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► **To cite this version:**

Beatrice Cesana, Claude Cochet, Odile Filhol. New players in the landscape of renal cell carcinoma bone metastasis and therapeutic opportunities. *International Journal of Cancer*, 2024, 2024, pp.1-13. 10.1002/ijc.35181 . hal-04723194

HAL Id: hal-04723194

<https://hal.science/hal-04723194v1>

Submitted on 7 Oct 2024

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REVIEW

New players in the landscape of renal cell carcinoma bone metastasis and therapeutic opportunities

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Funding information

Université Grenoble Alpes; Ligue Contre le Cancer; Institut National de la Santé et de la Recherche Médicale; Groupement des Entreprises Françaises dans la lutte contre le Cancer

Abstract

Approximately one-third of advanced renal cell carcinoma (RCC) patients develop osteolytic bone metastases, leading to skeletal complications. In this review, we first provide a comprehensive perspective of seminal studies on bone metastasis of RCC describing the main molecular modulators and growth factor signaling pathways most important for the RCC-stimulated osteoclast-mediated bone destruction. We next focus on newer developments revealing with in-depth details, the bidirectional interplay between renal cancer cells and the immune and stromal microenvironment that can through epigenetic reprogramming, profoundly affect the behaviors of transformed cells. Understanding their mechanistic interactions is of paramount importance for advancing both fundamental and translational research. These new investigations into the landscape of RCC-bone metastasis offer novel insights and identify potential avenues for future therapeutic interventions.

KEYWORDS

bone metastasis, immune cells, renal cancer cell, stromal cells, therapeutic options

1 | INTRODUCTION

Kidney cancer ranks as the seventh most common cancer worldwide, representing 2.4% of adult cancer cases.¹ Renal cell carcinoma (RCC) is its predominant form, with a 5-year overall survival rate of ~76%.² It encompasses various histological subtypes, including clear cell RCC (ccRCC) accounting for 70%–80% of patients and papillary RCC at 10%–15%.^{3,4} Initial treatment typically involves partial or total nephrectomy.⁵

Around 30% of RCC cases are diagnosed at a metastatic state, with metastasis to distant organs such as lungs (70%), lymph nodes (45%), bones (32%), liver (18%), and adrenal glands (10%) being common causes of RCC-related deaths.⁶ Although targeted treatments and immunotherapy extend patient lifespans, metastatic bone disease incidence in RCC remains high.⁷

RCC shows significant genomic transformation in advanced metastatic stages,⁸ with bone metastases (BM) presenting a particularly poor prognosis, with a median overall survival of only 14.9 months.⁹ Skeletal-related events, including pathological fractures and spinal cord compression, are frequent in RCC bone metastasis (RCC-BM).^{10,11} Prognosis-predictive risk factors for RCC-BM include sarcomatoid differentiation of the primary tumor, spinal involvement, extraosseous metastasis, increased alkaline phosphatase levels, and elevated C-reactive protein levels.¹²

Palliative treatment options aiming to improve quality of life, include surgery, radiotherapy, and pharmacological approaches.⁷ However, managing bone pain remains challenging and imposes an economic and psychosocial burden.¹³

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This review aims to integrate background knowledge with recent advancements in understanding the intricate interplay between RCC, bone cells, immune and stromal cells that contribute to RCC-BM. By elucidating these mechanisms, we can unveil potential new targets and develop more effective treatments for RCC-BM.

2 | BONE METASTASIS

Bone, comprising 60% inorganic material like calcium and phosphate, 25% organic material primarily collagen type I and 5% water, serves multiple functions like structural support and organ protection.¹⁴ It is a complex tissue composed of four cell types: osteoblasts, bone lining cells, osteocytes, and osteoclasts.

Osteoclasts, of hematopoietic origin, are multinucleated cells involved in bone resorption in response to mechanical signals. Their ability to resorb the mineral component relies on the production and release of organic acids, creating a low pH at the bone surface that dissolves the mineral component.¹⁵

Osteoblasts, of mesenchymal origin, synthesize the nonmineral components of bones and contribute to the mineralization of the bone matrix. Osteoblasts have three different fate: apoptosis, differentiation into osteocytes, or transformation into bone lining cells.¹⁶ Bone lining cells are quiescent osteoblasts covering the bone, while osteocytes, representing 90% of all bone cells, maintain the balance between bone resorption and formation through their mechanosensitive function.¹⁷

Bone maintains a delicate balance between formation and resorption under physiological conditions, orchestrated by the complex interplay of cytokines and hormones secreted by resident cell types. Bone remodeling begins with osteoclast-mediated bone resorption, followed by a reversal period transitioning to formation, ultimately leading to matrix mineralization.¹⁸

