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Roles of Matrix Metalloproteinases in Invasion and Metastasis of Clear Cell Renal Cell Carcinoma: A Narrative Review

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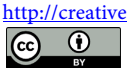

Abstract

Clear cell renal cell carcinoma (ccRCC) accounts for most kidney cancers, and metastatic dissemination rather than the primary tumor causes most kidney-cancer deaths. Degradation and reorganization of the extracellular matrix (ECM) are prerequisites for local invasion, intravasation, and colonization of distant organs, and matrix metalloproteinases (MMPs) are the principal effectors of these processes. This narrative review synthesizes peer-reviewed evidence published between 2021 and 2026 on the expression, regulation, mechanistic functions, and translational relevance of MMPs and their endogenous inhibitors, the tissue inhibitors of metalloproteinases (TIMPs), in ccRCC invasion and metastasis. Tissue and bioinformatic studies report overexpression of gelatinases (MMP-2, MMP-9) and membrane-type MMP-14, together with several other family members, in ccRCC; however, the direct ccRCC evidence is largely transcriptomic and immunohistochemical, whereas part of the supporting tissue-level data derive from mixed-histology renal carcinoma cohorts rather than pure clear cell populations. Higher MMP expression or enzymatic content generally associates with advanced stage, aggressive histology, and shorter survival. Mechanistic work converges on a small set of regulatory axes, including ERK/MAPK signaling through the transcription factors ETS1 and activator protein 1 (AP-1), metabolic reprogramming through G6PD, and epithelial-mesenchymal transition (EMT) programs driven by SPOCK1, CD44, and FXR, each of which funnels into MMP induction. Dysregulation of TIMPs, including TIMP-1 overexpression with pro-survival functions and TIMP-3 loss, further tilts the proteolytic balance toward invasion, while non-coding RNAs and macrophage-derived exosomes modulate the MMP/TIMP axis within the tumor microenvironment. Translationally, MMPs show promise as components of prognostic models, radiomic predictors, and liquid-biopsy readouts, but therapeutic targeting remains unrealized in ccRCC; the failure of broad-spectrum MMP inhibitors has shifted interest toward engi-

neered, highly selective protein inhibitors and rational combinations with anti-angiogenic and immune-checkpoint therapy. Realizing the clinical value of the MMP axis in ccRCC will require activity-based biomarkers, ccRCC-specific interventional studies, and trial designs that account for the context-dependent functions of individual family members.

Keywords

Matrix Metalloproteinases, Renal Cell Carcinoma, Neoplasm Invasiveness, Neoplasm Metastasis, Tissue Inhibitor of Metalloproteinases, Tumor Microenvironment

1. Introduction

Kidney cancer imposed an estimated global burden of more than 430,000 new cases and approximately 156,000 deaths in 2022, and its incidence continues to rise in most regions [1]. Renal cell carcinoma (RCC) comprises a group of histologically and molecularly distinct entities, of which clear cell RCC (ccRCC) is the most common, accounting for roughly 70% to 80% of cases [2]. Although localized ccRCC is frequently cured by surgery or ablation, approximately one third of patients present with synchronous metastases or develop metachronous dissemination after nephrectomy, and metastatic disease remains the dominant cause of kidney-cancer mortality [2] [3]. The biological behavior of ccRCC is anchored by biallelic inactivation of the VHL tumor suppressor in the large majority of sporadic tumors, which stabilizes hypoxia-inducible factors, particularly HIF-2*α*, and rewires transcriptional programs governing angiogenesis, metabolism, and cell motility [4].

Therapy for advanced ccRCC has changed substantially in the past five years. Combinations of immune-checkpoint inhibitors with tyrosine-kinase inhibitors (TKIs) are now first-line standards, and the HIF-2*α* inhibitor belzutifan has validated the VHL-HIF axis as a direct drug target, first in VHL disease-associated RCC and subsequently in previously treated advanced disease, where it improved progression-free survival over everolimus [3] [5] [6]. Nevertheless, primary and acquired resistance to these regimens is frequent, and long-term disease control is achieved in only a minority of patients [7]. Hypoxia itself has emerged as a determinant of both response and resistance in metastatic ccRCC, linking the defining molecular lesion of this disease to its clinical intractability [8]. Understanding the downstream machinery that converts hypoxic, VHL-deficient signaling into invasive and metastatic behavior therefore remains a priority.

Matrix metalloproteinases (MMPs) are zinc-dependent endopeptidases that collectively degrade essentially all components of the extracellular matrix (ECM) and many non-matrix substrates [9]. Proteolysis of basement membrane and interstitial matrix is a biochemical prerequisite for tumor cell escape from the primary mass, entry into and exit from the vasculature, and remodeling of metastatic

niches. MMPs were implicated in kidney cancer decades ago, and their roles in RCC pathophysiology have been reviewed periodically [10] [11]. However, the evidence base has expanded rapidly since 2021, driven by single-cell and spatial profiling of the ccRCC microenvironment, mechanistic studies of MMP regulation, protein-engineering approaches to selective inhibition, and renewed interest in ECM proteolysis as a modifier of anti-angiogenic and immunotherapeutic efficacy. A critical synthesis of this recent literature is lacking.

