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Research Advancements on the Axis of Cancer-Associated Fibroblasts and Matrix Metalloproteinases in Hepatocellular Carcinoma

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Abstract: Hepatocellular carcinoma (HCC) is a highly malignant tumor with poor prognosis, and the tumor microenvironment (TME) remodeling plays a pivotal role in its progression. Cancer-associated fibroblasts (CAFs) and matrix metalloproteinases (MMPs) form a bidirectional regulatory axis (CAFs–MMPs axis) that serves as a core driver of TME imbalance in HCC. This review systematically elaborates on the origin and functional characteristics of CAFs, the classification and regulatory mechanisms of MMPs, and the bidirectional interaction logic between CAFs and MMPs (including cytokine signaling, mechanotransduction, and exosome-mediated communication). We further discuss the critical roles of this axis in shaping key malignant phenotypes of HCC, such as proliferation, invasion, metastasis, angiogenesis, immune evasion, and therapy resistance. Through cross-cancer comparison with pancreatic ductal adenocarcinoma, breast cancer, and colorectal cancer, we highlight the unique features of the CAFs–MMPs axis in HCC, which is closely linked to the liver's chronic inflammatory and fibrotic microenvironment. Finally, we summarize the translational prospects of targeting this axis in clinical practice, including selective MMP inhibitors, CAF-targeted drug delivery systems, molecular imaging diagnosis, and combination strategies with immunotherapy. We also outline current challenges and future directions, aiming to provide a conceptual framework for microenvironment-oriented precision diagnosis and therapy in HCC.

Keywords: Hepatocellular carcinoma (HCC); Cancer-associated fibroblasts (CAFs); Matrix metalloproteinases (MMPs); Tumor microenvironment (TME); Malignant progression; Targeted therapy; Immunotherapy

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1. Introduction

Hepatocellular carcinoma (HCC) is the sixth most common malignancy worldwide and the third leading cause of cancer-related mortality. Despite advances in surveillance, molecular targeted therapy, and immunotherapy, the

long-term prognosis of HCC remains poor, with a 5-year survival rate below 20%, largely due to late diagnosis, frequent recurrence, and substantial therapeutic heterogeneity [1]. While earlier studies emphasized genetic alterations and oncogenic signaling within tumor cells, mounting evidence indicates that HCC progression and treatment responsiveness are critically shaped by the tumor microenvironment (TME).

This review uses HCC as a central model to systematically examine the mechanistic basis of the CAFs–MMPs axis, its roles in shaping malignant biological behaviors, and its distinctive features relative to other cancer types. We further discuss emerging clinical and translational implications, including diagnostic imaging, therapeutic targeting, and rational combination strategies with immunotherapy. By framing CAF–MMP interactions as a coherent regulatory axis, this review aims to provide a conceptual foundation for microenvironment-oriented precision strategies in HCC.

2. CAFs–MMPs interaction mechanism

2.1. Origin and functional characteristics of CAFs

In HCC, CAFs are thought to arise predominantly from activated hepatic stellate cells (HSCs), which remains the most widely accepted source pathway. During chronic hepatitis, progressive fibrosis, and cirrhosis, persistent inflammatory cues and cytokines (e.g., TGF-β, PDGF, and IL-6) drive the transition of quiescent HSCs into a myofibroblast-like state. This activated phenotype is characterized by increased α-SMA expression, enhanced collagen production, and strong profibrotic activity [2].

Within the HCC microenvironment, CAFs contribute to ECM remodeling by synthesizing structural components such as type I/III collagen, hyaluronic acid, and laminin. They also secrete a broad array of growth factors and chemokines (e.g., HGF, VEGF, CXCL12, and IL-6), thereby regulating tumor-cell proliferation, angiogenesis, and immune escape. Recent single-cell sequencing studies further indicate marked CAF heterogeneity in HCC, with major programs broadly categorized as ECM-remodeling, immune-regulatory, and angiogenesis-associated subtypes.