However, this balance is significantly disrupted in BM. According to Paget's "seed and soil" hypothesis, the distribution of the metastatic niches is not random, but determined through intricate modifications of the microenvironment at the metastatic tumor sites.¹⁹ Osteomimicry, which refers to the evolution of cancer cells to exhibit bone-resident cell phenotypes, may selectively favor metastatic seeds capable of surviving and thriving in the bone microenvironment. Bone-induced epigenomic reprogramming by tumor cells can dedifferentiate them, increasing their metastatic potential. Rather than a terminal destination, bone can also serve as a "launch pad" for secondary metastasis.²⁰

Once in the bone, cancer cells take advantage of products of bone remodeling, such as collagen type I, for growth. Preferential sites for BM, like vertebrae, ribs, and pelvis, feature active bone marrow environments containing crucial cells for metastatic progression.²¹ Upon entry into the bone, cancer cells stimulate bone cells to release cytokines like the ligand of the receptor activator of nuclear factor-kappa B (RANK-L) or epidermal growth factor (EGF).²² These signaling molecules can remodel the bone and the bone marrow into a permissive environment favoring the maturation of osteoclasts and tumor

cell expansion. This sets off a vicious cycle of tumor growth and bone destruction.²³

BM are classified as osteolytic, osteoblastic, or mixed lesions, with active involvement of both osteoclasts and osteoblasts.

- Osteolytic metastases involve bone destruction primarily driven by osteoclast activity. High levels of osteoclast-activating factors like RANK-L are common in breast cancer, RCC, multiple myeloma, melanoma, nonsmall cell lung cancer, and thyroid cancer.²³
- Osteoblastic metastases enhance osteoblast function, reducing osteoclast activity, resulting in new bone deposition, causing pain, and restricted movement. Often seen in prostate cancer, small cell lung cancer and medulloblastoma.²³
- Mixed BM occur when patients have both osteolytic and osteoblastic lesions, found in breast, gastrointestinal, and squamous cancers.²³

In RCC, BM are primarily osteolytic, leading to skeletal complications.¹⁰ No current biomarker is used in clinic to evaluate the potential formation of RCC-BM. However, preliminary studies suggest potential markers associated with a risk of BM,^{24–26} but further investigations are needed to assess their utility in clinical practice.

3 | GENERAL OVERVIEW OF CONTRIBUTING MOLECULAR COMPONENTS

Interactions between tumor cells and the bone microenvironment are well understood in breast cancer but less in RCC (Figure 1).

3.1 | Osteolytic signaling

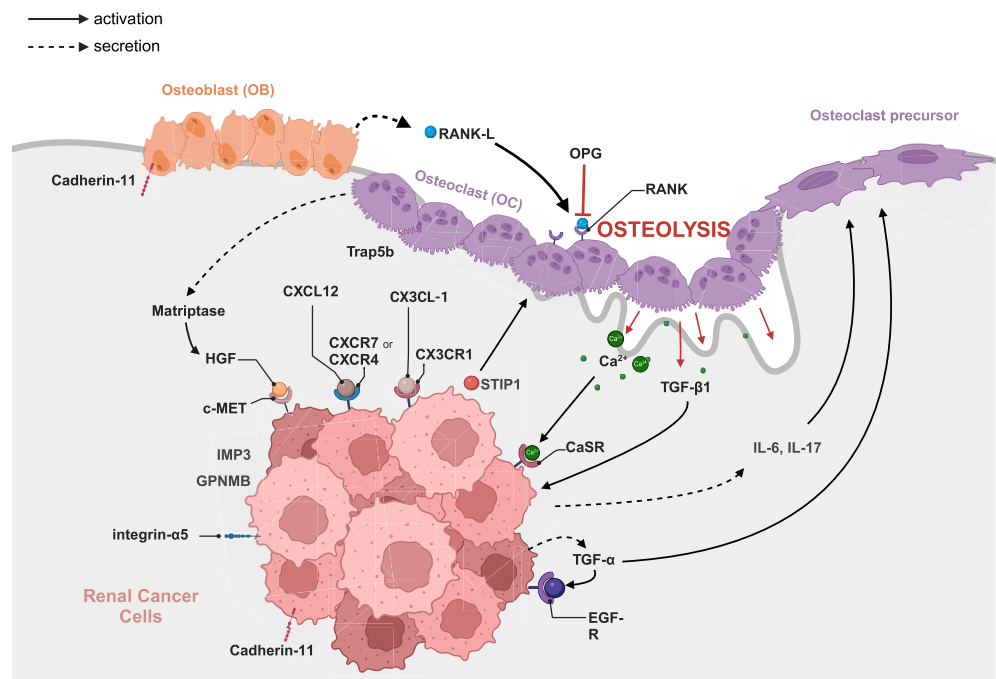
3.1.1 | RANK-L/RANK/osteoprotegerin

In bone, cancer cells stimulate osteoblasts to secrete RANK-L, interacting with its receptor RANK on osteoclasts, promoting bone resorption.²⁷ Osteoprotegerin (OPG) inhibits this interaction by binding with a strong affinity to RANK-L. High RANK-L: OPG mRNA ratios in RCC are associated with BM development. Furthermore, enhanced expression of RANK-L and RANK in primary RCCs served as significant predictors of RCC-BM.^{28,29} However, recent single-cell analysis suggests that tumor-associated mesenchymal stromal cells (TA-MSCs) are a significant source of RANK-L.³⁰

