TCGA, GTEx	The algorithm eXtreme Gradient Boosting (XGBoost)	1. Treg infiltration was negatively correlated with prognosis 2. PCBP1-AS1 was negatively correlated with Treg infiltration and TGF- β expression	(74)
Li <i>et al</i> , 2022	3	Prognostic model based on MTRGs	TCGA, GEO	1. Univariate Cox regression analysis 2. LASSO Cox regression analysis	1. The high-risk group was correlated with poor survival 2. Risk score was an independent predictor of LUAD prognosis 3. Treg infiltration was higher in the low-risk group	(75)
Gao <i>et al</i> , 2022	4	Prognostic risk score (PRS) model	TCGA, GEO	1. Univariate Cox regression analysis 2. LASSO Cox regression analysis	1. Tregs and PD-L1 were correlated with poor survival	(76)
Liu <i>et al</i> , 2022	6	Survival-predicting model	TCGA, GEO	1. CIBERSORT algorithm 2. ceRNA network	2. TH1Cs and IPSs are higher in the low-risk group Monocytes and Tregs were correlated with poor survival	(77)
Song <i>et al</i> , 2022	7	Immune-related risk model (IRM)	TCGA	LASSO algorithm	1. High-index group had lower relative infiltration of Tregs 2. The IRM index is positively correlated with PD-L1 expression	(78)
Wang <i>et al</i> , 2021	8	Prognostic nomogram model	TCGA, GEO	1. Nomogram algorithm 2. Cox regression analysis	High-index group was correlated with poor survival	(80)
Wu <i>et al</i> , 2020	9	Risk score model	TCGA, GEO	LASSO Cox regression analysis	Tregs enhanced activation and immunologic checkpoint molecular expression increase in the high-risk group	(79)
Szentkereszty <i>et al</i> , 2024	10	Retrospective study	A single-center case database	1. Immunohistochemical detection 2. Kaplan-Meier analysis 3. Multivariate Cox regression analysis	Detection of Nkp46 and FoxP3 positivity to identify NK and Tregs	(129)
Zhao <i>et al</i> , 2025	11.	Prognostic risk score (PRS) model	GEO	1. CIBERSORT and weighted correlation network analysis (WGCNA) 2. LASSO and univariate and multivariate Cox regression analyses	1. The expression of Treg surface markers in LUAD cells was increased 2. The expression of SCN9A was decreased compared with that in normal lung epithelial cells.	(130)

Table II. Continued.

First author/s, year	Number	Prognostic model	Database	Model algorithm	Function	(Refs.)
He <i>et al</i> , 2026	12	Single-cell Prognostic risk score (PRS) model	GEO	1. Univariate Cox and LASSO regression analyses 2. Kaplan-Meier and ROC curves 3. TMB, Spearman and functional enrichment analysis	1. The risk score could be an independent prognostic factor 2. CENPM, ZNF101, MAGEH1 and IKZF4 were up-regulated in LUAD	(131)
Xue <i>et al</i> , 2025	13	An anoikis- related prognostic model	GEO	1. Univariate Cox regression analysis, LASSO regression and random forest algorithms 2. Machine learning	1. This model can accurately predict the survival rate of LUAD patients 2. LUAD patients exhibited an immunosuppressive TME phenotype	(132)

molecules that directly impair effector immune responses. Tregs are known to highly express immune checkpoint molecules such as CTLA-4, PD-1, TIGIT and LAG-3, which suppress the activation and cytotoxic functions of CD8⁺ T cells and NK cells, thereby enabling tumor cells to evade immune surveillance (81). Among these molecules, CTLA-4 expressed by Tregs competitively binds to CD80/CD86 on antigen-presenting cells, reducing costimulatory signaling and limiting T cell activation. Studies indicate that blocking CTLA-4 signaling can diminish Treg-mediated immunosuppression and enhance antitumor immune responses, underscoring the significance of Treg-associated checkpoint regulation in cancer immunotherapy (82). In LUAD, tumor cells can further amplify Treg-mediated immune suppression by inducing immunoregulatory molecules. Tumor-derived factors, for example, promote Treg recruitment and activation through the CCL22/CCR4 axis, resulting in increased Treg accumulation at the tumor site and suppression of CD8⁺ T cell-mediated tumor killing (83,84). Additionally, tumor-associated immune checkpoint molecules and soluble immunosuppressive mediators contribute to sustaining Treg suppressive activity, facilitating immune escape (83,84).

