Review Article

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Insights into the mechanisms of drug resistance in renal cell carcinoma: from multi-omics perspective

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Abstract

Renal cell carcinoma (RCC) is a prevalent malignancy of the urinary system. Despite significant advances achieved through targeted therapies and immunotherapies, therapeutic resistance remains a major obstacle to sustained clinical efficacy. This review comprehensively examines the molecular mechanisms driving resistance to both targeted therapy and immunotherapy in RCC from a multi-omics perspective. By integrating findings across diverse omics layers, we underscore the pivotal role of multi-level regulatory networks in mediating drug resistance and immune evasion. Our objective is to provide an in-depth understanding of these resistance mechanisms and to establish a theoretical framework for developing innovative therapeutic strategies aimed at overcoming resistance, thereby facilitating the advancement of precision oncology in RCC.

Keywords: drug resistance, immunotherapy, multi-omics, renal cell carcinoma, targeted therapy

Introduction

Renal cell carcinoma (RCC) is one of the most prevalent malignancies of the urinary system, accounting for approximately 2%–3% of all global cancer cases. Established risk factors include smoking, obesity, and genetic predisposition[1–4]. According to GLOBOCAN data, more than 434 000 new RCC cases were diagnosed worldwide in 2022, resulting in nearly 156 000 deaths. Notably, RCC incidence is significantly higher in males than in females, with a male-to-female ratio of approximately 1.5:1[1]. While surgical resection remains the standard treatment for early-stage RCC, around 30% of patients with locally advanced disease experience postoperative recurrence. The prognosis for metastatic RCC (mRCC) remains poor, with a 5-year survival rate of less than 15%[5,6].

In recent years, targeted therapies against angiogenic and metabolic signaling pathways have markedly improved outcomes for patients with advanced RCC[7,8]. However, the emergence of therapeutic resistance has become a major clinical challenge. A substantial proportion of patients develop primary or acquired resistance within 6–15 months of treatment, resulting in tumor relapse or progression[9]. Similarly, although immune checkpoint inhibitors (ICIs) have revolutionized RCC management, their clinical efficacy is hampered by tumor microenvironment heterogeneity and immune tolerance mechanisms, with only 20%–30% of patients achieving durable responses.

Therefore, elucidating the molecular basis of resistance to targeted therapies and immune evasion has become a central challenge in overcoming therapeutic limitations in RCC. Increasing evidence indicates that genetic alterations, epigenetic remodeling, metabolic reprogramming, and modifications of the immune microenvironment collectively contribute to resistance[10–13]. However, traditional single-omics approaches are insufficient to comprehensively

HIGHLIGHTS

- Multi-omics approaches reveal complex regulatory networks driving therapeutic resistance and immune evasion.
- Tumor microenvironment heterogeneity contributes to immunotherapy failure and treatment relapse.
- Integration of genomics, transcriptomics, and epigenomics provides novel insights into resistance mechanisms.
- A systems-level understanding may guide precision strategies to overcome resistance in RCC.

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dissect the dynamic evolution of resistance or to elucidate the complex interplay between gene regulatory networks and phenotypic outcomes.

In this context, multi-omics strategies integrating genomics, transcriptomics, epigenomics, proteomics, and metabolomics provide a powerful framework for systematically deciphering resistance mechanisms[14]. These approaches not only identify key driver events but also reveal multi-layered regulatory networks and dynamic biomarkers[15]. Moreover, the integration of single-cell sequencing and spatial omics technologies enables precise mapping of tumor heterogeneity and microenvironmental interactions that contribute to resistance[16]. Combining multi-omics data with clinical insights holds great promise for developing rational combination therapies, such as targeted-immunotherapy regimens or epigenetic-metabolic interventions, to overcome resistance and advance precision medicine in RCC.

This review systematically explores the molecular mechanisms of resistance to targeted therapies and immune evasion in RCC through a multi-omics lens. We highlight recent advances in understanding the roles of genomic mutations, epigenetic regulation, transcriptional control, and post-transcriptional and post-translational modifications (PTMs) in driving resistance to targeted therapies. Subsequently, we delve into multi-omics studies of immune tolerance, examining how tumor genomic alterations, epigenetic remodeling, transcriptional dysregulation, and protein modifications shape the immunosuppressive microenvironment, thereby compromising the efficacy of immunotherapy. By integrating multi-omics data with clinical evidence, this review aims to provide a comprehensive overview of resistance mechanisms in RCC and to lay a theoretical foundation for developing innovative therapeutic strategies (Fig. 1). This review is compliant with the TITAN Guidelines 2025[17].

Genomics and mutations

Targeted therapy resistance

Gene mutations play a pivotal role in the initiation, progression, and treatment response of RCC, influencing the efficacy of targeted therapies through various mechanisms, including alterations in drug targets, activation of compensatory signaling pathways, and enhancement of immune evasion. Among these, inactivation mutations or deletions of the Von Hippel-Lindau (VHL) gene represent the most frequent genetic aberration in RCC, particularly in clear cell RCC (ccRCC), where approximately 90% of cases exhibit VHL alterations[18]. These mutations typically result in activation of the hypoxia-inducible factor (HIF) pathway, promoting angiogenesis, tumor proliferation, and metastasis[19,20]. Although VHL mutations are strongly associated with RCC pathogenesis, several studies have shown that they do not significantly influence resistance to VEGF or mTOR inhibitors (Fig. 2) [21,22].

Advances in genomics and multi-omics technologies have enabled the identification of additional genetic alterations associated with resistance, offering new avenues for personalized therapy. Beyond VHL, other frequently mutated genes are also commonly found in RCC include PBRM1, SETD2, KDM5C, PTEN, BAP1, mTOR, and TP53, many of which are involved in chromatin remodeling, DNA repair, and the PI3K/AKT/mTOR pathway[20,23]. Similarly, Sato *et al*'s study further elucidated the genetic background of ccRCC using whole-genome, exome, and RNA sequencing technologies[10,24]. Understanding these mutations not only elucidates tumor biology but also facilitates mechanistic investigations into therapeutic resistance.

Evidence regarding the clinical relevance of these mutations remains complex. In a study involving 79 patients with mRCC, Kwiatkowski *et al* reported that mutations in TSC1, TSC2, and mTOR correlated with favorable responses to mTOR inhibitors,

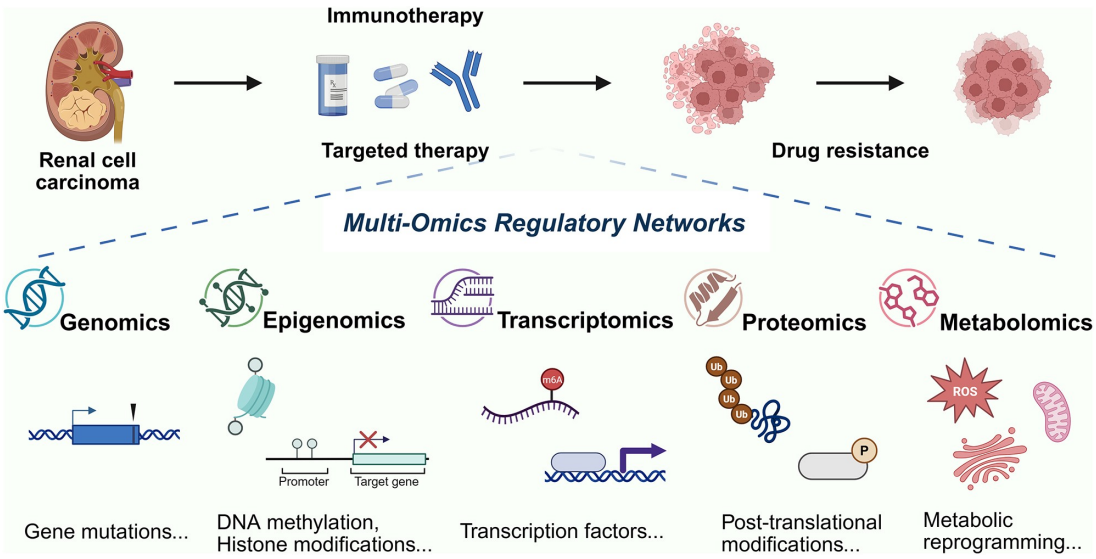

Figure 1. Multi-omics regulatory networks in RCC resistance mechanisms. The diagram depicts the interrelated multi-omics regulatory networks in RCC, illustrating how genomics, epigenomics, transcriptomics, proteomics, and metabolomics converge to drive resistance to targeted therapy and immunotherapy. These omics layers are interconnected, with each influencing the others to regulate tumor progression, immune evasion, and treatment resistance. This figure was created using BioRender (www.Biorender.Com).