This narrative review summarizes peer-reviewed evidence published between January 2021 and July 2026 on the roles of MMPs and tissue inhibitors of metalloproteinases (TIMPs) in ccRCC invasion and metastasis. The review is organized by theme rather than by chronology: we first outline MMP biology relevant to cancer invasion, then synthesize expression and prognostic data in ccRCC, then integrate mechanistic and microenvironmental findings, and finally evaluate translational opportunities and their limits, closing with a critical appraisal and outstanding questions for the field. An overview of the MMP/TIMP axis in ccRCC invasion and metastasis discussed in this review is presented in Figure 1.

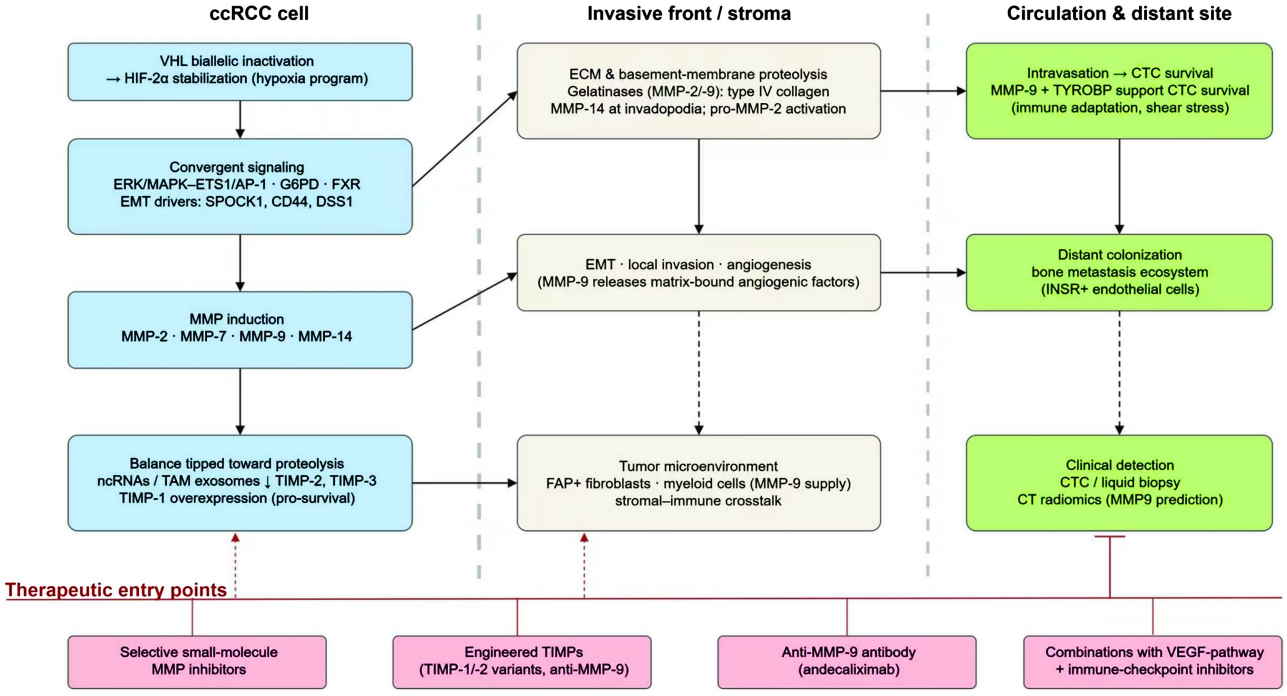

Figure 1. The matrix metalloproteinase (MMP)/tissue inhibitor of metalloproteinases (TIMP) axis in clear cell renal cell carcinoma (ccRCC) invasion and metastasis. Biallelic VHL inactivation stabilizes hypoxia-inducible factors and establishes a hypoxic transcriptional program in ccRCC cells. Upstream signals, including ERK/MAPK-ETS1/AP-1, metabolic reprogramming (G6PD), nuclear receptors (FXR), and epithelial-mesenchymal transition (EMT) drivers (SPOCK1, CD44, DSS1), converge on induction of MMP-2, MMP-7, MMP-9, and MMP-14, while non-coding RNAs and macrophage-derived exosomes erode TIMP-mediated restraint (TIMP-2, TIMP-3). Gelatinases and membrane-type MMP-14 then degrade basement-membrane and interstitial matrix at the invasive front and at invadopodia, enabling local invasion, angiogenesis, and intravasation. In the circulation, MMP-9 has been associated with circulating tumor cell (CTC) survival (association-based evidence); at distant sites such as bone, tumor and host compartments remodel a metastatic niche. Therapeutic entry points (red) include selective small molecules, engineered TIMPs, anti-MMP-9 antibodies, and rational combinations with VEGF-pathway and immune-checkpoint inhibitors. HIF, hypoxia-inducible factor; ECM, extracellular matrix; TAM, tumor-associated macrophage.

