Biomarkers for evaluating the clinical response to immune checkpoint inhibitors in renal cell carcinoma (Review)

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Abstract. Renal cell carcinoma (RCC) is a highly aggressive neoplastic disease of the renal parenchyma that is characterized by an intrinsic resistance to cytotoxic chemotherapy; for this reason, curative treatment is only achieved through surgical intervention in its early stages. The successful treatment of advanced or metastatic RCC will require the combined use of novel targeted therapies such as tyrosine kinase inhibitors, vascular endothelial growth factor blockers and immune checkpoint blockade therapies. Unfortunately, not all patients are candidates for such treatments, and at present, it is not possible to predict a patient's therapeutic response or likelihood to develop treatment-associated complications. The present review described the literature focusing on the use of biomarkers for predicting patients' responses to therapies that induce immune checkpoint blockade in RCC.

Contents

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Abbreviations: PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1

Key words: renal cell carcinoma, immunotherapy, predictive biomarkers, tumor-immune microenvironment, immune checkpoint blockade

1. Introduction

Renal cell carcinoma (RCC) is a group of neoplastic diseases that affect the renal parenchyma and represent 2-3% of all cancer diagnoses (1). In 2022, the GLOBOCAN database estimated the global incidence of RCC as 434,419 cases, which were associated with 155,702 deaths (2). RCC is more commonly diagnosed in men (ratio men to women, 2:1), and in the sixth decade of life (3). Up to 70% of patients are incidentally diagnosed with RCC, 50% of them with metastatic disease (4); although localized RCC is curable, in up to 30% of patients this will progress to metastatic disease, which has a median survival time of 6-10 months (5). Among the different types of RCCs, 80% of all diagnoses consist of the clear cell histological variety (ccRCC), which is followed in frequency by the papillary variant (10-15% of cases), the chromophobe cell variant (4-5% of cases), and other molecularly defined phenotypes (<1% of cases) (6).

The high rates of mortality that are observed in RCC have been associated with factors such as the high prevalence of advanced disease at diagnosis (7) and the intrinsic chemoresistance of RCC tumors, which is mostly related to apoptotic resistance, the upregulation of xenobiotic excretion systems (8-10) and the metabolic dependence of such tumors on the Warburg effect (11). In total, <10% of patients with RCC will respond to cytotoxic chemotherapy (12), which makes it necessary to use novel approaches for which little clinical information is available. Current RCC treatments can be grouped into the following categories: cytotoxic chemotherapy, surgery, local therapy, recombinant-cytokine therapy, targeted anti-angiogenic therapy, immunotherapy [immune checkpoint blockade (ICB)], and other therapies that include the use of inhibitors of the mechanistic target of rapamycin pathway (Table I). Despite the broad diversity and availability of RCC treatments, the need for a prognostic tool for use in selecting the treatment of choice and evaluating the clinical responses of patients remains a matter of controversy (13). Treatment selection depends on factors such as the histological variety, cellular grade and clinical stage of the disease, as well as the failure of previous treatments (14-16). In this regard, there are currently several scales that have been validated for risk classification and clinical decision-making in patients with

RCC; among these, the Heng score (International Metastatic RCC Database Consortium or IMDC), the MSKCC scale (Memorial Sloan-Kettering Cancer Center), and the general physical status according to ECOG-PS criteria (the Eastern Cooperative Oncology Group performance score) (17-19) stand out (Table II).

In the last decade, the use of monoclonal antibodies for reversing the 'exhaustion' state in tumor infiltrating lymphocytes (TILs) has proven to be a valuable treatment for numerous solid tumors and hematologic cancers. In 2015, the ChekMate-025 study demonstrated the efficacy of nivolumab (which was initially approved for treating melanoma and non-small cell lung cancer) in treating patients with RCC (20). In addition to nivolumab [which blocks the programmed cell death protein 1 (PD-1) receptor], four other monoclonal antibodies are currently approved for use in RCC, all of which reverse the inhibition of lymphocyte immune effectors: Pembrolizumab, which is also a PD-1 blocker; ipilimumab, which blocks the cytotoxic T-lymphocyte associated protein 4; and atezolizumab/avelumab, which blocks PD-1 ligand in myeloid and tumor cells and prevents PD-1 inhibitory signals in lymphocytes (Table III) (20-30).