3.1.2 | Calcium-sensing receptor

Upon bone matrix destruction by osteoclasts, high levels of extracellular calcium are released into the BM microenvironment.³¹ The calcium-sensing receptor (CaSR), abundant in metastatic RCC, is activated by excess of soluble calcium, contributing to its chemotactic attraction in bone, inducing cell proliferation.^{32,33}

FIGURE 1 Identified molecular mediators in the intricate interplay between renal cell carcinoma and bone cells. The cross talk between renal cancer cells (in pink) and bone cells (osteoblasts in orange or osteoclasts in purple) is mediated by factors or secreted molecules (full arrows for activation and dashed arrows for secretion). This cross talk favors osteolysis to create a niche for renal cancer metastasis. Created with BioRender.com.



3.2 | Growth factor signaling

The expression of growth factors and tyrosine kinases in the primary tumor cells is associated with unfavorable features of RCC.³⁴ Additionally, bone is a rich source of numerous growth factors, enabling the survival of metastatic tumor cells. Growth factor receptors play a crucial role in the spread of cancer and in the interactions between tumors and the bone environment.³⁵ In the pathogenesis of RCC-BM, a vicious cycle exists between tumor cells and bone. Osteoclast activation due to the presence of malignant cells leads to bone destruction, with secretion of different bone-derived growth factors and cytokines, which facilitate cancer cell proliferation and enhance tumor growth.

3.2.1 | TGF- α /EGF-R signaling pathway

Autocrine secretion of transforming growth factor- α (TGF- α), a ligand for EGF receptor (EGFR), has been observed in RCC.³⁶ The TGF- α /EGF-R signaling pathway plays a pivotal role in RCC-BM, impacting tumor proliferation and bone resorption.³⁷ Inhibiting these pathways has shown promise in reducing RCC growth in bone and mitigating bone destruction.³⁸

3.2.2 | Transforming growth factor- β

TGF- β 1, a potent and multifunctional cytokine, regulates microRNAs expression involved in RCC progression. It is released from the bone matrix during osteoclast-mediated bone destruction, promoting tumor growth and subsequent osteolysis *in vivo*.^{39,40}

3.2.3 | Hepatocyte growth factor/c-MET signaling pathway

c-MET receptor tyrosine kinase and its hepatocyte growth factor (HGF) ligand are often overexpressed in RCC. The HGF/c-MET pathway plays an important role in RCC-BM by promoting tumor cell survival and proliferation.^{41,42} HGF is activated by matriptase and is predominantly expressed in osteoclasts at the BM site.⁴¹ Both HGF/c-MET and CaSR signaling activation are interconnected and enhanced by Von Hippel Lindau mutations and hypoxia.³² Thus, growth factor signaling pathways play a vital role in RCC-activated osteoclast bone resorption and inhibition of these pathways decreases RCC bone metastasis.³⁶

3.3 | Cytokine signaling

3.3.1 | Chemokines

The primary tumor secretes several soluble factors into the bloodstream to create a premetastatic bone niche. CXCL12, also known as SDF-1, interacts with the CXCR4 or CXCR7 receptors on RCC cells, shaping their metastatic potential and defining the supporting niches in secondary organs.⁴³ High levels of CXCR4, CXCR7, and SDF-1 correlate with poor outcomes in RCC patients. Moreover, HIF2 α and nuclear factor-kappa B (NF- κ B) activate distant DNA enhancers, controlling CXCR4 expression in renal cancer cells.^{44,45}

High serum levels of CX3CL1, also called fractalkine, are observed in patients with spinal metastases from kidney cancer.⁴⁶ Similarly, high expression in RCC of CX3CR1, the specific chemokine receptor of

fractalkine, is associated with migration, metastasis, and poor prognosis.⁴⁷

3.3.2 | Interleukins

Interleukins (ILs) are key players in RCC-BM development. IL-6, expressed by RCC cells, stimulates cytotoxic T-cells and induces osteoclast differentiation, leading to bone resorption.^{48,49} IL-17 induces angiogenesis and increases the production of IL-6 in fibroblasts, creating a chronic inflammatory state that supports tumor growth and metastasis.^{50,51}

3.4 | Potential biomarkers in RCC-BM

3.4.1 | Cadherin-11

The calcium-dependent cell-cell adhesion molecule, Cadherin-11, exhibits a substantial increase on the cell surface of RCC-BM cells. Its enhanced expression promotes cell motility and leads to increased BM, facilitated by its strong affinity for homotypic interactions with native osteoblasts.⁵²