2. Literature Search Strategy

PubMed was searched in July 2026 for articles published between January 2021 and July 2026, using combinations of the terms "matrix metalloproteinase", individual MMP and TIMP designations, "clear cell renal cell carcinoma", "renal cell carcinoma", "invasion", "metastasis", "prognosis", and related variants. English-language original research and review articles were screened by title and abstract, and studies judged directly relevant to ccRCC biology, or to general MMP mechanisms applicable to it, were included; reference lists of included articles were examined for additional recent sources. Because this is a narrative rather than a systematic review, no formal protocol was registered, and the synthesis emphasizes thematic integration over exhaustive enumeration.

3. Matrix Metalloproteinase Biology Relevant to Cancer Invasion

Twenty-three human MMPs share a conserved catalytic architecture built around a zinc-binding motif, and they are conventionally grouped by domain organization and substrate preference into collagenases, gelatinases, stromelysins, matrilysins, membrane-type MMPs, and other minor classes [9]. Beyond the catalytic domain, ancillary modules such as hemopexin-like domains and fibronectin-type inserts govern substrate recognition and exosite interactions, features that have become central to the design of selective inhibitors discussed later in this review [9]. All MMPs are synthesized as inactive zymogens whose propeptide shields the catalytic zinc; activation occurs through proteolytic removal of the propeptide or through allosteric and oxidative mechanisms, providing a first layer of regulation that is spatially restricted to the cell surface or the pericellular environment [9] [12]. A second layer is provided by the four TIMPs, which bind active MMPs with high affinity and, at balanced stoichiometry, confine proteolysis to defined microdomains [13]. The biological output of the system is therefore determined not by MMP abundance alone but by the local ratio of activated enzyme to inhibitor, a point that has direct consequences for interpreting expression studies in ccRCC tissue.

MMP biology extends well beyond bulk matrix degradation. Gelatinases A and B (MMP-2 and MMP-9) cleave type IV collagen of basement membranes but also process cytokines, growth-factor precursors, and cell-surface receptors, thereby modulating inflammation, angiogenesis, and immune-cell trafficking within tumors [12] [13]. Membrane-type 1 MMP (MT1-MMP, MMP-14) occupies a special position in invasion: anchored to the plasma membrane, it concentrates proteolysis at the leading edge of migrating cells, activates pro-MMP-2 in a ternary complex with TIMP-2, and is enriched at invadopodia, the actin-rich protrusions through which cancer cells penetrate matrix barriers [14] [15]. Several MMPs also execute intracellular and even nuclear functions, including roles in DNA-damage responses and transcriptional regulation, which complicates the interpretation of both expression data and inhibitor studies [14]. These properties explain why

MMP activity in tumors is pro-invasive in most contexts but can be anti-tumorigenic in others, and they foreshadow the difficulties encountered in clinical translation.

4. Expression and Prognostic Significance of Matrix Metalloproteinases in Clear Cell Renal Cell Carcinoma

Evidence from human tissue indicates that gelatinase dysregulation is a consistent feature of renal carcinoma, but also that abundance and activity must be distinguished. In a cohort of 302 RCC tumors analyzed by immunohistochemistry, expression of MMP-2, MMP-9, and the adhesion receptor CD44 varied with histopathological subtype and was evaluated as a candidate prognostic panel in clear cell and non-clear cell disease [16]. Direct biochemical measurement adds an important qualification: in homogenates of human renal carcinoma, MMP-9 content was higher than that of MMP-2, yet its specific activity was not correspondingly elevated, indicating that a substantial fraction of the enzyme remains latent or inhibitor-bound in tumor tissue [17]. This discordance cautions against equating immunoreactivity or transcript level with proteolytic output and argues for activity-based readouts in future biomarker work. It also has a practical corollary: tissue-level measurements average contributions from malignant, stromal, and immune cells, so localization data from immunohistochemistry and single-cell studies are needed to attribute proteolytic activity to specific compartments [16] [17].

Membrane-type MMPs show a similar pattern of selective upregulation. In paired comparisons within human renal carcinoma specimens, MMP-14 exceeded MMP-15 in expression, protein content, and enzymatic activity. This comparison is restricted to the two membrane-type MMPs examined in the cited renal-carcinoma cohort and identifies MMP-14 as the more highly expressed and more active of the two in that setting, without implying dominance over other membrane-anchored proteases [18]. Consistent with a functional role, transcriptomic analyses of clear cell tumors have associated high MMP14 expression with poor prognosis, and MMP-12 has emerged as an independent predictor of postoperative relapse in conventional (clear cell) RCC [19] [20]. Beyond tissue, plasma levels of MMP-1, measured together with other circulating proteins, differ between RCC patients and controls and have been proposed as components of minimally invasive diagnostic panels [21]. Germline variation may also contribute: MMP9 genotypes have been associated with RCC susceptibility and clinical features, suggesting that constitutive differences in MMP-9 expression influence disease risk [22].