In the following section, the current knowledge of the cellular mechanisms that lead to lymphocyte exhaustion within the highly dynamic tumor-immune microenvironment (TIME) was reviewed. It was concluded with a short description of experimental biomarkers that have been used to predict the patients' responses to ICB therapy.

2. The TIME

The TIME comprises a network of interacting elements within the tumor tissue that can be categorized as follows: Cells (tumor, stroma and infiltrating immune cells), small soluble elements (proteins, cytokines, growth factors, metabolites and chemokines), and the extracellular matrix (31). The growth of tumors requires two conditions: Cell transformation, whether genetic or acquired (32) and immune dysfunction (33). This second requirement explains the association between immunodeficiency status and cancer development (34). The clearance of transformed cells from tissues requires the activation of cytotoxic immunity that is achieved through the infiltration of $CD8^+$ cytotoxic lymphocytes and natural killer cells into a tumor (35). Antitumor immunity is so efficient that even though transformation and cell damage occur over the course of every life, cancer develops only in a small proportion of patients; the occurrence of cancer is promoted by immune dysfunction.

Tumor cells proliferate at higher rates compared with normal cells. This accelerated proliferation, which is linked to metabolic changes that take place within the tumor bed, results in dysfunctional local immunity and further selection of the best-adapted tumor cells (36-38). Cytotoxic chemotherapy exploits this increased proliferative rate, and cytotoxic treatments are widely used in most neoplastic diseases other than RCC. The peculiarities of RCC include its intrinsic aggressive nature, its increased infiltration with lipids, its high rate of metastasis, and its resistance to cytotoxic chemotherapy (39). This chemo-resistance has numerous causal factors, both intrinsic (or genetic) and acquired. It is important to note that the epithelial renal cells normally have secretion systems for xenobiotics and intrinsic antioxidant mechanisms protecting the cells from toxic damage (40). Given that most RCC subtypes arise from renal epithelia, it is not surprising that such mechanisms are enhanced in renal carcinoma. In addition, renal tumor cells have increased expression of anti-apoptotic proteins Bcl-2, $Bcl\text{-}_{XL}$, ARC (apoptosis repressor with a caspase recruitment domain) and XIAP (X-linked inhibitor of apoptosis) while pro-apoptotic proteins such as Bim are decreased. Anti-apoptotic and pro-apoptotic proteins are regulated by NF-κB and von Hippel-Lindau (VHL) pathways, respectively (8,10,41).

A total of up to 2/3 of patients with RCC have mutations in VHL gene (42). Among its numerous functions, VHL targets proteins for proteasomal degradation, including the pro-apoptotic protein Bim, whose levels are increased in patients with RCC (41). Conversely, the increase in anti-apoptotic pathways has also been implicated in chemoresistance, specifically in the increased expression of anti-apoptotic proteins Bcl-2, ARC and XIAP (9). Concomitant to these mechanisms, renal cancer cells are highly dependent on aerobic glycolysis (Warburg effect), a phenotype associated to a lack of response after ICB therapy (43), and a recent putative target for enhancing combined treatments for RCC (11).

In addition, although the presence of TILs is a favorable prognostic factor for most cancers, such infiltrative cells are associated with poor outcomes in RCC (44,45). Consequently, a hostile TIME develops that leads to the selection of tumors that are resistant to hypoxia, acidosis and the low availability of nutrients. In addition, a hostile TIME negatively affects lymphocyte-dependent antitumor immunity (Fig. 1 and Table IV) (31,46-51). Previous studies suggested that dysbiosis is an important element to be considered when evaluating either the responses of tumors to ICB or the general prognosis of patients with neoplastic diseases (52,53). The molecular basis for lymphocyte dysfunction involves several mechanisms that are associated with peripheral tolerance, namely anergy, suppression and exhaustion (54). Immune cell exhaustion is reversed by ICB, which blocks interactions between the inhibitory receptors of lymphocytes and their ligands (55). The PD-1/programmed death-ligand 1 (PD-L1) axis is the most studied of these interactions within TILs (56,57).