3.4.2 | Insulin-like growth factor mRNA-binding protein-3

The insulin-like growth factor mRNA-binding protein-3 (IMP3) binds to a variety of mRNAs influencing gene expression linked with cell migration and proliferation.⁵³ IMP3 has been detected in several malignancies, including RCC, and is correlated with poor prognosis and metastasis.^{54–56} Immunohistochemical staining has confirmed its presence in RCC-BM, suggesting its role in the metastatic process.^{53,54}

3.4.3 | Glycoprotein nonmetastatic protein-B

Glycoprotein nonmetastatic protein-B (GPNMB), known as Osteoactivin, is expressed in various cell types, including osteoclasts, osteoblasts, macrophages, and dendritic cells. GPNMB is a positive mediator of tumor progression in solid cancers,⁵⁷ associated with osteolytic BM development.⁵⁸ In RCC, high GPNMB expression is associated with both the number and the extent of BM, correlating with a poor prognosis.^{57,59}

3.4.4 | Integrins

Integrins, key transmembrane glycoproteins mediate cell interactions with the extracellular matrix (ECM) and facilitate metastasis by guiding tumor cells to specific niches. The $\alpha 5\text{-}\beta 1$ integrin is a receptor for

fibronectin. In RCC patients, higher levels of integrin $\alpha 5$ correlate with tumor grade and the onset of RCC-BM.^{60,61} Furthermore, Integrin $\alpha 5$ promotes c-MET activation, promoting tumor invasion, metastasis and reducing survival.⁶⁰

3.4.5 | Stress-induced-phosphoprotein 1

Stress-induced-phosphoprotein 1 (STIP1), also known as HSP70/HSP90 organizing protein (HOP), plays a significant role in tumor progression. The STIP1-ALK2-SMAD1/5 pathway contributes to tumor cell survival through an autocrine mechanism and amplifies osteolysis via a paracrine mechanism. RCC cells with an affinity for bone exhibit intrinsic high levels of STIP1 expression and secretion, fostering tumor cell proliferation and promoting osteoclast maturation.⁶²

3.4.6 | Bone TRAP-5b

Tartrate-resistant acid phosphatase (bone TRAP-5b), also called ACP5, is secreted by osteoclasts and thus, is a relevant marker of bone resorption. TRAP-5b levels are higher in RCC-BM patients and elevated serum levels are associated with increased bone resorption. However, its levels may not correlate directly with the number of metastases.²⁶ Moreover, the sensitivity and specificity of TRAP-5b remain uncertain, suggesting caution in relying solely on it for diagnosis.⁶³

4 | MOLECULAR MEDIATORS IN OTHER OSTEOLYTIC CANCERS

The existing literature highlights in different solid tumors, particularly in breast cancer, numerous molecules whose high expression is associated with osteolytic BM.

4.1 | Bone morphogenetic protein 2

Bone morphogenetic protein 2 (BMP-2) is an osteo-inductive growth factor responsible for inducing osteoblastic differentiation and bone formation.⁶⁴

Inhibition of BMP-2 by Noggin has shown promise in preventing bone lesion in lung-derived BM.⁶⁵ Studies also show that BMP-2 might induce RCC cells to express an osteoblastic phenotype, potentially explaining why bone is one of the preferential niche for RCC.⁶⁶

4.2 | RunX1 and RunX2

Runt homology domain transcription factor (RunX2) is particularly crucial for osteoblast differentiation and bone formation. Its overexpression is observed in several metastatic cancers, including

osteosarcoma, breast, prostate, gastric, and colorectal cancers⁶⁷ and is correlated with activation of tumor-associated factors including vascular endothelial growth factor (VEGF), metallo-proteases (MMPs), and IL-6.⁶⁸ High expression of RunX2 is also found in RCC, suggesting potential osteomimetic features.^{69,70} Similarly, RunX1, associated with poor prognosis in breast cancer and RCC, impacts bone homeostasis through the WNT/ β -Catenin pathway.⁷⁰⁻⁷³ Targeting the RunX family holds promise for new therapeutic approaches.⁶⁷

4.3 | CD44

CD44, an adhesion molecule expressed on various metastatic cancer cells, favors migration during BM, facilitated by stemness acquired during the epithelial-mesenchymal transition (EMT). CD44 may induce an osteomimetic phenotype of cancer cells, promoting survival in bone.^{74,75} In breast and prostate cancer, activated CD44 on bone marrow endothelium aligns with tumor cell CD44, stimulating osteoclast activity and osteolytic BM.^{76,77} Elevated CD44 expression in RCC correlates with poor prognosis,⁷⁸ and metastasis.⁷⁹ While direct links to RCC-BM are lacking, CD44's potential importance warrants further investigation.