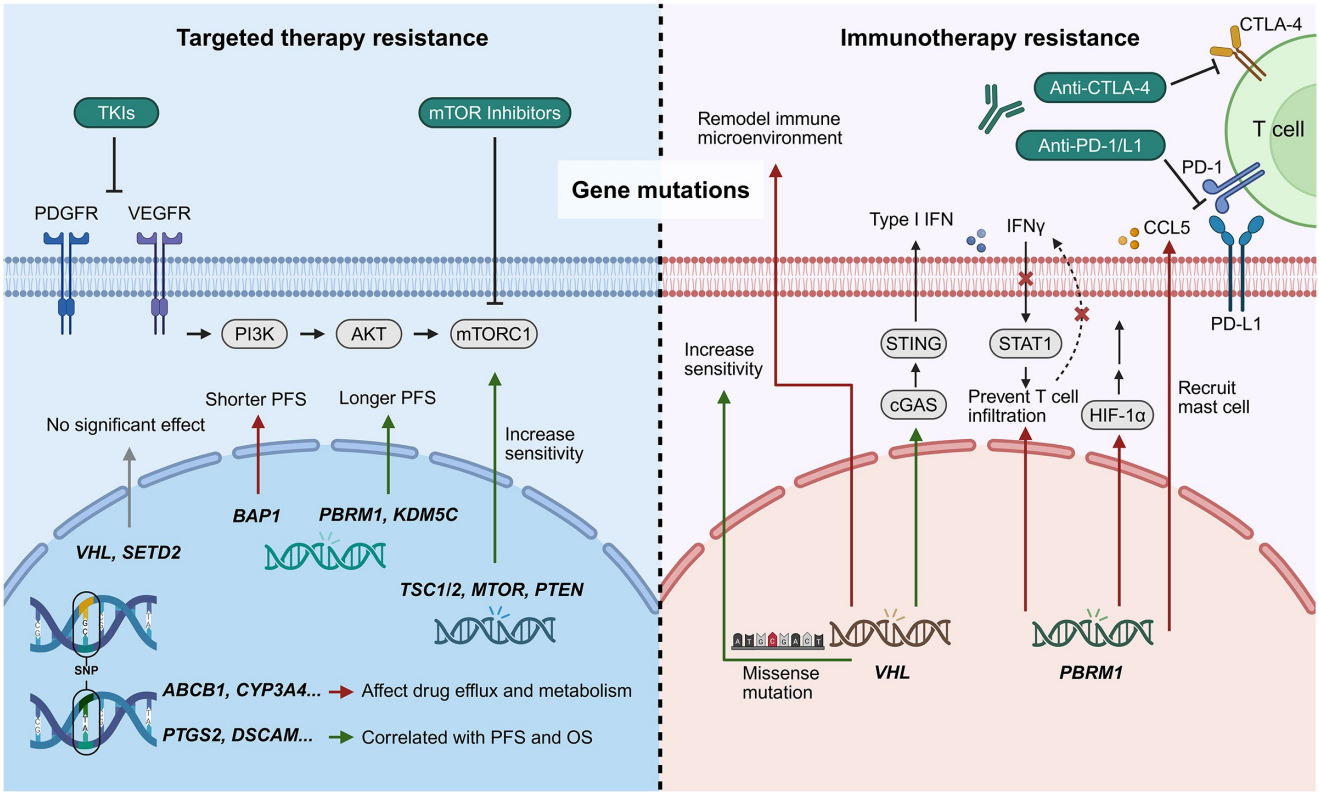

Figure 2. Genomic and mutational alterations contributing to resistance to targeted therapy and immunotherapy. The left panel illustrates representative gene mutations and single nucleotide polymorphisms (SNPs) associated with response or resistance to targeted therapies. The right panel illustrates key mutations involved in immunotherapy outcomes. The role of VHL mutations in immunotherapy response remains controversial, as they may affect efficacy through multiple pathways. This figure was created using BioRender (www.Biorender.Com).

with a higher frequency of mutations observed in partial responders (Fig. 2)[22].

Similarly, a study analyzing 105 mRCC samples found that patients harboring mutations in the mTOR pathway exhibited better responses to treatment[25]. Interestingly, patients with PTEN-deficient tumors were more likely to benefit from mTOR inhibitors, particularly when concurrent mutations in mTOR pathway genes were present. Supporting this observation, Liu *et al* further demonstrated that loss of PTEN enhances dependence on PI3K/AKT/mTOR signaling, increasing the sensitivity of ccRCC cells to mTOR inhibitors. In contrast, mutations in chromatin remodeling genes such as PBRM1, SETD2, BAP1, and KDM5C did not significantly affect mTOR inhibitor efficacy[26].

However, other studies have produced conflicting results. For example, Voss *et al* found no significant association between TSC1, TSC2, or mTOR mutation status and progression-free survival (PFS) in patients treated with everolimus[27]. In the RECORD-3 randomized trial, Hsieh *et al* reported that PBRM1 and KDM5C mutations were associated with longer PFS following treatment with everolimus or sunitinib, whereas BAP1 mutations predicted poorer prognosis (Fig. 2). Although high-frequency mutations such as VHL, SETD2, and PTEN were prevalent, they did not demonstrate significant associations with PFS or overall survival (OS) in patients receiving targeted therapy[21,28]. Overall, these findings underscore the complex and sometimes contradictory role of genetic mutations in mediating resistance, highlighting the need for further validation in large, well-characterized cohorts.

Beyond point mutations, single nucleotide polymorphisms (SNPs) are another important layer of genetic variation that may influence therapeutic response. SNPs are widespread throughout the genome, and accumulating evidence suggests that they contribute to resistance in mRCC[29,30]. Variants in genes such as ABCB1 and ABCG2, which encode ATP-binding cassette (ABC) efflux transporters involved in sunitinib pharmacokinetics, and CYP3A4/CYP3A5, which encode sunitinib-metabolizing enzymes, have been shown to affect drug metabolism, transport, and bioavailability, potentially leading to resistance (Fig. 2)[31–33].

Moreover, SNPs such as rs5275 (PTGS2), rs9582036 (VEGFR1), rs307821 (VEGFR3), rs231775 (CTLA-4), rs28520013 (PDLIM3), and rs2205096 (DSCAM) have been significantly associated with PFS and OS in sunitinib-treated patients (Fig. 2)[34–39]. These findings provide a genetic framework for understanding inter-individual variability in therapeutic efficacy. However, the precise molecular mechanisms by which these SNPs influence resistance remain to be elucidated, underscoring the need for further experimental studies and large-scale clinical validation.

Immunotherapy resistance

The frequent deletion of the VHL gene is a hallmark molecular event in RCC and is considered a key driver of tumor initiation, primarily by disrupting hypoxia-sensing and regulatory pathways[23]. Recent studies have further demonstrated that VHL loss also remodels the immune microenvironment

(Fig. 2). Specifically, VHL deletion in RCC has been associated with both reduced tumor proliferation and increased infiltration of conventional and regulatory CD4⁺ T cells, as well as the emergence of a glucose-consuming tumor-associated macrophage (TAM) subset with enhanced phagocytic capacity[40]. Concurrently, VHL knockout tumors show reduced responsiveness to anti-PD-1 therapy, potentially due to impaired lymphocyte activation.

Conversely, restoration of VHL expression upregulates vascular cell adhesion molecule-1 (VCAM-1), which promotes antitumor immunity through interaction with α4β1 integrins on immune cells[41]. However, VHL-deficient tumors may also exhibit enhanced anti-PD-1 efficacy under certain conditions. This has been attributed to HIF-1α/2α-mediated reduction in mitochondrial membrane potential, leading to cytoplasmic leakage of mitochondrial DNA, subsequent activation of the cyclic GMP-AMP synthase-interferon gene-stimulating factor (cGAS-STING) pathway, and induction of type I interferons, which enhance T cell-dependent antitumor responses (Fig. 2)[42]. These seemingly contradictory findings may reflect heterogeneity in VHL mutation types.

To address this, recent studies have stratified VHL mutations into two subtypes: truncating mutations (VHL^{Trunc}) and missense mutations (VHL^{Miss}). Notably, tumors harboring VHL^{Miss} mutations exhibit hyperactivation of cell cycle and NF-κB signaling pathways and show improved sensitivity to immunotherapy (Fig. 2)[43]. These findings underscore the importance of stratifying RCC patients based on VHL mutation subtypes to guide personalized treatment strategies.