Large-scale transcriptomic studies have extended these observations across the MMP family. Systematic characterization of MMP family members in kidney clear cell carcinoma datasets identified coordinated dysregulation of multiple family members, several of which correlated with stage, grade, and survival, supporting their evaluation as a biomarker panel rather than as isolated markers [23]. MMP-9 occupies a recurrent position in such analyses: combined assessment of MMP9

and insulin-like growth factor binding protein 1 (IGFBP1) correlated their expression with the immune microenvironment and tumor progression in ccRCC, and an MMP family-based risk model stratified patient outcomes, with serum amyloid A1 (SAA1) identified as an upstream promoter of ccRCC migration acting through an ERK-AP1-MMP axis [24] [25]. Efforts to move these signals toward the clinic include a computed-tomography radiomics model that noninvasively predicted MMP9 expression status and carried prognostic information, an approach that could eventually embed MMP biology into routine imaging [26].

Taken together, the expression literature supports four generalizations. First, upregulation of gelatinases and MMP-14 is reproducible across assay platforms and cohorts, but the evidence base is heterogeneous: the direct ccRCC-specific data are mainly transcriptomic and immunohistochemical, whereas the biochemical tissue measurements supporting gelatinase and MMP-14 upregulation were obtained in mixed-histology renal carcinoma cohorts, so the strength of this conclusion differs by molecule and cohort composition. Second, higher MMP expression or content generally tracks with adverse clinicopathological features and shorter survival, although effect sizes and optimal cut-offs vary between studies. Third, several tissue studies analyzed mixed-histology RCC cohorts rather than pure clear cell populations, and their findings should be extrapolated to ccRCC with caution [16]-[18] [21] [22]. Fourth, the field remains disproportionately reliant on transcript-level inference from public datasets; protein-level and, especially, activity-level measurements are scarce, and the available biochemical data indicate that they cannot be replaced by transcript surrogates [17]. The cellular sources of the measured enzymes, which bulk tissue studies cannot resolve, are considered in the microenvironment section below. Key findings for the individual family members discussed in this and the following sections are summarized in Table 1.

Table 1. Selected matrix metalloproteinases and tissue inhibitors implicated in clear cell renal cell carcinoma invasion and metastasis.

Molecule	Class	Key findings in ccRCC/RCC (2021-2026)	Prognostic association	Representative references
MMP-1	Collagenase	Plasma levels differ between RCC patients and controls; proposed for diagnostic panels	Associated with disease presence	[21]
MMP-2	Gelatinase A	Elevated tissue content; induced by ERK/MAPK-ETS1, SPOCK1-Snail/Slug, and FRL1-MAPK axes; activated at the cell surface by MMP-14	High expression/content linked to aggressive features	[14] [16] [17], [27] [28] [31]
MMP-7	Matrilysin	Mediates FXR-driven EMT and carcinogenesis in ccRCC models	Linked to EMT phenotype	[30]
MMP-9	Gelatinase B	Higher tissue content than MMP-2, but specific activity not correspondingly elevated (a substantial fraction latent or inhibitor-bound); induced by G6PD and CD44-HAS1; expression associated with CTC survival (transcriptomic, association-based); germline genotypes modify RCC risk	Poor prognosis, immune infiltration, association with CTC survival; radiomics-predictable	[17] [22] [24]-[26] [29] [32] [50]

Continued

MMP-12	Macrophage metalloelastase	Independently predicts postoperative relapse in conventional RCC	Independent adverse prognostic factor	[20]
MMP-14 (MT1-MMP)	Membrane-type	Exceeded MMP-15 in expression, content, and activity in the cited renal-carcinoma cohort; activates pro-MMP-2; invadopodia-associated	Upregulation associated with poor prognosis	[14] [15] [18] [19]
TIMP-1	Endogenous inhibitor	Promotes anoikis resistance and immunosuppression; accelerates tumorigenesis via EMT (non-canonical functions)	Poor prognosis	[35] [36]
TIMP-2	Endogenous inhibitor	Target of macrophage exosomal miR-193a-5p; TIMP-2-dependent vasculogenic mimicry	Context-dependent	[40]
TIMP-3	Endogenous inhibitor	Downregulated in tumor endothelial cells by hypertension-associated signaling (miR-21-5p/TGFBR2/P38/EGR1) and in tumor cells by FKBP51-mediated autophagic degradation; polymorphism interacts with cadmium exposure	Loss facilitates invasion; risk modification	[37]-[39]

Note: Reference numbers correspond to the numbered reference list of the main text. CTC, circulating tumor cell; EMT, epithelial-mesenchymal transition; RCC, renal cell carcinoma.