4.4 | Osteopontin

Osteopontin (OPN), or Secreted PhosphoProtein 1 (SPP1), is a multifunctional protein involved in cancer progression and bone remodeling. Released by osteoblasts and osteoclasts, it influences osteoclast function, matrix mineralization, and cell adherence through integrin and CD44 receptors.⁸⁰

During cancer progression, OPN regulates cell signaling, promoting affinity for bone,^{81,82} and contributing to bone resorption.⁸³ Upregulation of OPN in RCC correlates with poor prognosis and shorter metastasis time,⁸⁴⁻⁸⁷ and its role in invasion is linked to MMPs activation.⁸⁸ However, OPN's impact on RCC-BM remains unexplored.

4.5 | The Jagged1-Notch pathway

In breast cancer, tumor-derived Jagged1 activates Notch pathway in osteoblasts and osteoclasts, promoting the release of TGF- β and the development of osteolytic BM.⁸⁹⁻⁹¹ The inhibition of the γ -secretase, the enzymatic complex mediating the final cleavage of the Notch receptor, reduces Jagged1-Notch-mediated metastasis.⁸⁹

Similarly, in RCC, high TGF- β levels are linked to poor prognosis and BM.³⁹ Notch inhibition reduces RCC cell migration, suggesting a therapeutic potential for RCC-BM.⁹²

4.6 | CENP family

Aneuploidy resulting from dysregulated oncogenes may contribute to tumorigenesis and metastasis.⁹³ Dysfunction of the Centromere

protein family (CENPA and CENPF) leads to aneuploidy, chromosomal mismatches, or disruption of genomic integrity.⁹⁴ CENPA promotes ccRCC progression and metastasis via Wnt/ β -catenin signaling pathway.⁹⁵ Elevated CENPF expression is observed in breast cancer BM models, with computational analysis showing the involvement of the PI3K-AKT-mTORC1 pathway.⁹⁶ This could be relevant to RCC-BM, as mTOR pathway inhibition disrupts its development in vitro.⁹⁷

4.7 | Parathyroid hormone-related peptide

Breast and prostate cancer cells secrete parathyroid hormone-related peptide (PTHrP), triggering osteoblasts to secrete RANK-L, thereby inhibiting OPG expression and increasing osteoclast activity. This establishes a vicious cycle, promoting osteolytic BM and tumor growth.⁹⁸⁻¹⁰³ While PTHrP is vital for RCC proliferation, its role in RCC-BM remains unclear. Blocking PTHrP reduces RCC expansion in vitro,^{104,105} but its impact on bone cells and RCC-BM is inconclusive.^{38,52,106}

4.8 | Dickkopf 1

Wnt/ β -catenin signaling maintains bone homeostasis while aberrant expression of the Wnt inhibitor, Dickkopf 1 (DKK-1), impairs osteoblast activity influencing the balance between bone formation and resorption.¹⁰⁷⁻¹⁰⁹ Elevated DKK-1 serum levels are found in breast cancer osteolytic cell lines but not in osteoblastic models.¹⁰⁹⁻¹¹¹ In RCC, DKK-1 expression appears to induce apoptosis and inhibits cancer proliferation, but it is epigenetically silenced in advanced stages of kidney cancers.¹¹² DKK-1 serum levels were significantly lower in RCC patients, correlating with invasiveness and high-grade tumors.¹¹³ Thus, a link between DKK-1 and RCC-BM remains unexplored and warrants further investigations.

5 | COOPERATION BETWEEN RCC AND THE BONE METASTATIC ENVIRONMENT

5.1 | Recruitment of specific immune cells

Cancer cell migration to the bone marrow disrupt its homeostasis, leading to an immunosuppressive tumor microenvironment (TME), featuring tumor-associated macrophages (TAM) and different T-cells such as exhausted (T-ex), cytotoxic (CTL-3), and regulatory (T-reg) (Figure 2). RCC-BM progression is intensified by the interaction between TAM and T-cells, mediated by various ligand/receptors, notably SIRPA/CD47, CCL4L2/VSIR, CCL18/CCR8, CD68/CTLA4, and IL-10/IL10RB^{30,114} (Figure 2).

Recently, single-cell transcriptome profiling identified the presence of several populations of TAM within the TME of metastatic RCC. Metastasis-infiltrating TAMs in RCC-BM exhibit a hybrid phenotype, displaying characteristics of both M1 (pro-inflammatory) and M2