Similarly, PBRM1 loss-of-function mutations have been shown to impair the efficacy of ICI in RCC. Mechanistically, PBRM1 deficiency disrupts the binding of brahma-related gene 1 (BRG1) to the interferon-γ receptor 2 (IFNGR2) promoter, resulting in reduced expression and secretion of IFNγ (Fig. 2)[44]. Additionally, PBRM1 mutations activate HIF-related pathways and upregulate C-C motif chemokine ligand 5 (CCL5), promoting mast cell infiltration and the establishment of an immunosuppressive tumor microenvironment, thereby contributing to tumor progression and poor prognosis (Fig. 2)[45]. Therefore, stratifying patients based on PBRM1 mutational status may thus enhance the prediction of immune checkpoint blockade (ICB) response and enable the development of tailored therapeutic approaches[46].

Furthermore, deletion of the chromosome 9p21.3 region has been implicated in both pancreatic metastasis and the classification of a distinct RCC subtype, translocation RCC. This subtype exhibits variable responsiveness to anti-angiogenic therapies but tends to respond more favorably to immunotherapy, potentially due to increased CD8⁺ T cell infiltration[47,48]. These insights highlight the necessity of comprehensive mutational profiling in RCC, both for the identification of biologically distinct subtypes and as a foundation for personalized therapeutic decision-making.

DNA modifications and epigenetics

Targeted therapy resistance

Epigenetics refers to heritable alterations in gene expression that occur without changes to the underlying DNA sequence[49,50]. Epigenetic modifications play a crucial role in the initiation and progression of RCC and are considered key drivers of tumor progression[51]. In RCC, common mutations such as PBRM1 and SETD2 are closely linked to defects in chromatin remodeling and epigenetic regulation. These mutations influence the epigenetic landscape of tumor cells, thereby reshaping gene expression patterns, promoting tumor progression, and contributing to therapeutic resistance[52].

Major epigenetic mechanisms include DNA methylation, histone modifications, and chromatin remodeling. Increasing evidence indicates that these modifications are involved in resistance to tyrosine kinase inhibitors (TKIs), such as sunitinib, through regulation of gene transcription, activation of compensatory pathways, modulation of the tumor microenvironment, and enhancement of genomic instability[11,12,53].

DNA methylation involves the addition of a methyl group to the fifth carbon of cytosine residues in genomic DNA, catalyzed by DNA methyltransferases (DNMTs), resulting in the formation of 5-methylcytosine (5-mC). This typically occurs in CpG islands within gene promoter regions and represses gene transcription by inhibiting transcription factor binding[54]. In ccRCC, VHL gene inactivation is frequently caused by gene mutations or promoter hypermethylation[55,56]. Loss of VHL function leads to the accumulation of HIF-1α and HIF-2α, resulting in aberrant activation of HIF signaling pathways (Fig. 3)[57]. This activation promotes angiogenesis, metabolic reprogramming, and downstream gene expression changes, creating a favorable environment for resistance to targeted therapies[11].

Stewart *et al* reported that sunitinib treatment significantly increased methylation levels in the VHL promoter region in tumor samples, suggesting an adaptive epigenetic response to therapeutic pressure that may enhance tumor survival via HIF pathway regulation (Fig. 3)[58]. Alterations in other key genes such as PBRM1 and CAIX were also observed, further contributing to intratumoral heterogeneity and facilitating resistance mechanisms in mRCC[59]. However, in contrast, Choueiri *et al* found no significant correlation between VHL mutation or methylation status and objective response rate or PFS in ccRCC patients treated with pazopanib (Fig. 3)[60], highlighting the complexity of epigenetic regulation. Other epigenetically regulated genes have also been implicated in TKI resistance. Zhao *et al* showed that RCC patients with low expression of glutaminyl peptide cyclotransferase (QPCT) exhibited significantly improved PFS following sunitinib treatment[61]. Mechanistically, QPCT promoter hypomethylation enhances NF-κB (p65) binding and upregulates QPCT transcription. Elevated QPCT stabilizes HRAS by preventing its ubiquitin-mediated degradation, which in turn activates the ERK signaling pathway and promotes resistance (Fig. 3)[61,62]. Similarly, hypermethylation of the FLT1 promoter suppresses its expression, thereby impairing the anti-proliferative effects of sunitinib and axitinib, whereas FLT1 demethylation restores its expression and enhances treatment efficacy[63]. The metabolic gene PCK2 is also downregulated in RCC due to promoter hypermethylation. Restoring PCK2 expression through the demethylating agent 5-AZA or CRISPR/dCas9-mediated targeted demethylation sensitizes RCC cells to sunitinib by promoting endoplasmic reticulum (ER) stress (Fig. 3)[64]. Additionally, PON1 promoter hypermethylation has been linked to increased proliferation, migration, and invasion in sunitinib-resistant RCC cells. Treatment with 5-AZA and histone deacetylase (HDAC) inhibitors restores PON1 expression and improves sunitinib sensitivity[65]. Furthermore, methylation of other genes,

including NEFH, SYNPO2, CST6, and LAD1, has been linked to resistance to anti-angiogenic therapy (Fig. 3). Specifically, NEFH and SYNPO2 methylation are correlated with poor therapeutic response, whereas hypermethylation of CST6 and LAD1 is associated with shortened PFS and reduced OS in ccRCC patients[66–68]. Collectively, these findings highlight the central role of epigenetic dysregulation in driving resistance to targeted therapies and underscore the clinical potential of epigenetic biomarkers and epigenetic-based therapeutic strategies for personalized treatment of RCC patients.

Immunotherapy resistance

DNA methylation

Growing evidence indicates that aberrant DNA methylation plays a critical role in the progression of RCC by modulating gene expression patterns. For example, Deng *et al* reported that hypomethylation of the IL18 promoter contributes to its overexpression in RCC. This epigenetic change was also associated with downregulation of immune checkpoint molecules and increased infiltration of CD8⁺ T cells, suggesting its potential as a predictive biomarker for immunotherapy responsiveness (Fig. 3)[69].

In another study, Lu *et al* identified a subgroup of ccRCC tumors with high levels of enhancer demethylation (termed TED) through Illumina EPIC profiling of patient samples treated with ipilimumab plus nivolumab or sunitinib. This TED subgroup displayed poor prognosis and resistance to ICI therapy. Mechanistically, TED was linked to demethylation of the TET1 promoter and activation of specific downstream regulators, which together serve as predictors of immunotherapy resistance (Fig. 3)[70].

Based on the study of DNA methylation modification patterns in RCC, Bai *et al* further classified RCC into three distinct DNA methylation modification patterns, C1, C2, and C3, corresponding to immune-desert, immune-excluded, and immune-inflamed phenotypes, respectively. This classification provides an innovative complement to traditional subtyping methods and supports the stratification of patients for precision immunotherapy[71].

From a therapeutic perspective, targeting DNA methylation has shown promising potential. In a study by WK and colleagues, treatment with the DNMT inhibitor decitabine enhanced transposable element expression, activated innate antiviral signaling, and promoted T cell infiltration and activation, thereby enhancing ICI efficacy in RCC models (Fig. 3)[72].

Given the prominent role of DNA methylation in RCC, methylation-driven gene expression models have shown prognostic potential. Li *et al* constructed a risk model incorporating eight differentially methylated genes, stratifying patients into high- and low-risk groups, and providing a framework to assess immunotherapy efficacy based on risk profiles[73]. Among immune checkpoints, CTLA4 has emerged as both a therapeutic target and a biomarker of immunotherapy response. Hypomethylation of the CTLA4 promoter has been shown to correlate with

