Review

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Review

Kidney Injury Molecule-1 (KIM-1) in Renal Cell Carcinoma: Bridging Tumor Biology and Clinical Decision-Making

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Abstract

Renal cell carcinoma (RCC) remains a biologically heterogeneous disease with variable clinical outcomes, underscoring the need for robust biomarkers to guide risk stratification and therapeutic decision-making. Despite advances in immune checkpoint inhibitors and targeted therapies, clinically validated biomarkers are lacking, particularly in the perioperative setting. Kidney injury molecule-1 (KIM-1; also known as HAVCR1 or TIM-1) has emerged as a promising candidate with strong biological and clinical rationale. KIM-1 is a transmembrane glycoprotein minimally expressed in normal kidney tissue but markedly upregulated in injured and dedifferentiated proximal tubular epithelial cells, the cell of origin for clear cell RCC. Its extracellular domain is shed into circulation and urine, enabling non-invasive quantification. Beyond its role as a marker of renal injury, KIM-1 is implicated in immune modulation, chronic inflammation, and tumor biology, supporting its role as a dynamic indicator of tumor burden and disease aggressiveness. This review presents the current evidence supporting KIM-1 as a circulating biomarker and therapeutic target in RCC and discusses emerging strategies to address disease heterogeneity through biomarker-driven approaches. We examine its biological role, clinical utility in early detection and postoperative risk stratification, integration with other emerging biomarkers, and its development as a target for antibody–drug conjugates. The review concludes with a summary of the evolving landscape of KIM-1–directed biomarker strategies in RCC, which hold promise to refine patient selection, improve risk-adapted management, and advance precision oncology in this complex disease.

Keywords: kidney cancer; renal cell carcinoma; biomarker; KIM-1

1. Introduction

Renal cell carcinoma (RCC) is a biologically heterogeneous disease with highly variable clinical outcomes, even among patients with similar stage and histology. While advances in immune checkpoint inhibitors and targeted therapies have improved survival in advanced disease, there remains a critical unmet need for validated biomarkers to guide early detection, risk stratification, and perioperative management. In particular, the lack of reliable circulating biomarkers limits our ability to identify patients at the highest risk of recurrence following nephrectomy and to personalize

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surveillance and adjuvant treatment strategies. As adjuvant immune checkpoint inhibition and risk-adapted surveillance become increasingly integrated into RCC care, improved biomarkers are urgently needed to refine patient selection and minimize both overtreatment and missed opportunities for early intervention.

Kidney injury molecule-1 (KIM-1), also known as Hepatitis A Virus Cellular Receptor-1 (HAVCR1) or T-cell and Mucin Domain Containing Molecule-1 (TIM-1), has emerged as a compelling candidate biomarker in RCC. Originally developed as a sensitive indicator of proximal tubular injury [1,2], KIM-1 is now increasingly recognized for its role in renal carcinogenesis and tumor biology [3–5]. Unlike static genomic alterations, circulating KIM-1 offers a dynamic, phenotype-level biomarker that may complement genomic and transcriptomic profiling by capturing real-time tumor burden, microenvironmental interactions, and treatment response. Growing translational and clinical evidence suggests that circulating KIM-1 reflects underlying tumor burden and aggressive disease biology [3,5], positioning it as a promising biomarker in the contemporary management of RCC.

Among emerging circulating biomarkers in RCC, including circulating tumor DNA (ctDNA), circulating tumor cells, and protein-based markers, KIM-1 represents one of the most clinically advanced and biologically grounded candidates. Its proximal tubular origin, measurable shedding into circulation, and reproducible association with oncologic outcomes distinguish it from many exploratory biomarkers and position it uniquely for near-term clinical translation.

This narrative review synthesizes translational and clinical evidence supporting the role of KIM-1 as a circulating biomarker and therapeutic target in RCC. The biological and potential clinical roles of KIM-1 across the RCC disease continuum are summarized in Figure 1.