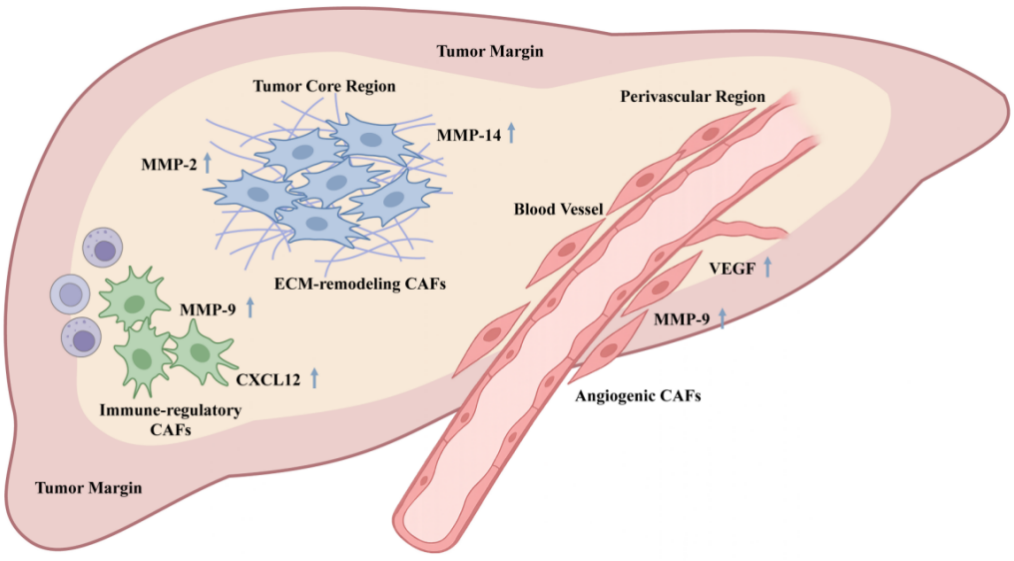

Figure 1. Spatial distribution and MMP lineage disparities among CAF subtypes in HCC.

CAF subtypes display spatial organization with distinct dominant mediators across tumor regions (**Figure 1**). In the tumor core, ECM-remodeling CAFs are enriched and show high expression of MMP-2/MMP-14; at the tumor margin, immune-regulatory CAFs are associated with elevated MMP-9 and CXCL12; and in perivascular regions, angiogenic CAFs align with increased VEGF and MMP-9. These niche-linked CAF programs suggest region-specific deployment of MMP activity and related signaling within the HCC microenvironment.

2.2. Classification and regulation of MMPs

MMPs constitute a family of Zn^{2+}-dependent proteolytic enzymes that exert pivotal functions in extracellular matrix (ECM) degradation, cell migration, and signal molecule release. To date, over 20 types of MMPs have been identified, which can be classified into secretory and membrane-bound types according to structural features and cellular localization. Secretory types primarily encompass collagenases (MMP - 1, MMP - 8, MMP - 13), gelatinases (MMP - 2, MMP - 9), and stromelysins (MMP - 3, MMP - 10); membrane-bound types (MT - MMPs) are typified by MMP - 14 (MT1 - MMP). In HCC, elevated MMP-2, MMP-9, and MMP-14 expression is closely associated with angiogenesis, capsular invasion, and distant metastasis [3].

2.3. Bidirectional interaction mechanism of CAFs–MMPs

The relationship between CAFs and MMPs is not adequately described by a one-way "secretion–action" model. Instead, it constitutes a bidirectional feedback system integrating structural remodeling and signal regulation. In HCC, CAFs promote MMP expression and activation through multiple mechanisms:

(1) Cytokine signaling: CAF-derived TGF-β and HGF can upregulate MMP-2 and MMP-9 transcription via Smad2/3 and PI3K/Akt signaling, respectively, thereby enhancing tumor-cell migration and invasion.