Even though numerous patients achieve complete clinical response to ICB therapy, a significant proportion of patients show only a partial response or no response at all, which is occasionally accompanied by signs of systemic toxicity (58). This situation explains why the search for prognostic markers for ICB in patients with RCC is a highly active area of research. Most prognostic markers for RCC can be divided into those addressing disease progression and those addressing responses to treatments, in particular immunotherapy and directed therapies. Thus, predicting the ICB responsiveness will impact in selecting the patients who will benefit the most and have the lowest probability of developing adverse events after receiving immunotherapy. There are currently no standardized and validated methods for properly assessing the risk/benefit ratio of using ICB therapy. Therefore, the goal of the present review was to synthesize the reported findings of the studies that have focused on this important topic.

Table I. Available treatments for renal cell carcinoma.

Category	Description
Cytotoxic chemotherapy	Currently not considered given the high intrinsic resistance
Surgery	Nephrectomy (simple, radical, cytoreductive, metastasectomy)
Local Therapy	SBRT, EBRT, arterial embolization, cryotherapy, thermal ablation
Cytokine Therapy	Interferon-α, Interleukin-2
Antiangiogenic targeted therapies	Anti-VEGF antibodies, multikinase inhibitors
Immunotherapy	Immune checkpoint inhibitors
Other	mTOR inhibitors

SBRT, stereotactic body radiation therapy; EBRT, external-beam radiation therapy; VEGF, vascular endothelial growth factor; mTOR, mechanistic target of rapamycin.

Table II. Renal cell carcinoma guide for treatment according to the American Joint Committee on Cancer Stages.

AJCC stage	TNM classification[a]	First-line therapy[b]	Second-line therapy[b]	Third- and fourth-line therapies[b]
I	T1, N0, M0	Nephrectomy[c]		
		Local Therapy[d]		
II	T2, N0, M0	Nephrectomy +/-adjuvant IT[e]		
		Palliative Local Therapy		
III	T1, N1, M0	Nephrectomy +/-adjuvant		
	T2, N1, M0	IT or TT[f]		
	T3, N0, M0	Palliative Therapy		
	T3, N1, M0			
IV	T4, Any N, M0	Radical or Cytoreductive	Axitinib	Tivozanib
	Any T, Any N, M1	Nephrectomy[j]		
		Ipilimumab + Nivolumab[k]	Sorafenib	
		Pembrolizumab + Axitinib or	Palliative care	
		Lenvatinib	(external-beam	
		Avelumab + Axitinib	radiation therapy)	
		Nivolumab + Cabozantinib	Nivolumab[i]	
		Bevacizumab +/-Interferon-α	Lenvatinib +	
		Cabozantinib or Sunitinib or	Everolimus[i]	
		Pazopanib or Sorafenib	Cabozantinib[i]	
		Temsirolimus[g]	Everolimus[i]	
		Interferon-α or Interleukin-2[h]		
		Palliative care		

[a]T1, tumor <7 cm; T2, tumor >7 cm, limited to the kidney; T3, tumor extension to perinephric tissues, but not Gerota's fascia; T4, tumor invasion beyond Gerota's fascia; N0, no regional lymph node metastasis; N1, metastasis in regional lymph nodes; M0, no distant metastasis; M1, distant metastasis. [b]There is always the possibility for the patient to be enrolled in an appropriate clinical trial. Most clinical trials available are for AJCC Stage IV and second- or subsequent line therapies. [c]Includes partial, simple and radical nephrectomies. [d]Includes stereotactic body radiation therapy (SBRT), cryotherapy/thermal ablation and palliative external beam radiation therapy (EBRT). [e]IT or immune checkpoint inhibitors, including the following antibodies anti-PD-1 (nivolumab, pembrolizumab), anti-CTLA-4 (ipilimumab), and anti-PD-L1 (avelumab, atezolizumab). [f]Anti-angiogenic TT, including anti-VEGF antibody (bevacizumab), and multitarget TKIs. [g]Mechanistic target of rapamycin inhibitors. [h]Cytokine therapy, including IFN-α and IL-2. [i]Second-line therapies after no response to first-line TKIs' monotherapy. [j]Metastasectomy or cytoreductive therapy in patients with low-risk according to MSKCC/ECOG. [k]In patients with intermediate to poor prognostic profile. IT, immunotherapy; TT, targeted-therapy; TKI, tyrosine kinase inhibitors.