5. Mechanistic Roles of Matrix Metalloproteinases in Clear Cell Renal Cell Carcinoma Invasion and Metastasis

5.1. Extracellular Matrix Proteolysis and Basement-Membrane Breach

The most direct route by which MMPs promote ccRCC dissemination is proteolysis of the physical barriers that confine tumor cells. Type IV collagen of the basement membrane is a preferred substrate of MMP-2 and MMP-9, and the elevated gelatinase content documented in renal carcinoma tissue provides the enzymatic capacity for local barrier destruction [12] [17]. MMP-14 complements the soluble gelatinases by focusing proteolysis at the cell surface and by activating pro-MMP-2 at the invasive front, a cooperation that couples pericellular and extracellular matrix degradation [14] [18]. Invadopodia, whose assembly and function depend on MT1-MMP and associated proteases, offer a structural framework for this activity: these protrusions degrade matrix at defined contact points and are increasingly recognized as druggable structures in metastatic disease [15]. Although most of this framework derives from pan-cancer studies, the finding that MMP-14 exceeded MMP-15 in expression, content, and activity in the cited renal-carcinoma cohort suggests that the same machinery operates in ccRCC [18].

5.2. Intracellular Signaling Networks Converging on Matrix Metalloproteinase Induction

Mechanistic studies in ccRCC models published since 2021 converge on a limited set of signaling nodes that drive MMP transcription. The ERK/MAPK cascade is the most consistently implicated: ERK signaling was shown to upregulate MMP2 through the ETS family transcription factor ETS1 in clear cell tumors, and the

acute-phase reactant SAA1 promoted ccRCC cell migration through an ERK-AP1 axis that induced multiple MMPs [25] [27]. Formin-related protein 1 (FRL1) similarly enhanced proliferation and aggressive phenotypes of ccRCC cells through MAPK/MMP2 signaling [28]. Metabolic reprogramming feeds into the same pathway: glucose-6-phosphate dehydrogenase (G6PD), a rate-limiting enzyme of the pentose phosphate pathway, upregulated Cyclin E1 and MMP9 to promote ccRCC progression, linking the characteristic metabolic rewiring of this disease to its proteolytic machinery [29]. Nuclear-receptor signaling contributes as well, with the farnesoid X receptor promoting ccRCC carcinogenesis through an MMP-7-regulated EMT pathway [30]. The recurrence of ERK-AP1/ETS1 across these otherwise diverse studies points to a convergent regulatory node for MMP induction in ccRCC, although this convergence is inferred from independent models rather than demonstrated within a single experimental system; it nonetheless nominates this node as a candidate point for therapeutic interception.

5.3. Coupling between Epithelial-Mesenchymal Transition and Matrix Metalloproteinase Expression

Epithelial-mesenchymal transition (EMT) equips carcinoma cells with motility and invasiveness, and in ccRCC the EMT program is tightly interwoven with MMP regulation. The proteoglycan SPOCK1, overexpressed in ccRCC and associated with poor prognosis, promoted malignant progression by triggering a Snail/Slug-MMP-2 axis, placing MMP-2 downstream of canonical EMT transcription factors [31]. CD44, a stemness-associated adhesion molecule enriched in aggressive ccRCC, facilitated migration and invasion through hyaluronan synthase 1 (HAS1)/MMP9 signaling [32]. Extending this theme to the metastatic niche, DSS1, a BRCA2 cofactor found upregulated in metastatic ccRCC, impaired autophagic flux and thereby activated EMT, enhancing both tumor growth and distant metastasis in experimental models [33]. The EMT-MMP coupling has a therapeutic dimension: EMT not only drives invasion but also contributes to sunitinib resistance in RCC, so MMP induction downstream of EMT may participate in both dissemination and treatment failure [34]. A qualification is nonetheless warranted: EMT in ccRCC is increasingly recognized as a partial, context-dependent state of epithelial plasticity rather than a single canonical, binary program, and the studies cited above differ in how they operationalize EMT. MMPs should therefore not be portrayed uniformly as downstream executors of one canonical EMT program; rather, within the plasticity states captured by each model, they appear to act predominantly as effectors of EMT-linked signaling rather than as its initiators, which may still explain why their expression so consistently marks aggressive disease.