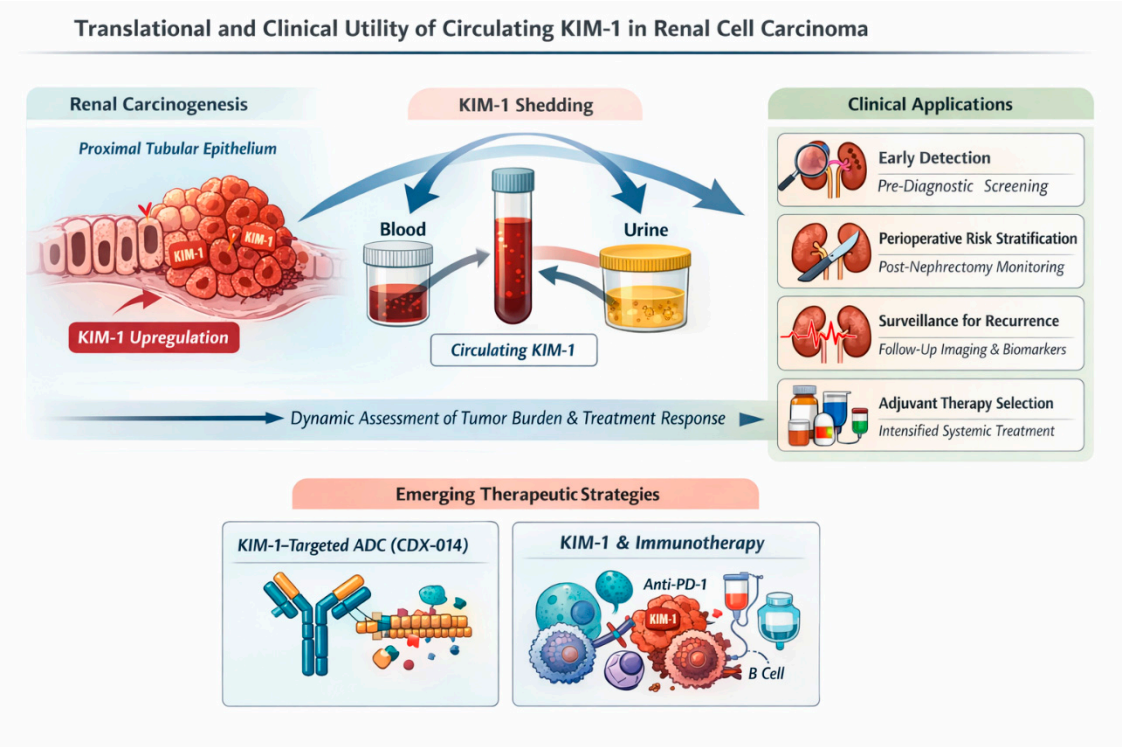

Figure 1. CAPTION ADC: antibody drug conjugate; KIM-1: Kidney Injury Molecule-1.

2. Biological Rationale for KIM-1 in RCC

KIM-1 is a type I transmembrane glycoprotein that is minimally expressed in normal renal tissue but markedly upregulated in injured or dedifferentiated proximal tubular epithelial cells [1,6–8]. Its extracellular domain can be cleaved and released into circulation and urine, enabling non-invasive measurement [1,7]. Given that clear cell RCC originates from proximal tubular epithelium, aberrant KIM-1 expression is biologically plausible and consistent with the cell of origin [3,4].

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Beyond its role as a passive injury marker, KIM-1 participates in immune modulation, phagocytosis of apoptotic debris, and chronic inflammatory signaling [9,10]. Persistent KIM-1 expression has been linked to kidney fibrosis [11,12] processes that may also contribute to tumor initiation and progression [4,13,14]. Importantly, sustained KIM-1 expression in malignant proximal tubular cells appears distinct from transient upregulation observed in acute kidney injury, supporting its relevance as a tumor-associated signal [8,14]. Together, these features provide a mechanistic framework supporting KIM-1 as a marker of both tumor presence and biologic aggressiveness.

3. KIM-1 in the Context of Emerging Biomarkers in RCC

The development of circulating biomarkers in RCC has accelerated, with approaches including ctDNA, circulating tumor cells, and radiomic signatures. However, each modality has limitations. ctDNA detection in RCC is challenged by relatively low tumor DNA shedding and inconsistent sensitivity in localized disease. Radiomic approaches, while promising, remain dependent on imaging standardization and external validation.

In contrast, KIM-1 offers several advantages: 1) a strong biological link to the cell of origin, 2) detectability in both plasma and urine, and 3) reproducible associations with clinical outcomes across independent cohorts. Importantly, KIM-1 may complement rather than compete with genomic approaches, enabling integrated biomarker strategies that combine protein-based, molecular, and imaging data.

4. Clinical Evidence Supporting KIM-1 as a Biomarker

Given the well-recognized intra- and inter-tumoral heterogeneity of RCC, circulating biomarkers such as KIM-1 may provide a more integrated reflection of global tumor biology than single-site tissue sampling. Multiple tissue-based studies have demonstrated overexpression of KIM-1 in RCC compared with adjacent normal kidney, with the highest levels observed in clear cell RCC [3,4,14]. Importantly, KIM-1 is detectable in plasma and urine, enabling its evaluation as a circulating biomarker [2]. Prospective and retrospective clinical studies have shown that elevated plasma KIM-1 levels are associated with the presence of RCC and adverse oncologic outcomes [5,14]. Notably, analyses of pre-diagnostic samples have demonstrated that increased circulating KIM-1 can be detected several years before RCC diagnosis, suggesting potential utility in early detection [12]. In the postoperative setting, data from large randomized clinical trial cohorts indicate that elevated baseline plasma KIM-1 is independently associated with increased risk of recurrence and RCC-specific mortality following nephrectomy, even after adjustment for established clinicopathologic factors [12].

Collectively, these findings position KIM-1 as a clinically actionable biomarker, with potential to refine existing prognostic models and guide perioperative decision-making, particularly in identifying high-risk patients who may benefit from intensified surveillance or consideration of adjuvant systemic therapy.