Table III. Clinical studies availing the use of immune checkpoint blockade for treatment in RCC.

First author, year	Study	Phase	Design	Intervention	Results	(Refs.)
Motzer *et al*, 2015	CheckMate 025	III	Randomized, open-label, N= 821, mRCC	Nivolumab vs. Everolimus	ORR: 25 vs.5%	(20)
Motzer *et al*, 2018	CheckMate 214	III	Randomized, open-label, N=1096, mRCC	Nivolumab/ Ipilimumab vs. Sunitinib	ORR: 42% vs. 27%	(21)
Rini *et al*,2019	Keynote-426	III	Open label, randomized, N= 861, mRCC	Pembrolizumab/ Axitinib vs. Sunitinib	ORR: 59.3 vs. 35.7%	(24)
Vogelzang *et al*, 2020	CheckMate 374[a]	IV	Multicenter, open-label, N=44, mRCC	Nivolumab	ORR: 22.7%	(26)
Choueiri *et al*, 2021	CheckMate 9ER	III	Randomized, open label, N=651, mRCC	Nivolumab/ Cabozantinib vs. Sunitinib	ORR: 55.7 vs. 27.1%	(29)
Rini *et al*, 2019	IMmotion151	III	Multicenter, open-label, N=915, mRCC	Atezolizumab/ Bevacizumab vs. Sunitinib	ORR: 37 vs. 33%	(25)
Motzer *et al*, 2021	CLEAR	III	Randomized, N=1069, mRCC	Lenvatinib/ Pembrolizumab vs. Lenvatinib/ Everolimus vs. Sunitinib	ORR: 71 vs. 53 vs. 36%	(22)
Choueiri *et al*, 2021	Keynote-564	III	Double-blind, N=994, locRCC	Adjuvant Pembrolizumab vs. Placebo	DFS 24-month: 77.3 vs. 68.1%	(30)
Tykodi *et al*, 2022	CheckMate 920[a]	IV	Multicohort, N=52, mRCC	Nivolumab/ Ipilimumab	ORR: 19.6%	(27)
Pal *et al*, 2023	Contact-03	III	Multicenter, randomized, open-label, N=522, locRCC/mRCC	Atezolizumab/ Cabozantinib vs. Cabozantinib	PFS: 10.6 vs. 10.8 months	(28)
Motzer *et al*, 2019	JAVELIN Renal 101	III	Multicenter, randomized, open-label, N=886, mRCC	Avelumab/ Axitinib vs. Sunitinib	ORR: 55.2 vs. 25.5%	(23)

RCC, renal cell carcinoma; mRCC, metastatic RCC; locRCC, localized RCC; PFS, progression-free survival; DFS, disease-free survival; ORR, objective response rate. [a]Studies evaluating non-clear cell RCC.