(2) Mechanotransduction and metabolic coupling: Increased matrix stiffness activates YAP/TAZ signaling in CAFs, which further induces MMP-14 expression and promotes ECM degradation and fibrotic remodeling. In parallel, lactate produced through CAF-associated metabolism can lower local pH and thereby enhance MMP activity, favoring sustained proteolytic activation.

(3) Exosome-mediated stromal communication: HCC-cell–derived exosomes are enriched in small RNAs such as miR-21 and miR-221. These miRNAs can inhibit PTEN and activate PDK1/Akt signaling in CAFs, inducing upregulation of MMP-2, MMP-9, and MMP-14 [4].

Conversely, MMPs can influence CAF formation and functional maintenance. For example, MMP-14–mediated pericellular proteolysis can facilitate the release/activation of TGF-β, thereby promoting HSC activation and CAF generation; In addition, MMP-1 can cleave insulin-like growth factor–binding proteins (IGFBPs), increasing local IGF-1 bioavailability and consequently enhancing CAF proliferation and α-SMA expression.

3. Role of the CAFs–MMPs axis in the biological characteristics of hepatocellular carcinoma

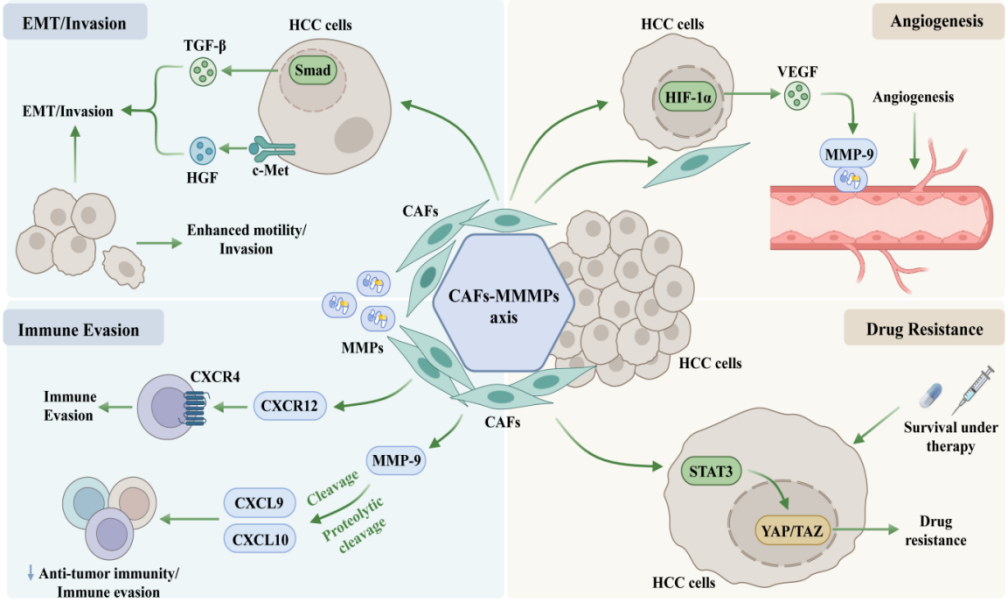

Figure 2. Malignant phenotype network in HCC driven by the CAFs–MMPs axis.

The CAFs–MMPs axis supports four interconnected malignant phenotypes (**Figure 2**). (1) EMT/Invasion: TGF-β and HGF activate Smad and c-Met signaling in HCC cells, promoting epithelial–mesenchymal transition (EMT) and invasive capacity. (2) Immune evasion: MMP-mediated proteolysis of chemokines (CXCL9/CXCL10) reduces recruitment of anti-tumor immune cells (e.g., T cells), while CXCR4/CXCL12 signaling further facilitates immune escape. (3) Angiogenesis: hypoxia-inducible factor-1α (HIF-1α) upregulates vascular endothelial growth factor (VEGF), and CAF-derived MMP-9 promotes angiogenesis. (4) Drug resistance: STAT3 and YAP/TAZ signaling in HCC cells (regulated by CAFs) contribute to resistance to therapeutic agents.