Metabolic regulation contributes to Treg-mediated immune tolerance. Beyond immune checkpoint pathways, metabolic reprogramming within the TME plays a key role in maintaining Treg function and promoting immune escape. Tumor cells commonly generate a metabolically unfavorable environment characterized by glucose depletion, heightened lactate accumulation, hypoxia and altered amino acid metabolism. Tregs exhibit significant metabolic adaptability, allowing them to survive under these challenging conditions while maintaining suppressive activity as effector T cells become functionally exhausted (85). Glucose competition is a critical metabolic mechanism regulating Treg-mediated immune suppression. Activated Tregs efficiently utilize available metabolic substrates and resist metabolic stress, while glucose deprivation impairs effector T cell proliferation and cytokine production, conferring a selective advantage to Tregs in the TME (85). Furthermore, metabolic pathways related to lipid metabolism, mitochondrial activity and oxidative phosphorylation contribute to Treg stability and functional maintenance. Consequently, alterations in tumor metabolism may indirectly enhance Treg-mediated immune suppression and promote immune escape in LUAD (86). Glutamine (Gln) metabolism plays a vital role in LUAD. Liu *et al* (87) constructed a risk model for LUAD using Cox regression and Lasso regression analysis based on genes associated with Gln metabolism, categorizing patients into low-risk and high-risk groups. The low-risk group was characterized by low Gln metabolism, a survival advantage, a 'hot' immunophenotype and benefits from immunotherapy. Among immune cells, tumor-infiltrating T cells exhibited the most active levels of Gln metabolism, particularly highlighting CD8 T cell depletion and Treg suppression. These findings suggest that targeting the metabolic function of Tregs may present a promising strategy for restoring antitumor immunity.

Interaction between Tregs and other components of the LUAD microenvironment. Treg-mediated immune escape is a complex process that relies on extensive interactions between Tregs and various cellular components within the

TME. Tumor cells, tumor-associated macrophages (TAMs), CAFs and other immune populations work together to regulate Treg recruitment, expansion and suppressive function. Currently, advancements in single-cell technology have markedly contributed to the analysis of TME-infiltrating Tregs and their roles in immune escape. For instance, by utilizing scRNA-seq to identify molecular subtypes and homologous immune metabolism characteristics of LUAD immune cell marker genes, researchers developed the LID-score model. Patients with low LID scores demonstrate higher survival rates due to abundant immune cell infiltration, immune activation and low genetic variation. However, elevated levels of Tregs in the immune microenvironment can lead to immune cell dysfunction, promoting tumor immune escape and reducing responsiveness to immunotherapy (88). Furthermore, fibroblast growth factor 11 (FGF11) has been observed to accelerate tumor proliferation in various cancer types. Notably, FGF11 gene expression is negatively correlated with most immune cell populations, particularly with characteristic genes of functional T cells such as Tregs and resting Tregs. This suggests that FGF11 could emerge as a new biomarker in LUAD patients, as it may enhance tumor cell immune escape by promoting T-cell depletion within the TME, leading to poorer prognoses (89). Chemokines also play a critical role in tumor immunotherapy, with studies showing that CCL28 secreted by LUAD can induce Treg infiltration, further supporting immune escape (90). Animal studies have demonstrated that CCR2 knockout mice exhibit fewer CD4⁺ T cells and Tregs in tumors, alongside increased infiltration of CD8 T cells producing IFN- γ and granzyme B (91). Additionally, TNF- α -dependent inflammation related to LUAD has been shown to upregulate MHC-II in alveolar type II cells via CXCR-2, promoting Treg expansion (92).

Treg-related molecular signatures and implications for immunotherapy. With the advancement of transcriptomic sequencing and bioinformatics, there is growing interest in Treg-associated molecular signatures as potential biomarkers for immune escape and treatment response. Various studies have identified immune-related gene signatures linked with Treg infiltration, tumor progression and LUAD prognosis (93-95). These findings suggest that Treg-related characteristics may reflect tumor immune status and hold predictive value for immunotherapy.

Nonetheless, Treg-targeted therapeutic strategies pose challenges. While the depletion or functional inhibition of Tregs may enhance antitumor immunity, systemic elimination may induce autoimmune toxicity due to Tregs' critical role in maintaining immune homeostasis. Therefore, selectively targeting tumor-associated Tregs or their specific suppressive pathways is seen as a more promising therapeutic approach (96-98).