3. Predictors of clinical response to the use of immune checkpoint inhibitors

ICB therapy is associated with an average mortality rate of 1%, with death mostly caused by immune-related adverse events (58). After the reporting of successful results from the CheckMate-025 study, and given the low predictability and consistency of ICB responsiveness (59), interest has been increasing in the search for reliable markers of ICB responsiveness. Among the biomarkers that have been studied, three stand out for their consistency: the level of C-reactive protein (CRP), the number of TILs and the basal expression levels of exhaustion markers in tumor tissue. CRP is an acute phase reactant that is frequently used for evaluating systemic inflammation, making it a logical putative marker for ICB responsiveness given the close association between inflammation and cancer. Previous studies have indicated that low basal CRP levels or low normalized levels of CRP measured after patients received their first ICB doses were predictive of their ICB responsiveness (60-63). Studies investigating TILs found that a patient's prognosis is associated with the nature of his or her infiltrating cells; infiltration with inflammatory leukocytes was associated with the best responses to ICB therapy (64-66). In peripheral blood, a recent study

Table IV. Tumor-immune microenvironment elements driving lymphocyte exhaustion in RCC.

First author, year	Element	Associated dysfunction	Clinical implications	(Refs.)
Kawashima *et al*, 2020	Lymphocytes	Cytotoxic T and NK lymphocytes are dysfunctional despite their increased infiltration	In RCC, lymphocyte infiltrates correlate with poor overall prognosis and decreased response to ICB	(46)
Wang *et al*, 2021	Macrophages	Tumor-supporting macrophages (M2 cells or TAM) enhances the tumor expression of 'exhausting' ligands for lymphocytes	Infiltration with M2-like TAM is associated with poor prognosis and resistance to therapy	(47)
Sabrina *et al*, 2023	Suppressor Cells	MDSC and T_{reg} cells antagonize the antitumor cytotoxic immunity. Suppressor cells increase the production of anti-inflammatory cytokines	Increased numbers of MDSC and/or T_{reg} lymphocytes correlate with RCC progression and resistance to immunotherapy	(48)
Liu *et al*, 2021	Fibroblasts	CAF cells support the ECM remodeling, promoting in turn the tumor growth and metastasis	Abundance of CAF is associated with poor prognosis and resistance to cancer therapy	(49)
Zhang *et al*, 2021	Hypoxia	Hypoxic microenvironment promotes tumor progression, angiogenesis, and immune suppression. Drives selection of cancer resistant cells	Hypoxia selects tumor clones resistant to chemotherapy leading to poor prognosis	(50)
Ballesteros *et al*, 2021	Cytokines	IL-10 and TGF-β lead to suppression of cytotoxic immunity	Immunosuppressive cytokines contribute to immune evasion and resistance to treatment	(51)
Monjarás-Avila *et al*, 2023	Low nutrient supply	Activated cytotoxic cells are highly dependent on glucose supply. Selects resistant cancer cells	Anaerobic metabolism supports the viability of tumor cells, a condition detrimental to cytotoxic lymphocytes	(31)

RCC, renal cell carcinoma; ICB, immune checkpoint blockade; TAM, tumor-associated macrophages; MDSC, myeloid-derived suppressor cells; T_{reg}, regulatory T lymphocytes; CAF, cancer-associated fibroblasts; ECM, extracellular matrix; IL-10, interleukin-10; TGF-β, transforming growth factor beta.

observed that increased numbers of circulating eosinophils were associated with an improved response to ICB, which is an intriguing result given the regulatory role that eosinophils play in systemic inflammation (67). Interestingly, the basal expression level of PD-L1 has not been consistently predictive of ICB responsiveness (68-70), whereas the basal expression level of T cell immunoglobulin and mucin-domain containing-3 (TIM-3) appears to be (71).

Several additional markers have been studied for predicting the response to ICB in patients with RCC. For example, longer responses to ICB have been associated with decreased levels of circulating tumor DNA, increased levels of chemokine CXCL14, increased levels of circulating miR-22 and miR-24, and the presence of immunogenic transcriptional signatures (72-75). In this context, several markers have been associated with poor responses after ICB therapy (increased levels of interleukin-8) or predictive of the development of immune-related adverse events (decreased levels of miR-146a) (76,77). All the studies described in this section are summarized in Table V.

From a technical perspective, the evaluation of leukocytes' exhaustion markers require the performance of histopathology after the direct sampling of tissue, which is not feasible for all diagnoses (78). In this context, the studies assessing the suitability of peripheral biomarkers for predicting ICB responsiveness are encouraging (79,80).