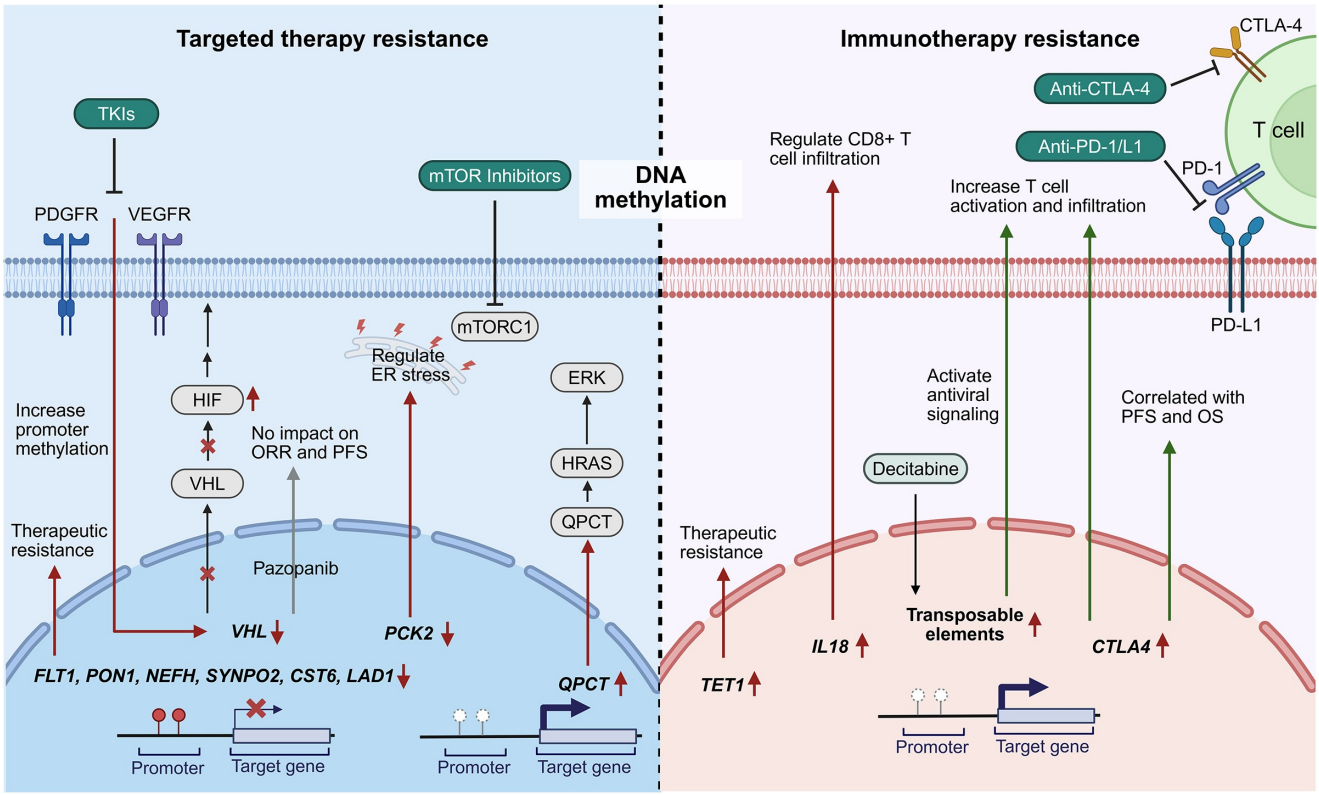

Figure 3. DNA methylation alterations contributing to resistance to targeted therapy and immunotherapy. The left panel shows that hypermethylation or hypomethylation of genes such as VHL, PCK2, and QPCT affects HIF signaling, ER stress, and other regulatory pathways contributing to resistance to targeted therapies. The right panel illustrates the impact of DNA methylation on immunotherapy outcomes, where changes in methylation status of IL18, TET1, and CTLA4 influence immune checkpoint expression and CD8⁺ T cell infiltration, thereby modulating sensitivity or resistance to immune checkpoint blockade. This figure was created using BioRender (www.Biorender.Com).

Table 1

Expression regulation of immune checkpoint molecules in immunotherapy resistance

Immune checkpoint molecule	Regulatory mechanism	Regulatory type	Resistance mechanism	Related studies	Reference PMID
PD-L1	Transcription factor activates PD-L1 transcription	Transcriptional regulation	Enhances PD-L1 expression, suppresses T-cell activity, and promotes immune evasion	PYK2 phosphorylates TAZ, enhancing its stability and promoting PD-L1 transcription	33 837 850
	Transcription factor activates PD-L1 transcription	Transcriptional regulation	Inhibits tumor-infiltrating CD8+ T-cell activity, mediates immune evasion	TFEB directly binds to the PD-L1 promoter, promoting its transcription	31 383 732
	Transcription factor activates PD-L1 transcription	Transcriptional regulation	Promotes immune evasion and is associated with Sunitinib resistance	TFE3 binds to the PD-L1 promoter, enhancing its expression	33 145 941
	Transcription factor activates PD-L1 transcription	Transcriptional regulation	Promotes tumor immune evasion	HIF-2α binds to the PD-L1 promoter, upregulating its expression	34 789 838
	m6A methylation regulates PD-L1 mRNA stability	Post-transcriptional modification	Enhances PD-L1 expression, suppresses T-cell activity	METTL3 mediates m6A methylation of PD-L1 mRNA, regulating its stability	35 197 058
	miRNA regulation of PD-L1 expression	Post-transcriptional modification	Regulates PD-L1 expression through miRNAs, affecting immune evasion	EBV miR-BART11 and BART17-3p inhibit FOXP1 and PBRM1, enhancing PD-L1 expression	35 165 282
	lncRNA regulation of PD-L1 expression	Post-transcriptional modification	Regulates PD-L1 expression through lncRNAs, affecting immune evasion	lncRNA SNHG1 regulates PD-L1 expression via the miR-129-3p/STAT3 axis	33 739 543
	lncRNA regulation of PD-L1 expression	Post-transcriptional modification	Linc00926 promotes PDL1 expression on the surface of RCC cells	Linc00926 promotes PDL1 expression on the surface of RCC cells	37 866 544
	Phosphorylation modification regulates PD-L1 expression	Post-transcriptional modification	Lack of glucose supply induces PDL1 expression	Glycolysis regulates PDL1 expression by modulating overall EGFR/ERK/c-Jun phosphorylation levels	33 462 221
	Phosphorylation modification regulates PD-L1 expression	Post-transcriptional modification	DCLK1 phosphorylation promotes PDL1 expression	DCLK1 phosphorylation promotes PDL1 expression	34 830 884
	Ubiquitination modification regulates PD-L1 expression	Post-transcriptional modification	GSK3β mediates phosphorylation-dependent proteasomal degradation of PDL1	GSK3β binds to non-glycosylated PDL1 and leads to phosphorylation-dependent proteasomal degradation of PDL1 via β-TrCP	27 572 267
	Ubiquitination modification regulates PD-L1 expression	Post-transcriptional modification	Inhibits PD-L1 expression, enhances immune response	STUB1 mediates PD-L1 degradation through ubiquitination	28 813 410
	Deubiquitination modification regulates PD-L1 expression	Post-transcriptional modification	Enhances PD-L1 expression, suppresses T-cell activity	USP22 stabilizes PD-L1 and CSN5 through deubiquitination, promoting PD-L1 expression	32 665 011
	Deubiquitination modification regulates PD-L1 expression	Post-transcriptional modification	Enhances PD-L1 expression, suppresses T-cell activity	USP9X stabilizes PDL1 by deubiquitination and enhances its expression in tumor cells	29 992 764
	Lactylation modification regulates PD-L1 expression	Post-transcriptional modification	Lactylation promotes PD-L1 expression, suppressing T-cell activity	Lactylation of H3K18 activates PD-L1 transcription	39 137 401
	Acetylation modification regulates PD-L1 expression	Post-transcriptional modification	Acetylation affects PD-L1 nuclear translocation, suppressing immune response	p300 mediates PD-L1 acetylation, HDAC2 mediates deacetylation, regulating PD-L1 nuclear translocation	32 839 551
PD-1	Ubiquitination regulates PD-1 degradation	Post-transcriptional modification	Inhibits PD-1 expression, enhances immune response	FBXO38 mediates PD-1 degradation through ubiquitination	30 487 606
	Phosphorylation regulates PD-1 function	Post-transcriptional modification	Phosphorylation of PD-1 promotes SHP2 signaling, suppressing T-cell activity	PD-1 Y248 phosphorylation promotes SHP2 recruitment, inhibiting T-cell activity	32 184 441
	Deubiquitination regulates PD-1 expression	Post-transcriptional modification	Enhances PD-1 expression, suppresses T-cell activity	USP9X stabilizes PD-1 through deubiquitination	25 200 027
CTLA4	DNA methylation regulates CTLA4 expression	DNA modifications	CTLA4 promoter hypomethylation enhances its expression, promoting immune evasion	CTLA4 promoter hypomethylation correlates with mRNA expression and CD8+ T-cell infiltration	34 446 578

elevated mRNA expression and increased immune cell infiltration, particularly by $CD8^+$ T cells (Fig. 3, Table 1). In a multicenter RCC-ICB cohort, CTLA4 promoter hypomethylation was associated with improved PFS and OS, supporting its potential as an independent predictor of immunotherapy benefit and a biomarker for response monitoring (Fig. 3)[74].

Histone modifications

Histone modifications also contribute significantly to the regulation of immune responses in RCC. Major histocompatibility complex class I (MHC-I) antigens are critical for tumor immune recognition, and their downregulation is a known mechanism of immune evasion. α-Ketoglutarate (αKG), a tricarboxylic acid cycle intermediate, has been shown to enhance MHC-I expression in RCC by modulating broad-spectrum histone demethylation and upregulating β2-microglobulin (B2M). Notably, transcriptional upregulation of B2M was dependent on demethylation at the H3K4me1 histone mark at its promoter[75].