In summary, Tregs facilitate immune escape in LUAD through a multifaceted regulatory network involving inhibitory molecules, metabolic adaptations and interactions with other TME components. Tregs influence tumor characteristics through cytokines and ligands, activating multiple signaling pathways. Additionally, tumor cells recruit Tregs via chemokines, cytokines and metabolic regulations to enhance immune escape. Thus, understanding the functional heterogeneity of tumor-associated Tregs and identifying tumor-specific regulatory mechanisms are critical for developing targeted

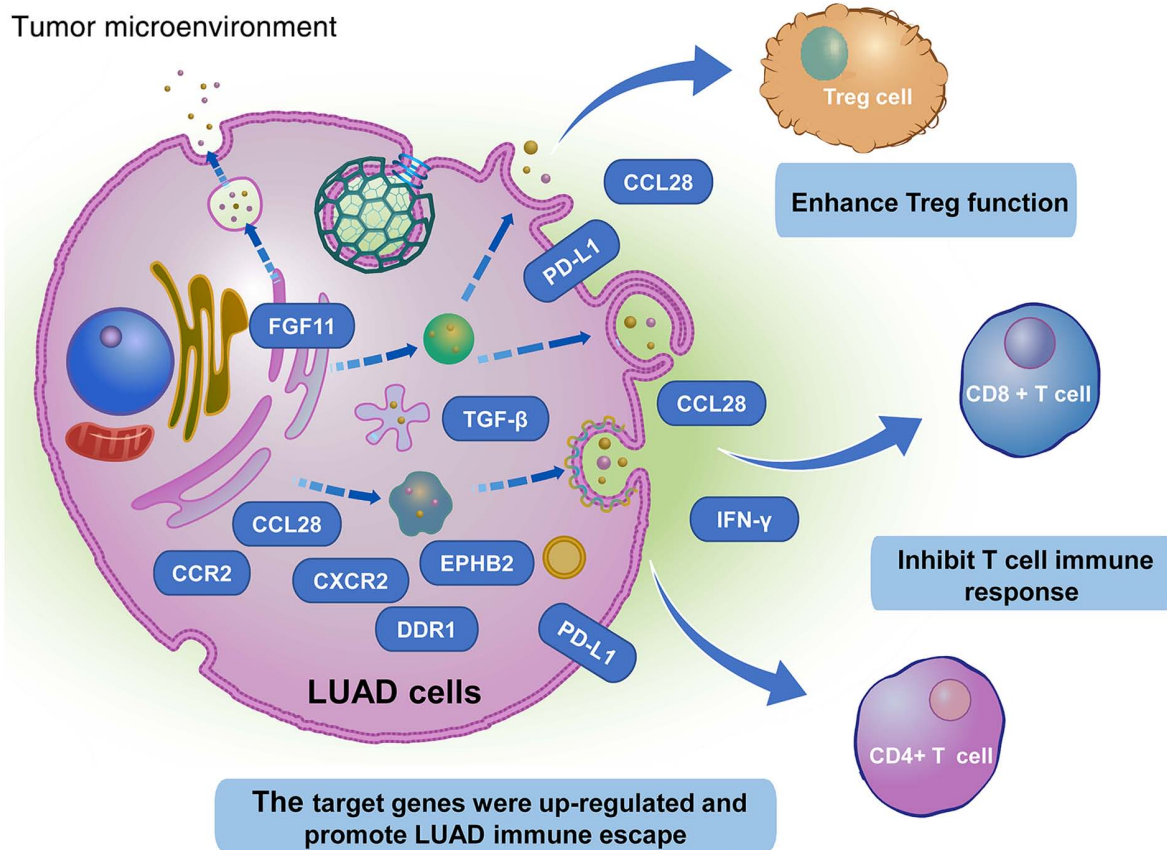


Figure 3. Biomarkers regulating Treg and T cell infiltration and promoting immune escape in LUAD. This schematic illustrates the major molecular pathways regulating the balance between immunosuppressive Tregs and antitumor effector T cells within the LUAD tumor microenvironment. Biomarkers such as FGF11, CCL28, CCR2, CXCR2, EPHB2, PD-L1, TGF-β and DDR1 are upregulated in LUAD and contribute to immune escape by promoting Treg recruitment, proliferation, or suppressive activity while impairing T cell-mediated antitumor immunity. These findings underscore the importance of targeting Treg-associated regulatory networks as a potential therapeutic strategy for LUAD. Treg, regulatory T cell; LUAD, lung adenocarcinoma; CCL28, C-C motif chemokine ligand 28; CCR2, C-C motif chemokine receptor 2; CXCR2, C-X-C motif chemokine receptor 2; DDR1, discoidin domain receptor tyrosine kinase 1; EPHB2, EPH receptor B2; FGF11, fibroblast growth factor 11; PD-L1, programmed death-ligand 1; TGF-β, transforming growth factor beta.

immunotherapeutic strategies. Biomarkers that promote immune escape in LUAD are illustrated in Fig. 3 and summarized in Table III.

Diagnosis of Tregs and LUAD. The prognostic value of tumor-infiltrating lymphocytes is critical in solid tumors, reflecting the immune response's ability to eliminate tumor cells and predicting the clinical efficacy of specific cancer therapies. The presence of Tregs is associated with patient survival across various tumor types (99). Numerous studies have reported correlations between Treg infiltration and disease prognosis in different tumors. However, methodologies to assess Treg levels in tumor tissue vary among studies; some have utilized immunohistochemical sections, while others have employed tissue microarrays (100). Recent analyses have highlighted the role of tumor-infiltrating Tregs in prognosis and diagnosis through bioinformatics, demonstrating their potential as markers for early tumor diagnosis and prognosis. Some studies have used FoxP3 as the sole marker for Tregs, while others have included FoxP3, CD25 and CCR4 (101). Furthermore, Treg prognostic significance is influenced by tumor site, molecular subtype and tumor stage (100). To accurately determine Treg levels in tumor tissues and assess their phenotypic characteristics and prognostic significance across