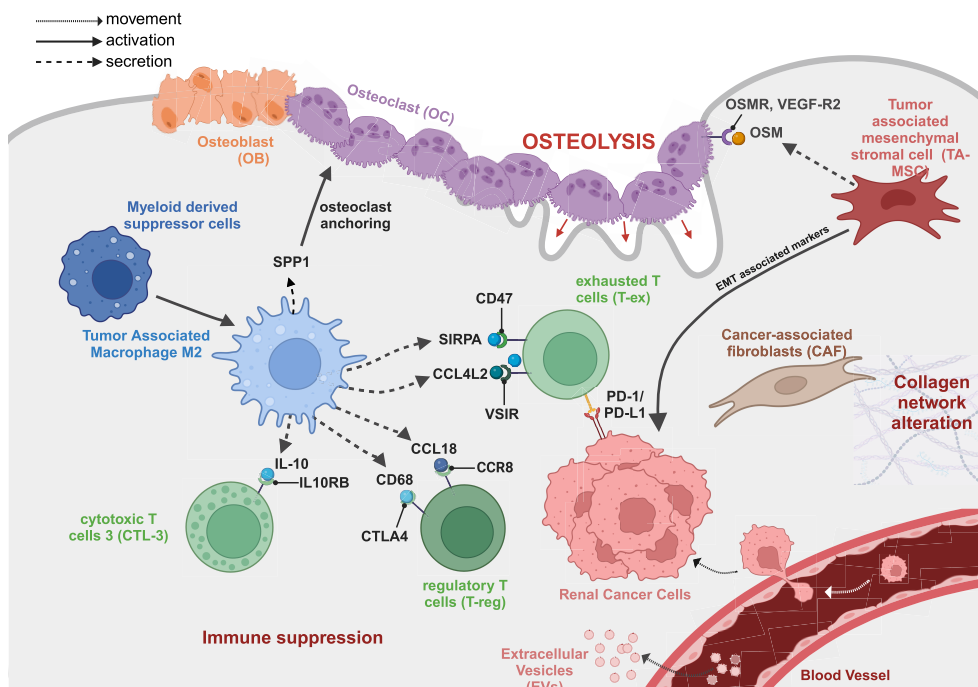


FIGURE 2 Interplay among stromal cells, immune cells and bone matrix in renal cell carcinoma bone metastasis. metastatic renal cancer cells (in pink) arriving in the bone niche communicate with the bone niche microenvironment composed of immune cells (in green), macrophages in (blue), Cancer associated fibroblasts (in gray) and tumor-associated mesenchymal stromal cells (in dark pink) to foster micrometastasis formation (full arrows for activation, tight dashed arrows for movement and large dashed arrows for secretion). Created with [BioRender.com](https://www.biorender.com).

(pro-tumorigenic) macrophages, and leading to an immunosuppressive microenvironment.^{30,114} Interestingly, the differentiation path of M2-TAMs primarily originates from myeloid-derived suppressor cells in RCC-BM.¹¹⁴ M2 TAM showed high expression of SPP1, CXCL5, CCL2, CCL7, and CCL18.¹¹⁵ They are involved in bone formation, osteoclast anchoring, and premetastatic niche formation in various cancers.^{80,116–119}

Overall, these findings underscore the coordinated interplay between tumor cells and bone-recruited immune cells in facilitating metastasis.

5.2 | Distinct stroma cell populations are enriched in RCC-BM

Single-cell transcriptome profiling of RCC-BM revealed the involvement of specific cancer-associated fibroblasts (CAFs) and TA-MSCs in bone remodeling, with their abundance correlating with poor survival (Figure 2).

Changes in TA-MSC abundance within the BM site are correlated with the bone environment remodeling and promotion of EMT in tumor cells. In addition, dysregulation of RANK/RANK-L/OPG signaling drives bone remodeling and osteoclast maturation,^{120,121} supported by increased expression of mediators like Oncostatin M (OSM) and its receptor OSMR, and VEGF-R2.³⁰ Moreover, RCC-BM demonstrated a pro-angiogenic signature, being enriched in blood vessel development and VEGFA-VEGFR2 signaling pathway.¹¹⁴

As the predominant cell type of the TME, CAFs play important roles in promoting tumorigenesis.¹²² Several subpopulations of CAFs (mCAF_1 and mCAF_2) have been identified in primary RCC and

RCC-BM. Elevated mCAF_2 presence, associated with elevated EMT markers, correlates with poor prognosis in RCC patients.¹¹⁴ Moreover, differential gene expression analysis revealed enrichment of EMT programs in RCC-BM, characterized by upregulation of actin cytoskeleton and ECM organization.³⁰

Collectively, these studies identified key stromal cell subsets and molecular features enriched in the environment of RCC-BM.

5.3 | Tumor-derived extracellular vesicles

Extracellular vesicles (EVs) are nanometer-sized lipid membrane-bound vesicles carrying RNA, DNA, proteins, and lipids. They play a crucial role in mediating communication between tumor cells and distant microenvironments, including the bone marrow. Tumor-derived EVs contribute to vascular leakiness, ECM remodeling, immune suppression, and tumor progression.¹²³ Several studies have explored EVs, particularly their microRNA content, as potential RCC biomarkers.^{124–126} Additionally, RCC-EVs induce EMT, angiogenesis, vascular permeability, and therapeutic resistance, modifying both local and distant microenvironments to establish premetastatic niches.^{127–129} For instance, EVs from renal cancer stem cells transform healthy lungs into receptive niches able to support metastatic RCC growth.^{125,130} Additionally, RCC-EVs containing a novel circular-RNA termed EHD2, promote RCC lung metastasis by converting fibroblasts into CAFs.¹³¹ A recent proteomic analysis unveiled the presence in BM-EVs of aminopeptidase N, which enhances angiogenesis in the bone marrow.¹³² Furthermore, injecting RCC-EVs into mice increases cancer cell invasiveness, upregulating pro-angiogenic factors, such as VEGF, MMPs, while also activating angiogenic phenotypes in endothelial cells.¹³⁰