5.4. Tissue Inhibitor of Metalloproteinase Dysregulation Tips the Proteolytic Balance

Because TIMPs set the ceiling on net proteolytic activity, their dysregulation can

be as consequential as MMP induction itself, and the ccRCC literature illustrates both arms of this balance. TIMP-1 behaves paradoxically as a pro-tumorigenic factor: it shaped an immunosuppressive microenvironment and promoted ccRCC progression by regulating anoikis resistance, and independent work linked TIMP1 to poor prognosis and accelerated tumorigenesis through EMT signaling [35] [36]. These findings indicate that TIMP-1 functions in ccRCC extend beyond MMP blockade and include cytokine-like, pro-survival activities. TIMP-3, in contrast, acts as an invasion brake whose loss facilitates disease, and its regulation illustrates the contribution of non-malignant compartments: hypertension-associated signaling reduced TIMP3 in tumor endothelial cells through the miR-21-5p/TGFBR2/P38/EGR1 axis, releasing a paracrine restraint on ccRCC cell proliferation and migration, while in tumor cells FKBP51 enhanced invasion by increasing autophagic degradation of TIMP3 [37] [38]. A TIMP3 polymorphism that interacted with blood cadmium levels to modify RCC risk further links environmental exposure to this inhibitory pathway [39]. TIMP-2 has been assigned a context-dependent role through studies of macrophage-tumor crosstalk, in which exosomal transfer altered TIMP-2-dependent vasculogenic mimicry [40]. The overall pattern in ccRCC is therefore a double hit on the inhibitory arm: gain of TIMP-1's non-canonical pro-survival functions together with erosion of TIMP-3-mediated restraint.

5.5. Non-Coding RNA and Exosomal Regulation of the Matrix Metalloproteinase/Tissue Inhibitor Axis

Post-transcriptional regulation adds a further layer of control that is intensively studied in ccRCC. These studies differ in mechanistic specificity, and we distinguish them accordingly. Two studies demonstrate direct regulation of an MMP/TIMP component: circular RNA CSNK1G3 upregulated miR-181b to promote growth and metastasis through TIMP3-mediated EMT, illustrating how competing-endogenous-RNA networks can release MMP activity by depleting inhibitors [41]; and tumor-associated macrophages transferred miR-193a-5p within exosomes to ccRCC cells, promoting progression through TIMP2-dependent vasculogenic mimicry, a process by which tumor cells form perfusable vascular-like channels that facilitate dissemination [40]. By contrast, the miR-146b-5p/SEMA3G axis regulated EMT in ccRCC without a demonstrated MMP- or TIMP-mediated mechanism, and the broader literature cataloguing exosomal non-coding RNAs as systemic modulators of RCC progression likewise addresses tumor progression and therapeutic potential rather than a defined MMP/TIMP target; these two sources are cited as context for the regulatory environment rather than as evidence of direct MMP/TIMP control [42] [43]. Collectively, the mechanistically direct studies extend MMP regulation beyond the tumor cell itself and implicate intercellular RNA traffic in setting the proteolytic tone of the tumor, whereas the remaining evidence is associative with respect to the MMP/TIMP axis.

6. Matrix Metalloproteinases at the Interface with the Tumor Microenvironment and the Metastatic Cascade

Invasion and metastasis unfold within a microenvironment that ccRCC cells share with stromal and immune populations, and recent single-cell and spatial studies have reframed MMP biology as a collective property of this ecosystem rather than of tumor cells alone. The ECM of ccRCC is extensively remodeled and carries prognostic information in its own right, with matrix organization and composition varying across tumor regions [44]. Single-cell transcriptomic atlases of advanced and localized kidney cancer have resolved the cellular sources of matrix-remodeling programs: cancer-associated fibroblasts, tumor-associated macrophages (TAMs), and the malignant cells themselves each contribute distinct repertoires of proteases, inhibitors, and matrix substrates [45] [46]. In RCC with venous tumor thrombus, a pattern of locally aggressive spread in which tumor extends into the renal vein and inferior vena cava, fibroblast activation protein (FAP)-positive fibroblasts orchestrate microenvironmental remodeling, linking stromal activation to the distinctive intravascular growth of this disease [47]. Myeloid populations, long recognized as MMP-9 suppliers in many tumors, execute metastasis-promoting functions that include matrix degradation, angiogenesis, and suppression of anti-tumor immunity [13] [48]. In this framing, the gelatinase measured in a tumor homogenate originates from several cell types, and therapeutic targeting of stromal MMP sources may be as important as targeting the malignant compartment. This compartmental view also reconciles an apparent paradox in the expression literature: transcript-level signals attributed to "tumor" MMP-9 in bulk datasets may in part reflect infiltrating myeloid cells, which strengthens rather than weakens the case for MMP-9 as a microenvironmental drug target [23] [48].