various tumor types, stages and histological or molecular subtypes, consistency in marker selection and meticulous analysis are essential. Such approaches will enhance the design of more effective immunotherapies and aid in identifying appropriate targets for Treg treatment in select solid tumor patients.

Recently, tumor mutation burden (TMB) has emerged as a promising biomarker for predicting immunotherapy efficacy across different tumor types (102). Tumor protein D52-like 2 (TPD52L2), a member of the TPD52 family, regulates tumor cell proliferation and apoptosis. Zhong *et al* (103) evaluated the correlation between TPD52L2 and levels of immune cell infiltration, immunosuppressive genes and TMB in LUAD. Results indicated that TPD52L2 was highly expressed in LUAD and predicted poorer survival outcomes, with a positive correlation identified between TPD52L2 expression and Treg infiltration levels, suggesting that TPD52L2 may serve as a potential prognostic biomarker. Additionally, Tregs play a role in the early development of lesions associated with LUAD. An independent study of resected lung nodules, including adenocarcinomas and associated precancerous lesions, confirmed increased Treg levels in these precancerous conditions (104). Zhao *et al* (105) collected blood samples from 35 healthy controls and 34 early-stage LUAD patients, with flow cytometry analysis revealing upregulated proportions and absolute

Table III. Biomarkers for regulating Treg infiltration and LUAD immune escape.

First author/s, year	Number	Target Genes	Expression level	Location	Function	(Refs.)
Zhai <i>et al</i> , 2023	1	FGF11	Upregulation	LUAD	1. Correlated with poor survival 2. Enhance infiltration of Tregs	(89)
Su <i>et al</i> , 2023	2	CCL28	Upregulation	LUAD	1. Enhance infiltration of Tregs 2. Inhibited the immune response to treatment	(90)
Mittal <i>et al</i> , 2020	3	CCR2 MCP-1	Upregulation	LUAD	1. Promote MDSC recruitment to TME 2. Inhibition of the host T cell immune response	(91)
Guo <i>et al</i> , 2020	4	CXCR-2 TNF- α	Upregulation	LUAD	Enhance the proliferation of Tregs	(92)
Liu <i>et al</i> , 2022	6	EPHB2	Upregulation	LUAD	1. Promote LUAD proliferation, invasion and migration 2. Enhance the suppressive function of Tregs	(87)
Liu <i>et al</i> , 2021	7	CCL28	Upregulation	LUAD	1. Enhance the angiogenesis and metastasis of LUAD 2. Enhance the proliferation of Tregs	(95)
Shima <i>et al</i> , 2020	8	PD-L1	Upregulation	LUAD	Enhance the proliferation of Tregs	(96)
Islas-Vazquez <i>et al</i> , 2015	9	TGF- β (LAP)	Upregulation	Tregs	Enhance the suppressive function of Tregs	(97)
Maitz <i>et al</i> , 2023	10	DDR1	Upregulation	LUAD	Knockout of DDR1 increased the tumor burden, decreased CD8 ⁺ cytotoxic T cells, increased CD4 ⁺ helper T cells and Tregs.	(98)
Huang <i>et al</i> , 2024	11.	Ku70	Upregulation	Tregs	1. Repair DNA double-strand breaks 2. Enhance the suppressive function of Tregs	(133)