5.4 | Epigenetic rewiring in RCC-BM

Recent studies emphasize the importance of nongenetic factors in tumor initiation and metastasis.¹³³ In this context, epigenetic, as a nongenetic regulation of heritable traits, plays a pivotal role through mechanisms such as DNA methylation, histone modifications, non-coding RNAs, chromatin accessibility, and enhancer reprogramming.¹³⁴ RCC tumors display a relatively low tumor mutational burden but an elevated epigenetic heterogeneity compared to healthy kidney.^{135,136} Mutations in genes encoding epigenome modifiers and chromatin remodelers like PBRM1, SETD2, KDM5C, KDM6, and BAP1 are evident in RCC.^{137–140} Experimental analysis have showed that HIF1 α signaling activation in RCC promotes mitochondrial DNA hypermethylation, contributing significantly to BM progression.^{141,142} Given that these alterations may be reversible with small molecules or inhibitors targeting *epi-modifiers*, the prospect of novel epigenetic therapies is promising.^{143,144}

6 | CURRENT RESEARCH/CLINICAL TRENDS FOR RCC-BM

The identification of biomarkers is vital for delivering accurate diagnoses and enhancing the prognosis of RCC-BM patients. Hence, this section aims to discuss the latest research on the clinical application of several important developments in this field.

6.1 | Local therapies

Treatment objectives for RCC-BM patients involve palliative surgery alongside non-surgical interventions to maintain neurological function and manage pain. Surgical intervention may include resections, internal fixation, and neural decompression, often preceded by preoperative embolization in RCC metastasis to reduce bleeding.¹⁴⁵ Conventional radiation therapy typically yields limited response in RCC; however, higher doses per fraction and techniques like stereotactic ablative radiotherapy show promise.¹⁴⁶ Radiofrequency ablation or cryoablation can effectively target and destroy metastatic tumor tissue, alleviating pain.^{147,148} There are increasing trend for metastasis-directed resections and slightly declining numbers for radiation therapy for RCC-BM.¹⁴⁹

6.2 | Targeted therapies and bone targeting agents

Metastatic RCC is commonly treated with tyrosine-kinase inhibitors (TKIs), approved especially in cases with bone involvement. Preclinical evidence suggests that TKI can inhibit osteoclastic activity and bone resorption activity. Cabozantinib, that targets both c-MET and VEGFR2, was related to a significant improvement of overall survival and progression-free survival in RCC-BM patients.¹⁵⁰

Bone-targeting agents (BTAs) include bisphosphonates, zoledronic acid, and anti-RANK ligand antibody (denosumab). By interrupting the “vicious cycle” of bone metastasis, RANKL inhibition and

bisphosphonates have been successfully approved for the treatment of patients with BM from various solid tumors, including prostate and breast cancers. Zoledronic acid inhibits osteoclast activity and reduce skeletal lesions in RCC-BM.¹⁵¹ Denosumab targets RANK-L to reduce bone resorption.¹⁵² However, the extent to which patients benefit from BTAs treatment depends on the origin and stage of BM. In comparison to other solid tumors, patients with RCC-BM are particularly resistant to bone modifying agents, reflecting unique cellular and molecular mechanisms in the bone microenvironment that promote progression via inhibition of the bone anabolic reparative response.⁴⁵ Recent evidence indicates that in earlier steps, RCC inhibits the bone anabolic reparative response via a paracrine mechanism mediated by BIGH3/TGF β 1 thereby impairing osteoblast differentiation and inducing osteocyte apoptosis.¹⁵³ To enhance synergistic anticancer activity and improve treatment outcomes, TKIs are often combined with BTAs. Combining TKIs with BTAs has shown favorable results in managing RCC-BM, however further data is required to validate this therapeutic strategy/these therapeutic molecules.¹⁵⁴