Importantly, combined treatment with αKG and PD-1 blockade in murine models led to improved immunotherapy efficacy and prolonged survival, offering a potential synergistic therapeutic strategy for RCC. Additionally, histone deacetylase 3 (HDAC3) has been implicated in modulating immune responses. While HDAC3 suppresses RCC cell proliferation, its activity also promotes T cell activation and elevates IFN-γ production, thereby enhancing T cell-mediated tumor cytotoxicity[76].

Together, these findings demonstrate that histone modifications can reshape the tumor immune microenvironment and provide new opportunities to improve the efficacy of immunotherapy in RCC.

Transcriptional modification

Targeted therapy resistance

Transcriptional regulation refers to the modulation of gene activity at the transcriptional level, governed by transcription factors and various co-regulators that respond to intracellular and extracellular cues[77]. Signals such as cell cycle progression, environmental fluctuations, nutrient availability, and cellular stress influence the initiation, elongation, and termination of gene transcription[78].

The core mechanisms of transcriptional regulation include: (1) transcription factors, which bind to specific DNA sequences (promoters/enhancers) to recruit or inhibit RNA polymerase, thus initiating or repressing transcription[79]; (2) epigenetic modifications, such as DNA methylation and histone acetylation/methylation, which alter chromatin accessibility to the transcriptional machinery[80]; and (3) transcriptional initiation complexes, where multiple transcription factors assemble at promoter regions to facilitate polymerase recruitment and transcription start[81].

Transcriptional control operates through positive and negative regulation. In positive regulation, proteins bind promoters to activate transcription, typically by enhancing RNA polymerase recruitment and facilitating initiation and elongation[82,83]. In negative regulation, proteins repress transcription by binding regulatory elements, altering chromatin dynamics, or inducing transcriptional pausing or termination[84,85]. This intricate regulatory network allows cells to adapt their gene expression programs to specific developmental stages, environmental changes, and metabolic demands. However, dysregulated transcriptional control can profoundly alter cellular homeostasis and drive drug resistance in RCC.

Excessive activation of NRF2 is frequently observed in multiple cancer types and has been implicated in tumorigenesis, metastasis, and therapy resistance[86,87]. Chang *et al* identified dipeptidyl peptidase 9 (DPP9) as a regulator of the KEAP1–NRF2 axis, where DPP9 binds KEAP1 via a conserved ESGE motif and inhibits ferroptosis, promoting sorafenib resistance in ccRCC (Fig. 4)[88]. Similarly, Wang *et al* revealed that AIM2 drives RCC progression and sunitinib resistance in an inflammasome-independent manner by promoting FOXO3a phosphorylation and proteasomal degradation, thereby reducing ACSL4 transcription and inhibiting ferroptosis (Fig. 4)[89]. Furthermore, NUPR1 silencing reverses sorafenib resistance[90], while SEC14L3 downregulation enhances sunitinib sensitivity and inhibits ccRCC progression by disrupting the SEC14L3/RPS3/NF-κB feedback loop[91]. Thus, targeting SEC14L3 may provide a novel therapeutic strategy. YTHDC1, an m6A reader, inhibits ccRCC progression via the ANXA1/MAPK axis and regulates TKI sensitivity (Fig. 4)[92]. Additionally, HDAC2 inhibitors restore drug response by disrupting the YY1/HDAC2 transcriptional complex.

The newly identified form of cell death, cuproptosis, has also been implicated the antitumor activity and drug resistance[93,94]. Wang *et al* discovered that adrenomedullin (ADM) upregulation activates p38/MAPK signaling and forkhead box O3 (FOXO3) nuclear translocation, which suppresses FDX1 transcription and apoptosis, leading to sunitinib resistance (Fig. 4)[95]. In addition, Ruan *et al* identified Y-box binding protein 1 (YB1) and EphA2, a receptor tyrosine kinase (RTK) family member, as drivers of sunitinib resistance in mRCC[96].

Emerging evidence highlights the contribution of non-coding RNAs to TKI resistance. CircPTPN12 promotes RCC cell proliferation, migration, and invasion while facilitating sunitinib resistance by interacting with hnRNPM to stabilize IL-6 mRNA, leading to STAT3 activation (Fig. 4)[97]. Likewise, SIX1 induces metastasis and resistance through focal adhesion (FA) signaling. Mechanistically, integrin subunit β1 (ITGB1), an upstream gene of FA signaling, serves as a direct transcriptional target of SIX1. Furthermore, DHX9, a critical SIX1 cofactor, mediates SIX1-driven ITGB1 transcription. Silencing SIX1/DHX9 disrupts DHX9 nuclear translocation and its binding to the ITGB1 promoter, effectively reducing ITGB1 expression and attenuating TKI resistance[98].

He *et al* elucidated the role of CHD1L in sunitinib resistance, demonstrating that SIRT7 physically interacts with CHD1L and mediates its deacetylation, with SIRT7 exerting its pro-tumorigenic effects in a CHD1L-dependent manner. Accumulated CHD1L amplifies HIF-2α-driven transcriptional programs by directly binding HIF-2α, while CHD1L overexpression sustains VEGFA-mediated resistance, an effect that can be reversed by CHD1L inhibition[99]. He *et al* discovered that sunitinib treatment upregulates lncRNA ECVSR, which enhances ERβ mRNA stability and drives HIF-2α transcription, promoting resistance. Combining sunitinib with the anti-estrogen PHTPP significantly improves efficacy and reduces vasculogenic mimicry formation[100]. Similarly, Gu *et al* reported that targeting the ERβ/ANGPT-2/Tie-2 signaling pathway with the FDA-approved anti-estrogen Faslodex enhances sunitinib response

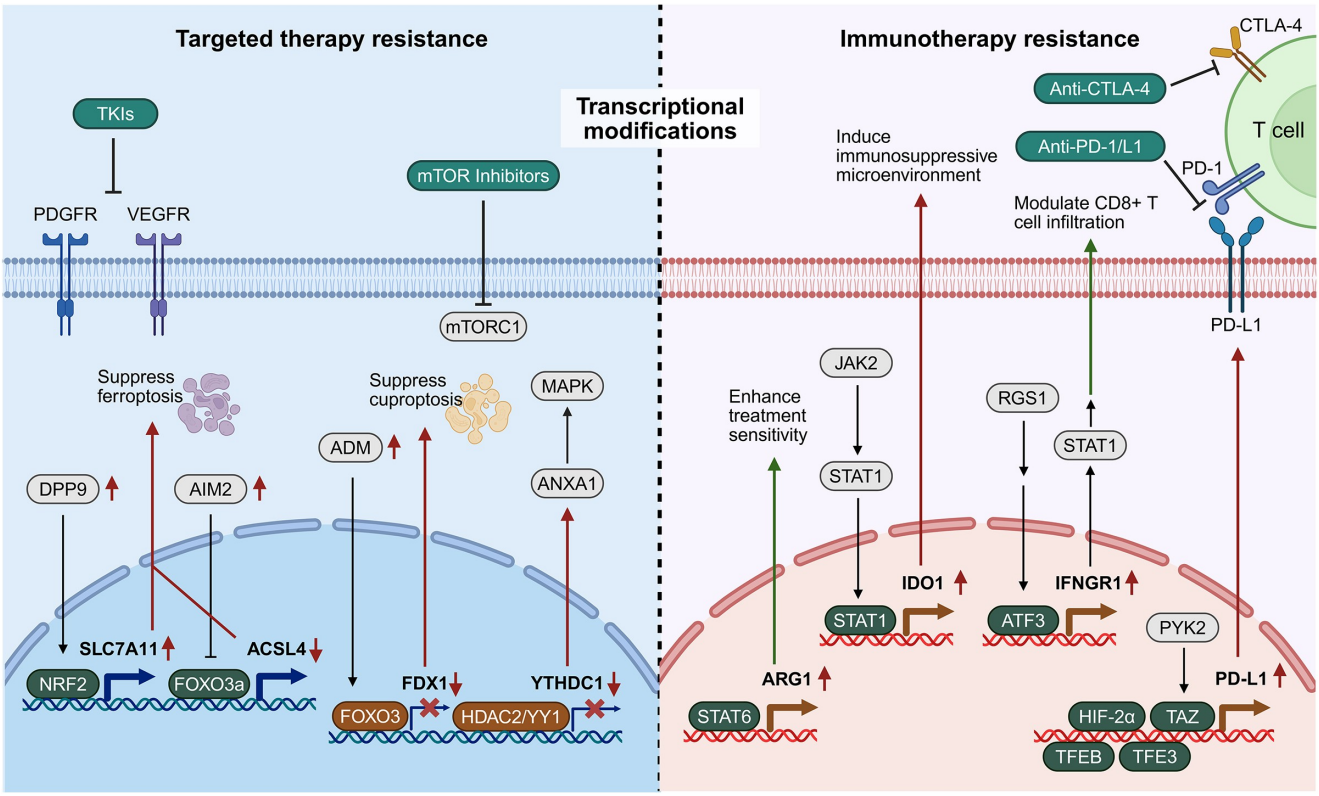

Figure 4. Transcriptional alterations contributing to resistance to targeted therapy and immunotherapy. The left panel illustrates key transcriptional regulators such as NRF2 and FOXO3, and their downstream targets including SLC7A11 and FDX1, which modulate ferroptosis, cuproptosis, and other regulatory pathways contributing to resistance to targeted therapies. The right panel summarizes transcriptional mechanisms of immune resistance, where upregulation of ARG1, IDO1, IFNGR1, and PD-L1 driven by transcription factors such as STAT1, STAT6, ATF3, and TAZ suppresses CD8⁺ T cell activity and promotes an immunosuppressive tumor microenvironment. This figure was created using BioRender (www.Biorender.Com).