CCL28, C-C motif chemokine ligand 28; CCR2, C-C motif chemokine receptor 2; CD4, cluster of differentiation 4; CD8, cluster of differentiation 8; CXCR2, C-X-C motif chemokine receptor 2; DDR1, discoidin domain receptor tyrosine kinase 1; DNA, deoxyribonucleic acid; EPHB2, EPH receptor B2; FGF11, fibroblast growth factor 11; Ku70, Ku autoantigen 70 kDa; LAP, latency-associated peptide; LUAD, lung adenocarcinoma; MCP-1, monocyte chemoattractant protein 1; MDSC, myeloid-derived suppressor cell; PD-L1, programmed death-ligand 1; TGF- β , transforming growth factor beta; TME, tumor microenvironment.

numbers of Tregs in the peripheral blood of LUAD patients. Moreover, INTS7, a subunit of the integrin complex, is found to be upregulated in various tumors (106). INTS7 expression negatively correlates with the infiltration of memory B cells, Tregs, monocytes and activated mast cells. Consequently, INTS7 may serve as a potential diagnostic marker for LUAD (106). Thus, Treg upregulation contributes to the early diagnosis of LUAD.

Therapeutic strategies and research progress of targeting Tregs. Due to the role of Tregs in tumor immunity, various therapeutic approaches targeting Tregs have emerged in tumor therapy, including the disruption of their immunosuppressive function, blockade of their transport to tumors and inhibition of their development and activation (107,108). Currently, targeting Tregs in LUAD therapeutic strategies often involves

two or more of these approaches to enhance antitumor immunity (109). Research by Zhang *et al* (110) demonstrated that Pexidartinib reduces the CCL22 source from TAMs in LUAD, thereby suppressing Treg infiltration and enhancing the efficacy of PD-1 antibody therapy. Following Pexidartinib treatment, the total number of T cells, CD8⁺ T cells and Tregs decreased, while the CD8⁺/Treg ratio markedly increased. When Pexidartinib was combined with PD-1 antibody in LUAD subcutaneous tumor models, this combined treatment improved tumor treatment efficacy compared with monotherapy (111). Monocarboxylate transporter 4 (MCT4), responsible for lactate efflux, has been associated with poor prognosis in various tumors (112). TMPs coated with Fluvastatin (TMP-F) were found to slow LUAD progression by inhibiting MCT4 expression and blocking lactate outflow. TMP-F induced infiltration of NK cells and CD8⁺ T cells while

polarizing M2 macrophages to M1 macrophages. The depletion of Tregs and myeloid-derived suppressor cells (MDSCs) reversed the immunosuppressive TME. Additionally, TMP-F enhanced the antitumor effects of cisplatin and inhibited lung metastasis. Overall, TMP-F treatment, alone or in combination with cisplatin, represents a promising strategy to improve efficacy in LUAD (112). Fu-Zheng-Qu-Xie decoction, a traditional Chinese medicine, has shown potential in improving immune function and survival in early lung cancer patients (113). Zhang *et al* (113) evaluated the clinical efficacy of this herbal prescription in preventing postoperative recurrence and metastasis of early-stage LUAD. Following administration of FZQX, positive immune indicators ($CD4^+$ T/ $CD8^+$ T) increased, while negative immune indicators ($CD8^+$ T, MDSCs, Tregs) decreased. Furthermore, FZQX prescription regulated MDSCs to remodel the immunosuppressive TME, thereby contributing to the prevention of lung cancer recurrence. Ganesan *et al* (114) utilized CD25-depleting mAb monotherapy to preferentially deplete Tregs, thereby enhancing $CD8^+$ T-cell-mediated antitumor immunity. The combination with Carboplatin therapy markedly improved survival in LUAD patients, indicating that Treg depletion coupled with cytotoxic therapy may serve as an advantageous treatment strategy for advanced LUAD.