4. Future directions and conclusions

Several limitations currently prevent the formal use of markers to predict ICB responsiveness. First, the inconsistency of reported outcomes is mostly related to heterogeneity in the target population and the low number of patients that have been studied. In addition, a lack of standardization in the use of methods and reagents is complicating the replication of pioneering studies. Furthermore, the relationship between the

Table V. Predictive biomarkers for clinical response to immune checkpoint blockade in patients with RCC.

First author, year	Biomarker	Predictor → Response	RCC type	Tissue	Technique	Study phase	Treatment	No. of patients	(Refs.)
Ishihara *et al*, 2020	CRP	↓CRP → increased OS/ PFS	mRCC	Serum	ELISA	I	Nivolumab	70	(60)
Noguchi *et al*, 2020	CRP	↑CRP → poor response	mRCC	Blood	Bio-Plex	I	Nivolumab	64	(61)
Yano *et al*, 2022	CRP	↑CRP → decreased OS	mRCC	Serum	ELISA	III	Dual ICB	74	(62)
Koh *et al*, 2022	ctDNA	↓ctDNA → longer PFS	mRCC	Plasma, tumor	DNA-seq	I	Dual ICB	14	(72)
Pan *et al*, 2023	CXCL14	↑CXCL14 → longer OS	mRCC	Kidney, tumor	IHC	III	Nivolumab	120	(74)
Schalper *et al*, 2020	IL-8	↑IL-8 → poor outcome	mRCC	Serum	ELISA	III	Nivolumab	392	(76)
Incorvaia *et al*, 2020	miRs[a]	↑miRs[a] → long response	RCC	Blood	qPCR	I	Nivolumab	23	(73)
Ivanova *et al*, 2022	miRs[b]	↓miRs[b] → irAEs to ICB	RCC	Blood	qPCR	Pilot/ PoC	Nivolumab	86	(77)
Atkins *et al*, 2022	PD-L1	↓PD-L1 → poor response	mRCC	Tumor	IHC	II	Dual ICB	123	(68)
Pabla *et al*, 2021	GES	↑TIGS → improved response	mRCC	Tumor	RNA-seq	III	Nivolumab	54	(75)
Motzer *et al*, 2022	PD-L1	PD-L1>1% → ↑PFS, no association in OS	mRCC	Tumor, blood	IHC/GES	III	Dual ICB	498	(69)
Kim *et al*, 2022	TIL	↑Th, Tc, and M1 cells → longer PFS	mRCC	Tumor	IHC	Pilot/ PoC	Dual ICB	24	(64)
Sammarco *et al*, 2024	TIL	↑163^{+} macrophages → poor response	mRCC	Tumor	IHC	Pilot/ PoC	Dual ICB/ ICB^{+}TKI	28	(65)
Herrmann *et al*, 2021	Eosino-phils	↑AEC → improved response to ICB	mRCC	Blood	CBC	Retros-pective	Nivolumab	64	(67)
Kato *et al*, 2020	TIM-3	↑TIM-3 → response to ICB	mRCC	Tumor	IHC/IF	Retrospective	Dual ICB	25	(71)
Brown *et al*, 2022	PD-L1, CTLA-4	Failed to predict ICB	mRCC	Tumor	IHC/qPCR	Retrospective	Dual ICB	62	(70)
Kazama *et al*, 2022	TIL	↑CD8/↑CD68 → response to ICB	mRCC	Tumor	IHC	Pilot/PoC	Not specified	60	(66)
Tomita *et al*, 2022	CRP	CRP normalization predicts response	mRCC	Serum	ELISA	Pilot/PoC	Avelumab + TKI	789	(63)