and may provide a novel combination therapy for advanced ccRCC[101]. Wang *et al* identified that inhibition of RBCK1 suppresses AKT and MAPK signaling, reversing sunitinib resistance. Mechanistically, RBCK1 promotes ANKRD35 degradation, which destabilizes MITD1 via SUMO2 binding, forming the RBCK1–ANKRD35–MITD1–ANXA1 axis that regulates AKT/ERK phosphorylation and mediates drug resistance[102]. Zhu *et al* demonstrated that ZHX2 promotes tumor growth and sunitinib resistance by upregulating VEGF, activating the MEK/ERK1/2 pathway, and inducing protective autophagy, highlighting a potential therapeutic target in advanced ccRCC[103]. Guo *et al* showed that TFE3-driven PD-L1 upregulation contributes to sunitinib resistance via immune evasion mechanisms[104]. Yao *et al* reported that sunitinib downregulates GATA1, reducing its binding to the MIR885 promoter and increasing miR-885-5p activity, which directly upregulates PLIN3 expression, enhances lipid droplet formation, and diminishes drug sensitivity[105]. Liu *et al* revealed that the lncRNA SNHG12/SP1/CDCA3 axis promotes RCC progression and sunitinib resistance, suggesting a potential therapeutic target for drug-refractory tumors[106]. Shi *et al* reported that the TR4 nuclear receptor regulates lncTASR transcription, stabilizing AXL mRNA and enhancing AXL protein expression, thereby promoting sunitinib resistance[107].

Resistance to bevacizumab poses a significant challenge in ccRCC, and the underlying epigenetic regulators of bevacizumab sensitivity remain largely unexplored[108]. Cheng *et al* demonstrated that UCHL1 mediates KDM4B deubiquitination, stabilizing KDM4B, which binds the VEGFA promoter and removes the inhibitory H3K9me3 modification. Inhibition of UCHL1 using the small-molecule inhibitor 6RK73 significantly suppressed ccRCC progression and enhanced bevacizumab sensitivity[109]. The findings reported by Schiavoni *et al* demonstrate that downregulation of PON2 can elicit a reduction in the proliferation and migration of ccRCC cells, along with an enhancement in cellular sensitivity to chemotherapy[110]. Lu *et al* identified the Solute Carrier Family 27 Member 3 (SLC27A3), a lipid transporter highly expressed in lipid-rich ccRCC, as a driver of pazopanib resistance Elevated SLC27A3 enhances long-chain fatty acyl-CoA production, fueling mitochondrial β-oxidation and generating excess reactive oxygen species (ROS), which activate mitophagy. A resulting ROS/mitophagy feedback loop maintains ROS homeostasis but consumes CPT1A, inhibiting fatty acid oxidation and forcing lipid storage in droplets, thereby mediating resistance[111]. Xiao *et al* reported that RNF7 promotes STAT3 signaling by ubiquitinating SOCS1, which suppresses apoptosis, enhances glycolysis, and reduces sunitinib sensitivity[112]. Xu *et al* experimentally demonstrated that the traditional Chinese medicine Sanhuang decoction restores axitinib sensitivity and inhibits tumor growth in resistant models by modulating immune infiltration and ADAMTS18 expression[113]. In addition, Yu *et al* described a regulatory axis whereby BMP8A promotes Nrf2 phosphorylation and activates TRIM24 to enhance survival and drug resistance in ccRCC[114].

Cowman *et al* utilized single-cell sequencing to reveal that HIF-1α is predominantly expressed in TAMs, with elevated levels of HIF-1α in TAMs showing a significant correlation with resistance to anti-angiogenic therapy[115]. Consistent with this, ccRCC is characterized by high angiogenic activity and robust vasculogenesis[116]. Marona *et al* found that both sunitinib and sorafenib resistance can lead to c-Met/IRAK1 activation and MCPIP1 downregulation, which collectively enhance tumor metastasis, likely due to increased vascularization in resistant tumors[117]. Wang *et al* further revealed that UBB regulates VEGFA transcription by directly interacting with specificity protein 1 (SP1), and a disrupted UBB/VEGFA ratio drives pazopanib resistance in ccRCC[118]. In a genomic and transcriptomic analysis, Dizman *et al* identified frequent alterations in VHL (64%), PBRM1 (38%), SETD2 (24%), KDM5C (17%), and TERT (12%), underscoring their potential roles as predictors of TKI response[119]. Wang *et al* observed that gankyrin overexpression in ccRCC cell promotes proliferation, invasion, migration, and pazopanib resistance while suppressing apoptosis. Mechanistically, gankyrin recruits STAT3, which transcriptionally activates CCL24. The elevated CCL24 then signals through CCR3 to further enhance gankyrin expression and STAT3 activation, establishing a gankyrin/STAT3/CCL24/CCR3 positive feedback loop. Disrupting this autocrine circuit may represent a promising strategy for treating advanced ccRCC[120].

Interestingly, studies identifying resistance mechanisms also reveal potential sensitization strategies. For instance, Hu *et al* found that the AKT activator SC79 can reverse the inhibitory effect of TAF1D knockdown in ccRCC cells. Notably, TAF1D knockdown sensitizes ccRCC cells to sunitinib and enhances sunitinib-induced tumor cell suppression[121]. Cabozantinib, a c-Met/RTK inhibitor, has been approved for the treatment of advanced RCC[122]. In a recent study, LaRawat *et al* reported that combining cabozantinib with honokiol synergistically suppresses RCC cell growth by increasing ROS production, suggesting that honokiol may enhance cabozantinib efficacy and represents a potential therapeutic option for overcoming resistance[123].

Immunotherapy resistance

Transcriptional regulation of immune checkpoint molecules

The regulation of the transcriptional expression of immune checkpoint molecules has been an area of intense research interest in RCC. It has been found that the PDZ-binding motif (TAZ) protein is able to activate PD-L1 transcription by binding to its promoter region, while the upstream kinase proline-rich/Ca-activated tyrosine kinase 2 (PYK2) phosphorylates TAZ, thereby stabilizing the protein and enhancing its activity (Fig. 4)[124]. Thus, inhibition of the PYK2/TAZ/PDL1 signaling axis may enhance the response of RCC cells to immunotherapy. Transcription factors EB (TFEB) and E3 (TFE3) also play critical roles in immune escape in RCC (Fig. 4). TFEB directly binds to the PD-L1 promoter, promoting its transcription and suppressing tumor-infiltrating CD8+ T cells activity, thereby facilitating immune escape[125]. Similarly, TFE3, a key oncogene for RCC proliferation, enhances PD-L1 transcription by interacting with its promoter, leading to both immune escape and sunitinib resistance[104]. However, compared with ccRCC and papillary RCC, significantly fewer M1-macrophages (0.8%) were observed in TFE3-rearranged renal cell carcinoma (rRCC; $P < 0.05$), predicting a colder tumor immune microenvironment. However, the increased proportion of PD-L1$^+$ tumor cells in rRCC paradoxically enhances the therapeutic benefit of ICI therapy[126]. In addition, HIF-2α was significantly expressed in RCC and promoted tumor immune escape by binding to the hypoxia-responsive element of the PD-L1 promoter and upregulating PD-L1 transcription (Fig. 4)[127]. Together, these mechanisms reveal a complex network of immune checkpoint molecules regulation in RCC and its role in tumor progression (Table 1).