3.1. Regulation of tumor growth and apoptosis

HCC progression results from sustained positive feedback between tumor cells and the surrounding microenvironment. CAFs directly promote HCC-cell proliferation and resistance to apoptosis by secreting growth factors (e.g., HGF, fibroblast growth factor [FGF], and IGF) and inflammatory cytokines (e.g., interleukin-6 [IL-6] and TGF-β). IL-6 upregulates Cyclin D1 via the JAK/STAT3 pathway, thereby accelerating cell-cycle progression. Meanwhile, in HCC, TGF-β can shift from a pro-apoptotic signal to a pro-growth factor, inducing anti-apoptotic proteins such as B-cell lymphoma 2 (Bcl-2) and Survivin through PI3K/Akt signaling [5].

3.2. Tumor invasion and metastasis

The invasiveness of HCC is closely linked to its highly fibrotic microenvironment. CAF-derived TGF-β and HGF activate PI3K/Akt signaling, thereby inducing EMT in tumor cells and enhancing migratory capacity. Concurrently, CAFs upregulate EMT-associated transcription factors such as Twist and Snail through IL-6/STAT3 signaling. This promotes E-cadherin downregulation and N-cadherin upregulation, reinforcing a mesenchymal phenotype.

3.3. Angiogenesis

The hypervascular nature of liver cancer is intricately associated with the activation of MMPs. Factors, including VEGF, FGF-2, and CXCL12, secreted by CAFs offer chemotactic cues for endothelial cells. Meanwhile, the ECM degradation function of MMP-2 and MMP-9 creates avenues for vascular "sprouting." Under hypoxic circumstances, hypoxia-inducible factor-1α (HIF-1α) is stably expressed in CAFs and induces the concurrent upregulation of VEGF, MMP-2, and MMP-9, establishing a cycle of "hypoxia–angiogenesis–ECM remodeling".

3.4. Immune escape and therapeutic responsiveness

Immune evasion is a central mechanism driving HCC progression and resistance to immunotherapy. CAFs reshape immune-cell distribution and establish an immunosuppressive TME by secreting factors such as CXCL12, TGF-β, and IL-6. Specifically, the CXCL12-CXCR4 axis restricts the infiltration of $CD8^+$ T cells, whereas TGF-β can induce the expansion of regulatory T cells (Treg). Matrix metalloproteinases (MMPs) exert multi-level regulatory effects in this process: MMP-9 can cleave the chemokines CXCL9/CXCL10, thereby blocking the recruitment of effector T cells; MMP-2 can cleave FasL on the surface of T cells, thus impairing the cytotoxic response [6].