a, miR-22, -24, -99a, -194, -214, -335, -339, -798. b, miR-146a. PoC, proof of concept; mRCC, metastatic/advanced RCC; Dual ICB, dual immune checkpoint blockade (nivolumab + ipilimumab); CRP, C-reactive protein; ctDNA, circulating tumor DNA; miRs, micro-RNA molecules; PD-L1, programmed cell death receptor-ligand 1; TIL, tumor infiltrating leukocytes; ELISA, enzyme-linked immunosorbent assay; DNA-seq, DNA sequencing; RNA-seq, RNA sequencing; IHC/IF, immunohistochemistry/immunofluorescence; qPCR, quantitative polymerase chain reaction; WB, western blotting; OS, overall survival; PFS, progression-free survival; GES, Gene Expression Signature; TIGS, Tumor Immunogenic Signature; irAEs, immune-related adverse events; ICB, immune checkpoint blockade; CBC, complete blood count; AEC, absolute eosinophils count; TKI, tyrosine kinase inhibitors.

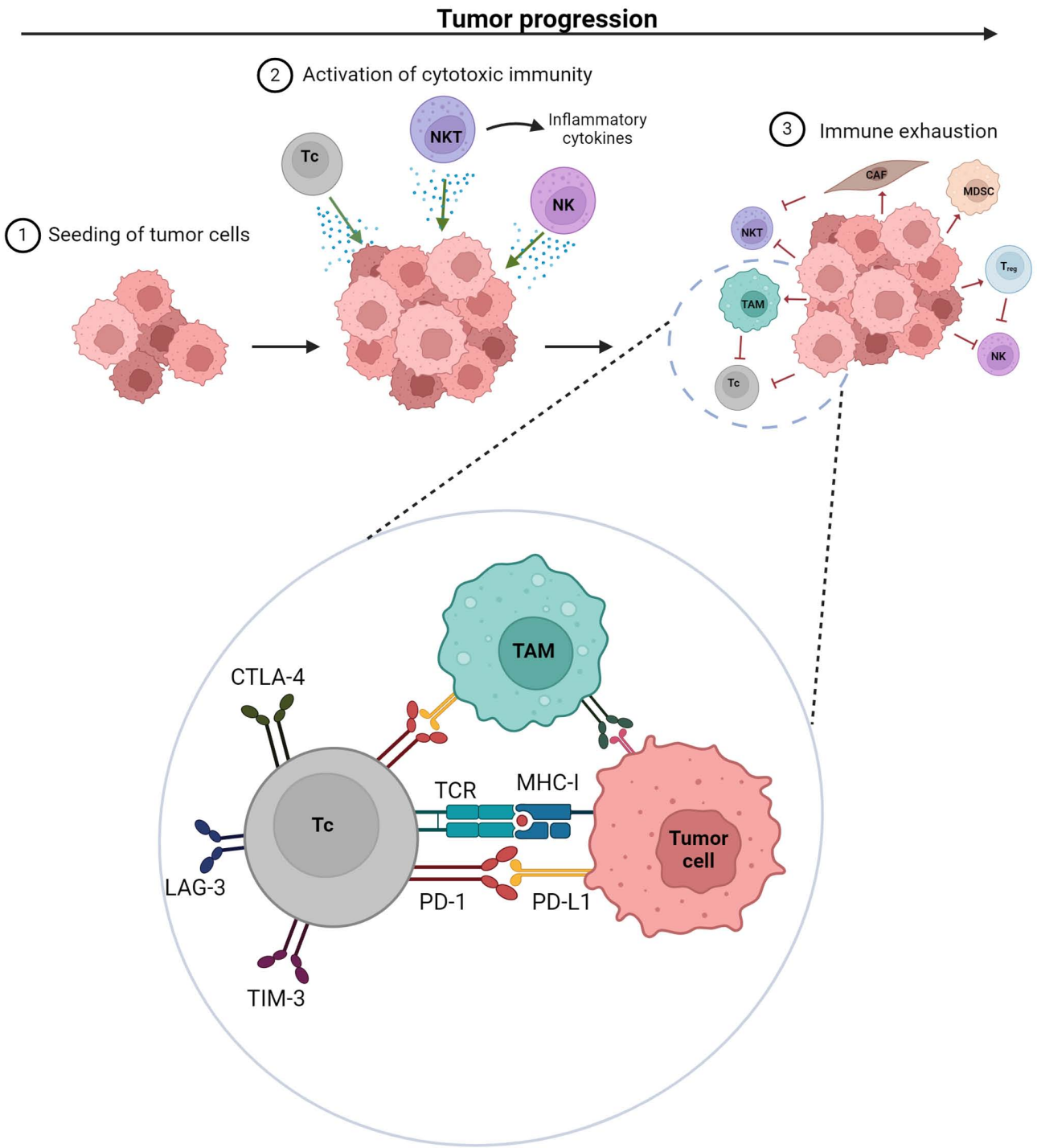

Figure 1. Tumor immune microenvironment in RCC. (1) Risk and causal factors converge into tumor formation in renal cell epithelia. (2) In early disease, immunity drives the control of tumor growth through several mechanisms, namely cell cytotoxicity, cytokine-mediated inflammation and ligand-induced apoptosis. This stage of antitumor immunity is mediated mostly by Tc, NK and NKT. (3) As cancer turns into a chronic disease, the antitumor immunity is negatively regulated by tumor cells (direct inhibition) or by infiltrated leukocytes and metabolic factors produced by tumor cells within the tumor microenvironment (indirect regulation). Direct inhibition is mediated by the tumor expression of PD-L1 and B7 ligands. Indirect regulation is more complex and involves the synthesis and secretion of IL-10 by Treg and MDSCs, the expression of the ligands PD-L1 and B7 by TAMs, and the hostile tumor microenvironment characterized by the low availability of nutrients, tissue acidosis and hypoxia. Inset: Antitumor immunity is antigen-specific, requiring lymphocyte activation through TCR ligation + co-stimulation. Co-stimulatory signals could be either activating or inhibitory, favoring the latter in advanced disease. Excessive negative co-stimulation leads to lymphocyte exhaustion, a functional negative state therapeutically reverted by immunotherapy (also known as immune checkpoint blockade). In