Transcriptional regulation of cytokines and chemokines

Cytokines and chemokines play critical roles in modulating immune cell infiltration, activation, and tumor immune responses in RCC, thereby contributing to the development of immunotherapy resistance. Several immunosuppressive cytokines, such as transforming growth factor-β (TGF-β), interleukin-10 (IL-10), interleukin-6 (IL-6), VEGF, interleukin-23 (IL-23), and interleukin-17 (IL-17), have been demonstrated to inhibit antitumor immunity directly or indirectly and thus might affect the effect of immunotherapy[128–133]. Transcriptional studies targeting these factors are expected to reveal new mechanisms of immunotherapy resistance. For example, STAT3 and NF-κB regulate the transcriptional expression of IL-10 and directly bind to the IL-6 promoter and promote its transcription[134–136]. Meanwhile, STAT3 also directlyactivates IL23 transcription and cooperates with interferon regulatory factor 4 (IRF4) to induce IL-23-dependent downstream gene expression[137,138]. In addition, the transcription factor RORγt (RORC), a master regulator of Th17 cell differentiation, directly binds to the IL-17A promoter to promote the transcription of IL-17A and simultaneously upregulates IL-23 receptor expression, thus enhancing the activity of the IL-23 signaling pathway[133]. These studies provide new insights for deeper elucidation of immunotherapy resistance mechanisms.

Some chemokines also exert potent immunomodulatory effects. For example, CXCL12 is able to recruit regulatory T cells (Tregs) and thus shape the suppressive immune microenvironment, whereas its receptor, C-X-C chemokine receptor type 4 (CXCR4), is significantly expressed in RCC, and its transcription is tightly controlled by HIF-1α, which directly binds the CXCR4 promoter. Therapeutic strategies targeting CXCR4 markedly reduced FOXP3-TSDR demethylation and downregulated DNMT1 and FOXP3, thereby inhibiting Tregs function and potentially enhancing the efficacy of immunotherapy[139,140]. In a study on the mechanism of action of cabozantinib, researchers found that the drug induces the expression of neutrophil-associated chemokines (e.g., CCL11 and CXCL12) and T-cell-associated chemokines (e.g., CCL8 and CX3CL1), potentially driving long-term antitumor T-cell responses. These findings provide a theoretical rationale for combining cabozantinib with T-cell-targeted therapies or ICI agents[141]. Moreover, Regulator of G-protein signaling 1 (RGS1) promotes the binding of activating transcription factor 3 (ATF3) to the interferon gamma receptor 1 (IFNGR1) promoter, thereby upregulating STAT1 and IFNγ-inducible genes such as CXCL9 and MHC-I. This modulation of antigen presentation and CD8$^+$ T-cell infiltration identifies a novel pathway contributing to RCC immunotherapy resistance (Fig. 4)[142].

Transcriptional regulation of metabolism-related pathways

Given the critical role of metabolic reprogramming in RCC, alterations in the transcriptional regulation of metabolism-related

factors substantially affect the tumor microenvironment and contribute to immune escape and therapeutic resistance[143,144]. In a clinical study of targeted therapy combined with immunotherapy in RCC, Xue and colleagues found that treatment-sensitive patients exhibited significantly higher expression of arginase 1 (ARG1)[145]. Mechanistically, ARG1 transcription is predominantly regulated by the signal transducer and activator of transcription 6 (STAT6) pathway, which directly binds to the ARG1 promoter and enhances its expression (Fig. 4)[146]. Another key immune-metabolic factor, indoleamine 2,3-dioxygenase 1 (IDO1), plays a pivotal role in immune tolerance and tumor immune evasion. IDO1 expression leads to T cell and NK cell inactivation while simultaneously promoting the recruitment and functional activation of Tregs and myeloid-derived suppressor cells (MDSCs), collectively establishing an immunosuppressive tumor microenvironment[147–149]. Importantly, studies have shown that the IDO1 transcription is primarily regulated by the JAK2-STAT1 signaling pathway, which exhibits enhanced stability upon activation by upstream signals. This cascade promotes increased IDO1 expression, thereby attenuating the efficacy of anti-PD-1 therapy in RCC (Fig. 4)[150].

Immune cell regulation in the tumor microenvironment

The infiltration and functional activation of suppressive immune cells represent major mechanisms driving immunotherapy resistance in RCC[151]. Single-cell and spatial transcriptome RNA sequencing results demonstrated that Tregs are enriched in the RCC microenvironment, where they potently suppress antitumor immune responses. The differentiation and immunosuppressive function of Tregs are tightly controlled by the transcription factor FoxP3[152,153]. Mechanistically, nuclear FoxP3 directly binds DNA-associated proteins generated during Treg activation or differentiation, thereby stabilizing its association with chromatin and dynamically regulating Treg function according to the immune context[154]. Interestingly, recent studies found that FoxP3 is also highly expressed in RCC cells and correlates with poor prognosis, which may be caused by BAP1 or SEDT2 mutations, suggesting that FoxP3 could also function as a potential oncogene during RCC progression[155].

The differentiation and function of MDSCs are also regulated by transcription factors. CCAAT/Enhancer Binding Protein ß (C/EBPß) controls emergency myelopoiesis, and dysregulation of C/EBPß activity leads to abnormal myelopoiesis and pronounced MDSC expansion[156,157]. Similarly, STAT3 coordinates both MDSCs and the acquisition of immunosuppressive properties. Inhibition of STAT3 induces apoptosis in MDSC, increases upregulated molecules involved in antigen processing and presentation, and suppresses immunosuppressive factors expression, thus diminishing the MDSC-mediated suppression of antitumor immunity[158]. Beyond its role in MDSCs, STAT3 critically regulates CD8⁺ T-cell differentiation. Studies have shown that STAT3 enhances the T_{ex}^{term} transcriptional program by activating T_{ex}^{term}-associated genes and repressing the expression of T_{ex}^{prog} genes through epigenetic mechanisms. In addition, STAT3 synergizes with basic leucine zipper ATF-like transcription factor (BATF) and IRF4 to mediate T_{ex}^{term} cell differentiation[159]. These findings indicate that STAT3 signaling plays a critical role in the terminal

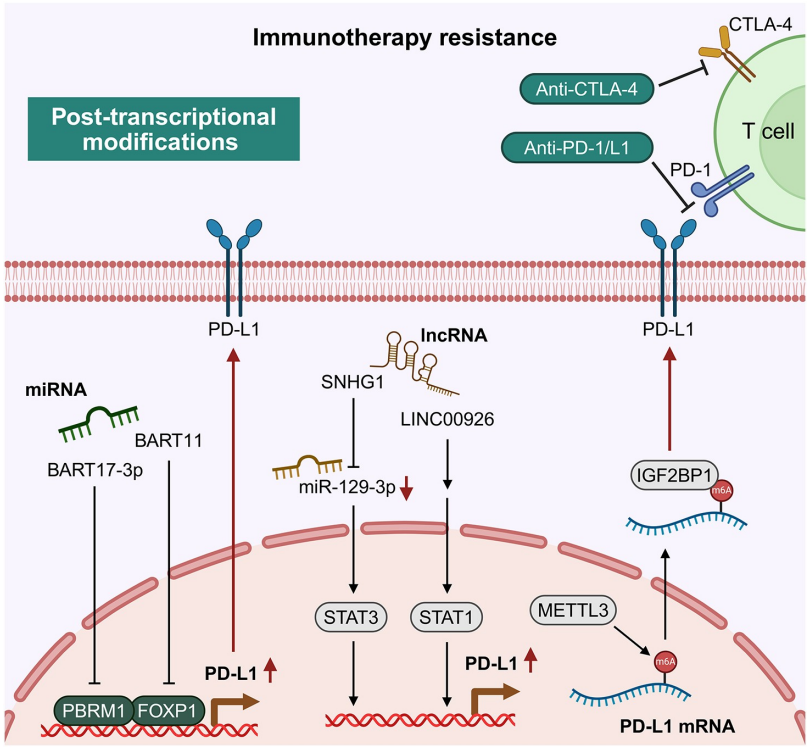

Figure 5. Post-transcriptional modifications associated with immunotherapy resistance. Post-transcriptional mechanisms, including non-coding RNAs (miRNAs and lncRNAs) and m6A RNA methylation, regulate PD-L1 expression and mediate immunotherapy resistance in RCC. This figure was created using BioRender (www.Biorender.Com).