5. Implications for Therapy and Drug Development

The translational relevance of KIM-1 extends beyond risk stratification. Its tumor-associated expression has made it an attractive therapeutic target, as exemplified by early-phase clinical studies of antibody–drug conjugates directed against KIM-1 [14,15]. Although clinical efficacy data remain preliminary, these efforts underscore the dual role of KIM-1 as both a biomarker and a potential therapeutic vulnerability. In this regard, previous data has suggested that KIM-1 may have a role in inhibiting the metastatic potential of KIM-1 in RCC cells [2,9,10]. Moreover, recent work by the Kuchroo laboratory suggests that KIM-1/TiM-1 expression on B cells may influence anti-tumour immunity, raising the possibility that KIM-1 biology intersects with immune regulation in RCC [16]. These observations suggest that KIM-1 may ultimately inform responsiveness to immunotherapy,

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although this hypothesis requires evaluation in prospective biomarker-driven clinical trials incorporating immune and translational endpoints.

6. Key Clinical Trials of KIM-1

KIM-1 has been investigated both as a circulating prognostic biomarker and as a therapeutic target in RCC. In the ECOG-ACRIN E2805 (ASSURE) trial [14], post nephrectomy plasma samples demonstrated that elevated levels of circulating KIM-1 were an independent predictor of poor disease-free and overall survival; thus, supporting the use of KIM-1 as both a marker of minimal residual cancer and postoperative risk stratification. On the translational front, KIM-1 was the target of the antibody drug conjugate CDX-014, which was the first-in-human study evaluating this type of therapy using a human IgG1 antibody against KIM-1 linked to the cytotoxic payload monomethyl auristatin E (MMAE) [17]. In a phase I/II trial of heavily pretreated patients with advanced or metastatic RCC, CDX-014 was associated with significant but limited tolerability, as well as modest but promising signs of anti-tumour activity [18]. However, limited sample size and mixed responses underscored challenges in establishing clear efficacy and optimal dosing as well as patient selection.

In conjunction with these initiatives, we note two methodologies that will complement one another for exploiting KIM1 biology in RCC: First, the development of circulating KIM-1 as a prognostic biomarker that could provide more accurate risk stratification following nephrectomy [19]. Second, using KIM-1 as a prospective therapeutic target through antibody-drug conjugate platforms. However, both require additional refinement and prospective validation before widespread clinical implementation.

Table 1. Selected Clinical Trials Evaluating KIM-1 (TIM-1) as a Biomarker or Therapeutic Target in Renal Cell Carcinoma.

Trial / Agent	Phase	Study Population	KIM-1/TIM-1 Application	Treatment / Study Context	Key Translational Findings
ECOG-ACRIN E2805 (ASSURE) [14]	III (post-hoc biomarker analysis)	Resected high-risk RCC	Circulating prognostic biomarker	Adjuvant sunitinib vs sorafenib vs placebo; plasma collected post-nephrectomy	Elevated plasma KIM-1 independently associated with inferior DFS and OS across treatment arms
CDX-014 (anti–TIM-1 ADC) [18]	I/II	Metastatic RCC, heavily pretreated	Therapeutic target	TIM-1–directed ADC conjugated to MMAE	Acceptable safety profile; limited overall activity with durable partial response in select patients

7. Challenges and Future Directions

Despite promising early data, several challenges must be addressed before KIM-1 can be integrated into routine clinical practice. First, circulating KIM-1 levels may be influenced by non-malignant acute or chronic kidney injury [11,12], necessitating careful interpretation, particularly in patients with chronic kidney disease. Second, standardization of assays, definition of clinically meaningful cut-offs, and prospective validation across diverse populations are essential next steps. Given the potential role of KIM-1 in tumor biology and metastasis, therapeutic targeting warrants caution, as receptor engagement may have context-dependent effects that are not yet fully

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understood. Moreover, more research is needed to better understand the biological significance of soluble (shed) KIM-1 in RCC.

Future research should prioritize prospective biomarker-driven trials incorporating serial KIM-1 measurements to evaluate its role in minimal residual disease detection and early relapse prediction. Integration into adjuvant immunotherapy trials may enable risk-adapted treatment escalation or de-escalation strategies. In parallel, combination biomarker approaches, incorporating KIM-1 with ctDNA, transcriptomic profiling, and radiomic features, may provide a more comprehensive framework for precision risk stratification. Finally, next-generation KIM-1–targeted therapeutics [18], including optimized antibody–drug conjugates, require refinement in patient selection and dosing strategies to fully realize clinical benefit.

8. Conclusions

KIM-1 represents a biologically grounded and clinically promising circulating biomarker in renal cell carcinoma. Its association with tumor presence, recurrence risk, and survival across multiple studies highlights its potential as a leading candidate for integration into perioperative and systemic treatment paradigms. Beyond prognostication, the dual role of KIM-1 as both a biomarker and therapeutic target underscores its translational significance. Prospective validation and incorporation into biomarker-driven clinical trials will be critical to establishing KIM-1 as a component of precision oncology strategies in RCC.

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Ethical Statement: The author is accountable for all aspects for the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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