5. Prospects

Tregs play a pivotal role in maintaining immune homeostasis and modulating antitumor immune responses. In LUAD, increasing evidence indicates that tumor-associated Tregs contribute to tumor progression, immune escape and resistance to immunotherapy by suppressing effector immune cells and remodeling the TME. Consequently, targeting Tregs has emerged as a promising therapeutic strategy to enhance treatment outcomes in LUAD. However, despite significant advances in understanding Treg biology, challenges persist regarding the precise identification, selective targeting and clinical translation of Treg-based therapies.

While Treg depletion or functional inhibition can enhance antitumor immunity, the systemic elimination of Tregs carries a risk of autoimmune toxicity due to their vital role in maintaining immune tolerance. Future studies should therefore concentrate on developing strategies that selectively target tumor-infiltrating Tregs while preserving peripheral immune homeostasis. Potential approaches may involve targeting tumor-enriched Treg-associated molecules, chemokine receptors, immune checkpoints, or signaling pathways that are preferentially activated in tumor-associated Tregs. For instance, identifying LUAD-specific Treg surface markers and developing antibody-based therapies, small-molecule inhibitors, or engineered immune cells aimed at these molecules could lead to more precise therapeutic strategies compared with global Treg depletion (115).

Another significant challenge is the functional heterogeneity of Tregs within LUAD. Current evidence suggests that Tregs constitute a diverse population comprising multiple subsets with distinct transcriptional profiles, spatial distributions and immunosuppressive functions. Traditional bulk transcriptomic approaches cannot accurately differentiate these functional subsets. Therefore, techniques such as scRNA-seq, single-cell epigenomic analysis and spatial transcriptomics

offer powerful methodologies for identifying tumor-specific Treg populations while revealing their developmental trajectories, cellular interactions and regulatory mechanisms. Future integration of single-cell multi-omics and spatial analysis may facilitate the identification of highly suppressive Treg subsets and unveil new targets for precision immunotherapy (116).

In addition to directly targeting Tregs, combination therapeutic strategies may represent a more effective means of overcoming Treg-mediated immune suppression. Given that Tregs extensively interact with metabolic pathways and other TME components, combining Treg-targeted therapies with metabolic inhibitors may disrupt the metabolic advantages that sustain Treg survival and function. Furthermore, combining these therapies with ICIs, tumor vaccines, or other immunotherapeutic approaches could enhance effector immune responses and improve treatment efficacy. Such strategies may help overcome the limitations of single-agent immunotherapy and achieve more durable antitumor responses in LUAD patients (117,118).

Studies have demonstrated that immune-related gene signatures and Treg-associated molecular characteristics may serve as potential biomarkers for predicting LUAD prognosis and responses to immunotherapy (119-125). However, most current prediction models rely on bulk sequencing data, which may not fully capture the complex spatial and functional heterogeneity of Tregs within tumors. The rapid advancement of artificial intelligence (AI) and machine learning approaches offers new opportunities for integrating transcriptomic, spatial, clinical and immunological data, potentially enhancing patient stratification and treatment selection. AI-based models may assist in identifying patients with Treg-dominant immunosuppressive microenvironments and predicting their responses to Treg-targeted therapies or combination immunotherapies (126).

Moreover, the translation of Treg-related findings into clinical applications necessitates further investigation into treatment safety, optimal therapeutic timing and patient selection criteria. Dynamic changes in Tregs during tumor progression and therapeutic intervention remain inadequately understood. Longitudinal studies that combine clinical samples, single-cell sequencing and functional validation will be essential in elucidating how Treg populations evolve throughout PD and treatment resistance. In conclusion, Tregs represent a key regulatory component of the LUAD immune microenvironment, markedly influencing tumor immune escape and therapeutic resistance. Future advancements in selective Treg targeting strategies, single-cell and spatial technologies, combination immunotherapy and AI-driven precision medicine will create new avenues for understanding and manipulating Treg biology, ultimately enhancing the clinical management of LUAD patients.

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Authors' contributions

LJW was responsible for conceptualization and supervision and writing-review and funding acquisition and editing. CJR was responsible for conceptualization and supervision and writing-review and editing. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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