The later steps of the metastatic cascade also bear an MMP signature. A transcriptional metastatic signature derived from single-cell data predicted survival in ccRCC; because this evidence is prognostic and association-based, it indicates that dissemination-related programs are detectable early in primary tumors but does not by itself establish that the signature causally encodes metastatic capacity, which would require functional validation [49]. Circulating tumor cells (CTCs) must survive hemodynamic shear and immune attack in the bloodstream, and comparative transcriptomics identified MMP9 and TYRO protein tyrosine kinase binding protein (TYROBP) as genes associated with CTC survival in ccRCC through adaptation to the tumor immune microenvironment; this evidence is transcriptomic and association-based, and a causal contribution of MMP-9 to CTC survival remains to be validated functionally [50]. At the distant site, single-cell profiling of ccRCC bone metastases revealed a distinct ecosystem in which insulin receptor (INSR)-positive endothelial cells play a pivotal role, underscoring that colonization involves reciprocal remodeling between tumor and host tissue [51]. Clinical detection of these steps is advancing in parallel: systematic evaluation of CTC detection methods in RCC and broader liquid-biopsy approaches

now offer platforms through which MMP-related readouts could be captured longitudinally during therapy [52] [53]. Hypoxia, the defining feature of VHL-deficient ccRCC, permeates each of these steps and has been shown to shape therapeutic response and resistance in metastatic disease, providing a mechanistic thread that connects the primary lesion to the metastatic niche [8].

Angiogenesis deserves separate emphasis because it is both a hallmark of ccRCC and a process tightly coupled to MMP activity. MMP-9 releases matrix-bound pro-angiogenic factors and remodels the perivascular matrix during vascular sprouting, and MMPs more generally shape the tumor microenvironment in which vessels form [12] [13]. The relationship is not unidirectional: pharmacological inhibition of MMPs was reported to support amoeboid angiogenesis, an alternative, protease-independent mode of vascularization that hampered VEGF-targeted therapies through myosin light chain and ERK signaling [54]. This observation derives from non-renal cancer models, and whether the same compensatory route operates in ccRCC is untested; even so, it carries a caution for a disease treated predominantly with VEGF-pathway inhibitors: MMP blockade could, in principle, relieve one invasive mechanism while unleashing another, and any therapeutic strategy directed at proteolysis must anticipate such escape routes.

7. Translational and Therapeutic Implications

7.1. Matrix Metalloproteinases as Biomarkers in Clear Cell Renal Cell Carcinoma

The biomarker literature supports a role for MMPs as components of prognostic instruments rather than as standalone tests. Family-wide expression signatures stratify outcome in ccRCC, and MMP-14, MMP-12, and MMP-9 have each been associated with relapse or survival in independent cohorts [19] [20] [23]-[25]. Noninvasive assessment is a particularly attractive direction: a CT-based radiomics model predicted MMP9 expression and prognosis, raising the possibility of imaging surrogates for proteolytic activity, and CTC and liquid-biopsy platforms provide repeat access to tumor material across the treatment course [26] [52] [53]. Several qualifications temper this promise. Most models are retrospective and single-cohort; cut-offs and assay platforms differ between studies; and, as noted above, transcript and antigen measurements do not reliably report enzymatic activity [17]. Prospective validation in ccRCC-specific cohorts, ideally with activity-based or imaging readouts, is the necessary next step before any MMP-related biomarker can inform standard of care.

7.2. Therapeutic Targeting of Matrix Metalloproteinases: Lessons and New Directions

The therapeutic history of MMP inhibition is a cautionary tale that the ccRCC field should study carefully. Broad-spectrum small-molecule inhibitors, developed largely in the 1990s, failed in phase III trials across several cancers because of dose-limiting musculoskeletal toxicity, poor selectivity among family members,

and trial designs that ignored the context-dependent and sometimes protective functions of individual MMPs [55] [56]. Medicinal-chemistry and patent literature from the past five years documents sustained efforts to overcome these barriers through improved selectivity, alternative zinc-binding chemotypes, and structure-based design [55]-[57]. The most conceptually advanced strategies now exploit protein engineering rather than small molecules: engineered variants of TIMP-2 with narrow MMP-9 specificity inhibited cancer-cell invasion and proliferation, directed evolution produced TIMP-1 variants selective for MMP-9, and engineered protein inhibitors more broadly have achieved discrimination between closely related MMP catalytic domains that small molecules cannot match [58]-[60]. Antibody-based inhibition has likewise been evaluated only preclinically in this context: the anti-MMP-9 antibody andecaliximab was tested as an anti-invasive therapeutic in head and neck squamous cell carcinoma models, and the evidence cited here (Reference 61) is therefore preclinical rather than a clinical trial [61]. None of these agents has yet been tested in ccRCC. Two practical barriers explain this gap beyond the historical toxicity of the class: ccRCC-specific preclinical efficacy data for selective inhibitors are almost entirely lacking, and no validated biomarker exists to stratify patients by MMP dependency. The tools for a selective, biomarker-guided trial nonetheless now exist.