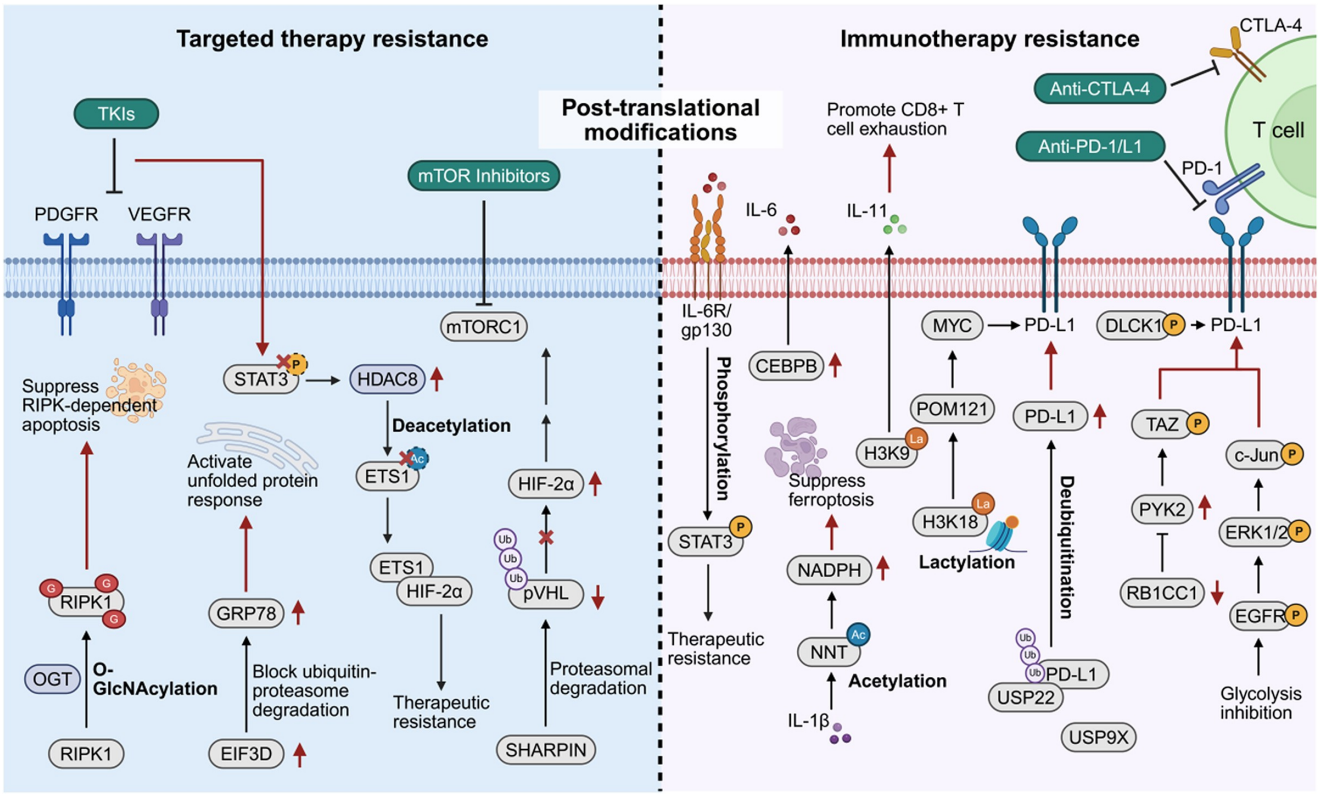

Figure 6. Post-translational modifications contributing to resistance to targeted therapy and immunotherapy. The left panel summarizes post-translational mechanisms involved in targeted therapy resistance, including O-GlcNAcylation, deacetylation, phosphorylation, and ubiquitination, which affect apoptosis, unfolded protein response, and HIF signaling. The right panel illustrates post-translational events contributing to immunotherapy resistance, including acetylation, lactylation, phosphorylation, and deubiquitination, which modulate ferroptosis, immune checkpoint stability, and T cell exhaustion. This figure was created using BioRender (www.Biorender.Com).

differentiation of CD8+ T cells, offering a theoretical basis for developing novel immunotherapies targeting STAT3-driven immune dysfunction.

Post-transcriptional modifications

Post-transcriptional modifications refer to a series of chemical processes that alter RNA molecules after transcription is complete, including 5' capping, 3' polyadenylation, RNA splicing, m6A methylation, RNA editing, and non-coding RNA-mediated regulation. These modifications finely tune RNA stability, processing, and function, representing crucial steps for accurate gene expression and the production of functional RNA molecules. Recent research has increasingly revealed that post-transcriptional modifications play a central role in resistance to both targeted therapy and immunotherapy in RCC by regulating the expression of immune-related genes (such as PD-L1), shaping the tumor microenvironment, and mediating immune escape (Fig. 5). Therefore, elucidating the molecular mechanisms underlying these RNA modifications is essential for uncovering resistance pathways and developing novel therapeutic strategies for RCC.

For a detailed description of the role of post-transcriptional modifications in mediating RCC drug resistance, as illustrated in Figure 5 and Table 1, please refer to the description in Supplemental Digital Content File S1, available at: http://links.lww.com/JS9/G864.

Post-translational modifications

PTMs encompass a range of covalent alterations to amino acid residues after protein synthesis on ribosomes[160]. Although PTMs do not alter the primary amino acid sequence, they profoundly influence protein conformation, biological functions, subcellular localization, and molecular interactions[161]. Essentially, PTMs represent "post-processing" mechanisms that enable proteins to execute precise and dynamic functions within diverse cellular contexts[162]. The spectrum of PTMs is extensive, encompassing acetylation[163], methylation[164], ubiquitination[165], phosphorylation[166], glycosylation[167], and acylation[168], among others.

By modifying specific amino acid residues, PTMs regulate protein–DNA, protein–RNA, and protein–protein interactions, thereby modulating gene expression and cellular responses[169]. Moreover, PTMs orchestrate signal transduction pathways: following environmental stimuli, many signaling molecules undergo PTM-dependent conformational and functional changes, transmitting cues to downstream effectors and coordinating adaptive responses[170]. In addition, PTMs influence protein degradation, subcellular trafficking, and other essential processes, maintaining normal cellular homeostasis[171].

For a detailed description of the role of PTMs in mediating RCC resistance, as illustrated in Figure 6 and Table 1, please refer to the description in Supplemental Digital Content File S1, available at: http://links.lww.com/JS9/G864.

Conclusion and future directions

Recent advances in multi-omics technologies have provided unprecedented insights into the complex mechanisms underlying resistance to targeted therapies and immune tolerance in RCC[172]. By integrating data from genomics, epigenomics, transcriptomics, proteomics, and metabolomics, researchers have begun to unravel the dynamic, multi-layered evolution of drug resistance and immune evasion. These findings not only deepen our understanding of RCC biology but also hold significant promise for clinical translation.

From a clinical perspective, multi-omics approaches have enabled the identification of robust biomarkers for predicting therapeutic response and resistance, facilitating patient stratification and personalized treatment strategies. For instance, genomic and epigenomic profiling of VHL and PBRM1 mutations, PD-L1 promoter methylation status, and immune-related lncRNA signatures offers valuable tools for anticipating outcomes to ICIs[173–175]. Similarly, transcriptomic and proteomic signatures associated with metabolic reprogramming or PTMs may guide the selection of combination therapies, such as mTOR inhibitors with epigenetic modulators or ICIs with metabolic interventions[75,176].

The integration of liquid biopsies and longitudinal multi-omics profiling into clinical workflows represents a transformative approach for dynamic monitoring of treatment response and resistance evolution[177,178]. Such strategies could enable real-time adjustment of therapeutic regimens, minimize toxicity and maximize efficacy. Furthermore, the discovery of novel therapeutic targets, such as lactylation-regulated immune suppression, ubiquitination-mediated PD-L1 stability, and transcriptional networks controlling cytokine secretion, paves the way for developing next-generation drugs and rational combination therapies[179,180].

To accelerate clinical translation, future efforts should focus on validating these multi-omics-derived biomarkers and targets in large, prospective clinical cohorts. Collaborative initiatives integrating multi-omics data with electronic health records and real-world evidence will be essential for refining predictive models and advancing precision oncology. Ultimately, the convergence of multi-omics insights with clinical practice promises to redefine therapeutic paradigms in RCC, overcoming resistance and improving survival outcomes for patients.

In conclusion, the in-depth application of multi-omics technologies will drive a paradigm shift in the study of resistance mechanisms in RCC, laying a solid foundation for precision medicine in the era of individualized therapy. Through interdisciplinary collaboration and technological innovation, we are poised to achieve transformative advances in the treatment of RCC.

Ethical approval

Not applicable.

Consent

Not applicable.

Sources of funding

Not applicable.

Conflicts of interest disclosure

All the authors declare to have no conflicts of interest relevant to this study.

Research registration unique identifying number (UIN)

Not applicable.

Guarantor

Not applicable

Provenance and peer review

Not commissioned, externally peer-reviewed.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request

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