RCC, two pathways are successfully reverted by immunotherapy: The pathway PD-1/PD-L1 (blocked by pembrolizumab and atezolizumab, respectively) and the pathway CTLA-4/B7 (blocked by ipilimumab). Other proteins involved in lymphocyte exhaustion but currently lacking approved monoclonal antibodies for treating RCC disease are the receptors LAG-3 and TIM-3 on the surface of lymphocytes. Green arrows, perforin release; red arrows, upregulation of lymphocyte's exhaustion ligands on myeloid cells and stromal cells; block red arrows, direct lymphocyte inhibition mediated by the B7 family of ligands. Figure was constructed using BioRender (www.Biorender.com). RCC, renal cell carcinoma; Tc, cytotoxic T lymphocytes; NK, natural killer cells; NKT, $CD3^+$ natural killer cells; PD-L1, programmed death-ligand 1 (also known as B7-H1); Treg, T regulatory lymphocytes; MDSCs, myeloid-derived suppressor cells; TAM, tumor-associated macrophages; TCR, T cell receptor; PD-1, programmed cell death protein 1; CTLA-4, T-lymphocyte associated protein 4; LAG-3, lymphocyte-activation gene 3; T cell immunoglobulin and mucin-domain containing-3; CAF, cancer-associated fibroblasts; MHC I, MHC-I, major histocompatibility complex class I.

expression of such potential biomarkers and the underlying mechanisms of resistance to ICB is not fully understood, making it difficult not only to predict ICB responsiveness but also to know the clinical safety of using ICB. Finally, the intrinsic resistance of RCCs to chemotherapy and the complex combinations required for treatment make it difficult to determine a logical approach for studying the expression of putative cancer biomarkers. In the future, by integrating multi-omics data and machine-learning approaches, it should be possible to create more accurate prediction models that will help in the identification of novel biomarkers for ICB responsiveness.

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Authors' contributions

RGG and MMT performed the literature review, wrote the manuscript, made the illustrations and constructed the tables. AGG, MCSC and MMT revised the manuscript. RGG and MMT were involved in the conception of the study. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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