We argue that ccRCC is a rational setting in which to revisit MMP-directed therapy, for three reasons. First, the expression and mechanistic data converge on a small number of family members, principally MMP-2, MMP-9, and MMP-14—recognizing that this evidence combines direct ccRCC studies (transcriptomic, immunohistochemical, and mechanistic) with biochemical data from mixed-histology renal carcinoma cohorts—which narrows the target space for selective agents [16]-[20] [25]. Second, the disease is treated with VEGF-pathway inhibitors and immune-checkpoint blockade whose efficacy is modulated by matrix proteolysis, offering rational combination strategies, although the amoeboid-angiogenesis data demand careful sequencing and pharmacodynamic monitoring [7] [54]. Third, metastatic ccRCC retains its driver biology, including hypoxia signaling, across the treatment course, so a downstream executor of invasion such as the MMP axis is unlikely to be silenced by selective pressure against upstream nodes [7] [8]. Against these considerations stands the historical record, which teaches that indiscriminate inhibition of this family is toxic and futile [55]. A credible path forward would pair a selective inhibitor or engineered TIMP with an activity-based companion biomarker, tested first in biomarker-selected, metastatic ccRCC cohorts, with pharmacodynamic readouts of target engagement and prespecified monitoring for the musculoskeletal toxicity that ended earlier programs [55] [56].

8. Limitations of the Current Evidence

This review and the literature it summarizes share several limitations. As a narrative rather than systematic review, the synthesis is subject to selection and inter-

pretation biases, although the search strategy was specified and the inclusion window was restricted to recent, peer-reviewed work. Within the primary literature, transcript-level analyses of public datasets predominate, and the biochemical data caution that transcript abundance is an imperfect surrogate for proteolytic activity [17] [23]. Mechanistic studies rely heavily on cell lines and xenografts whose microenvironments differ from human ccRCC, and almost no interventional study of an MMP-directed agent has been performed specifically in this disease. In coverage, this review does not attempt exhaustive treatment of all 23 family members: MMPs for which recent ccRCC-specific evidence is scarce, including stromelysins and membrane-type MMPs other than MMP-14, are not discussed individually, and their roles in this disease remain open questions. Finally, publication bias toward positive mechanistic findings is likely, and contradictory or null results are underrepresented in the cited evidence.

9. Conclusion

Evidence published between 2021 and 2026 positions matrix metalloproteinases as central executors of invasion and metastasis in clear cell renal cell carcinoma. Gelatinases and MMP-14 are consistently upregulated across ccRCC transcriptomic and immunohistochemical studies, with corroborating biochemical evidence from mixed-histology renal carcinoma cohorts that should be extrapolated to pure clear cell disease with caution; their induction is driven by convergent ERK/MAPK-ETS1/AP-1 signaling, metabolic reprogramming, and EMT programs; and their activity is further unleashed by TIMP-3 loss and TIMP-1 overexpression, all within a microenvironment whose stromal and immune compartments both supply and respond to proteolysis. The translational opportunity is real but unrealized: MMP-related readouts are promising components of prognostic and imaging biomarkers, yet none has been prospectively validated for clinical use, and no selective MMP-directed agent has been tested in ccRCC despite a mature protein-engineering toolkit. The field's priorities are correspondingly clear. Activity-based and spatially resolved measurements should replace transcript surrogates in biomarker development; selective inhibitors should be evaluated in biomarker-selected ccRCC cohorts with rational combinations against VEGF and immune-checkpoint pathways; and trial designs must respect the context-dependent, occasionally protective functions of this protease family. If these conditions are met, the MMP axis could move from a descriptive marker of aggressive disease to an actionable component of ccRCC management; until then, its direct impact on the standard of care lies in refining prognostic stratification and in identifying the patient subsets most likely to benefit from future protease-directed trials.

Declaration on the Use of Artificial Intelligence Tools

During the preparation of this work, the authors did not use any artificial-intelli-

gence-assisted writing tools. All content was written, reviewed, and edited solely by the authors, who take full responsibility for the integrity and accuracy of the manuscript.

Author Contributions

B. L. conceived the review, performed the literature search, and drafted the manuscript. B. L. curated and verified the references. Y. L. supervised the work and critically revised the manuscript. All authors read and approved the final version.

Conflicts of Interest

The authors declare no conflicts of interest.

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Abbreviations

AP-1	activator protein 1
ccRCC	clear cell renal cell carcinoma
CTC	circulating tumor cell
DSS1	deleted in split hand/split foot 1
ECM	extracellular matrix
EMT	epithelial-mesenchymal transition
ERK	extracellular signal-regulated kinase
ETS1	ETS proto-oncogene 1
FAP	fibroblast activation protein
FRL1	formin-related protein 1
FXR	farnesoid X receptor
G6PD	glucose-6-phosphate dehydrogenase
HAS1	hyaluronan synthase 1
HIF	hypoxia-inducible factor
ICI	immune-checkpoint inhibitor
IGFBP1	insulin-like growth factor binding protein 1
INSR	insulin receptor
MMP	matrix metalloproteinase
RCC	renal cell carcinoma
SAA1	serum amyloid A1
TAM	tumor-associated macrophage
TIMP	tissue inhibitor of metalloproteinases
TKI	tyrosine-kinase inhibitor
TYROBP	TYRO protein tyrosine kinase binding protein
VHL	von Hippel-Lindau
VM	vasculogenic mimicry