6.3 | Enhancing endogenous antitumor immunity

TAM enrichment showed its contribution to resistance to chemotherapy or immunotherapy.¹⁵⁵ Targeting TAMs shows promise in treating RCC-BM. Approaches include TAM removal, which reduces BM growth in breast and prostate cancer.^{156,157} TAM depletion from the TME with bisphosphonates demonstrated the ability to inhibit macrophage proliferation and induce apoptosis in vitro.¹⁵⁸ Alternatively, reprogramming TAMs from a pro-tumorigenic to antitumorigenic phenotype can be achieved using CD40 monoclonal agonist antibodies or Toll-like receptor agonists.^{159,160} Additionally, immune checkpoint ligand blockade like PD-1, PD-L1, and CTLA-4 offer alternative strategies for TAM targeting, and has shown benefit in RCC.^{161–163} Recent research demonstrated that ID3 expression in macrophages enhances their antitumor activity, restricting the growth of various tumors.¹⁶⁴ There have been few studies on the therapeutic effect of immunotherapeutic modalities such as immune checkpoint inhibitors (ICIs) in RCC-BM. However, a case of complete remission of bone metastasis was reported after ICIs treatment.¹⁶⁵ Furthermore, the introduction of novel combination therapies involving TKIs and ICIs have resulted in improved oncological outcomes compared to traditional TKI monotherapy.¹⁶⁶

Cell-based immunotherapies, like tumor-infiltrating lymphocyte, are still emerging for solid tumor metastasis treatment, with cases of complete remission in RCC lung metastasis showcasing their potential.^{167,168} Advancing immunotherapeutic interventions in RCC-BM requires a deeper understanding of this specific immune landscape.

6.4 | Targeting metastasis-associated fibroblasts

In RCC-BM, CAFs originating from TA-MSCs, contribute to bone lesion.^{169,170} Targeting CAFs, particularly through FAP protein-directed therapy, shows promise in various metastatic cancers, with ongoing clinical trials exploring this approach.¹⁷¹ In RCC, CAFs promote tumor

metastasis by upregulating angiogenic factors like HGF and facilitating MMP-9 accumulation.¹⁷² Targeting CAFs through immunotherapies holds promise for treating RCC-BM. Notably, recent single-cell RNA profiling by Ma et al.¹¹⁴ has identified a subcluster of FAP⁺ CAFs associated with RCC-BM and poor patient prognosis, further emphasizing the importance of targeting CAFs in RCC treatment.

6.5 | Microbiome-oriented strategies

Emerging evidence suggests that complex microbial communities, within primary tumors, influence responses to anticancer therapies.¹⁷³ Genomics and transcriptomic profiling have revealed the presence of a rich microbiome in metastatic tumor biopsies, with certain microbes linked to resistance to checkpoint blockade.^{174,175} Interestingly, renal metastases show a higher fraction of bacterial-derived reads compared to other metastatic cancers.¹⁷⁶ Moreover, research highlights the interplay between the gut microbiome and the bone microenvironment, indicating altered microbial compositions in patients with BM.¹⁷⁷ Future studies targeting the intra-tumor microbiome may lead to bacteria-focused strategies to improve cancer therapies.

7 | CONCLUSION

The bidirectional interplays involving metastatic tumor cells, bone cells, the mineralized bone matrix, osteoclasts and osteoblasts, immune cells, and CAFs are governed by complex molecular mechanisms that profoundly influence metastatic progression and treatment responses. This complexity greatly hinders progress in drug development, reflecting the high failure rate of drugs developed for this disease. Although less well known than breast cancer BM, RCC-BM also pose significant challenges that can lead to skeletal complications and reduced quality of life for patients. Therefore, better understanding of inherent features underlying the dynamic heterogeneity within this tumor ecosystem and the application of this knowledge are essential for future development of effective and durable therapeutic strategies for RCC patients with bone metastasis.

Treatment strategies for RCC-BM encompass a multidisciplinary approach, including surgical interventions, radiotherapy, targeted therapies, BTAs, and now emerging immunotherapeutic modalities.

Overall, continued collaboration between clinicians, researchers, and pharmaceutical companies is crucial for translating scientific discoveries into clinical applications for precision medicine and addressing the evolving challenges associated with metastatic RCC, particularly in the context of bone involvement. The aforementioned findings could lead to innovative therapeutic strategies, thereby creating optimism for advancing the management of RCC-BM and ultimately improving patient survival and quality of life.

AUTHOR CONTRIBUTIONS

Beatrice Cesana: Conceptualization; writing—original draft. **Claude Cochet:** Conceptualization; supervision. **Odile Filhol:** Funding acquisition; supervision.

ACKNOWLEDGMENTS

We would like to thank Dr. Elisa Lambert (CEA Grenoble) for her invaluable feedback and insightful comments during the relecture of this article. This work was supported by recurrent institutional funding from INSERM, CEA, and Ligue Comité de l'Isère, University Grenoble Alpes, Centre Hospitalier Universitaire de Grenoble-Alpes (CHUGA), Groupement des Entreprises Françaises dans la Lutte contre le Cancer (GEFLUC).

CONFLICT OF INTEREST STATEMENT

The authors declare no competing conflict of interests.

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How to cite this article: Cesana B, Cochet C, Filhol O. New players in the landscape of renal cell carcinoma bone metastasis and therapeutic opportunities. *Int J Cancer.* 2024; 1-13. doi:[10.1002/ijc.35181](https://doi.org/10.1002/ijc.35181)