4. Cross-cancer comparison: Differences in CAFs–MMPs mechanisms centered on HCC

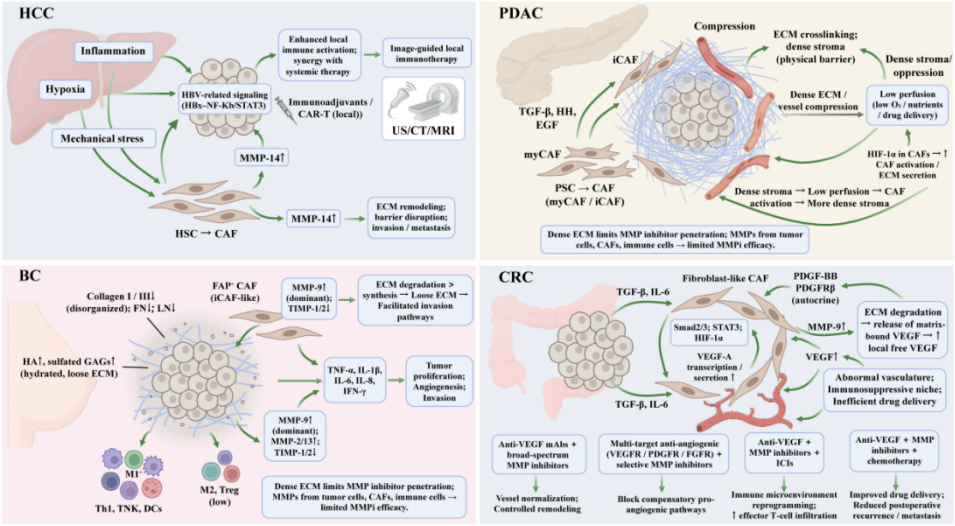

Figure 3. Cross-cancer comparison of CAF origins, key mediators, and CAF–MMP regulatory effects centered on HCC.

Figure 3 summarizes shared and cancer-specific CAF–MMP features across four malignancies. In HCC, hepatic microenvironmental inflammation, injury, and mechanical stimulation activate hepatic stellate cells to generate HSC-derived CAFs, which promote EMT, stemness acquisition, and angiogenesis via mediators including MMP-9 and IL-6, and can regulate tumor progression through exosome-delivered miRNAs. In pancreatic ductal adenocarcinoma (PDAC), tumor-derived factors (e.g., TGF-β and EGF) induce pancreatic stellate cells to form PSC-derived CAFs that drive ECM remodeling and dense stromal barrier formation, while secreting factors such as SDF-1α and IL-6 to promote tumor proliferation, immunosuppression, invasiveness, and therapeutic resistance.

In breast cancer (BC), collagens (Col I/III) and TGF-β induce mesenchymal stem cells to generate MSC-derived CAFs that support proliferation, EMT, and angiogenesis through IL-6 and HGF, modulate stemness via exosomal miR-21, and suppress anti-tumor immunity by recruiting immunosuppressive cells (e.g., M2-type macrophages). In colorectal cancer (CRC), tumor and inflammatory factors (e.g., TNF-α) activate fibroblasts into CAFs that promote proliferation and angiogenesis via TGF-β and VEGF, enhance invasiveness through ECM remodeling (e.g., MMP-2/9-mediated degradation), and suppress T-cell function via immunosuppressive molecules (e.g., PD-L1), contributing to metastasis and immune evasion.

4.1. Differences in origin and cellular composition

In HCC, CAFs are mainly derived from HSCs and periportal fibroblasts. Under long-term inflammatory stimulation, these cells acquire a myofibroblast-like activated phenotype. Importantly, CAF emergence in HCC often overlaps with the fibrosis stage, enabling CAFs and MMPs to participate in carcinogenic microenvironment remodeling at relatively early time points. In contrast, CAFs in PDAC are predominantly derived from pancreatic stellate cells and include distinct subsets such as myCAF, iCAF, and apCAF. Among these, myCAFs often express high levels of MMP-2 and MMP-14 and contribute to ECM remodeling and increased stromal stiffness, whereas iCAFs preferentially secrete IL-6 and CXCL12 and are more biased toward immune regulation. CAF origins in breast cancer are more heterogeneous, arising from activated local fibroblasts and, in some settings, tumor epithelial cells undergoing EMT. In this context, elevated MMP-11 and MMP-9 expression is frequently linked to matrix remodeling and hormone receptor status. In CRC, bone marrow–derived fibroblasts constitute a relatively higher proportion, and corresponding CAF subsets often display a $FAP^{+}MMP\text{-}13^{+}$ phenotype that correlates with metastatic progression [7].

4.2. Differences in MMP lineage and functional bias

CAF-associated MMP programs vary substantially across cancer types. In HCC, MMP-2, MMP-9, and MMP-14 are dominant and are broadly linked to gelatin degradation, angiogenesis, and pericellular invasion, respectively. In pancreatic cancer, MMP-11, MMP-14, and MMP-7 are more prominent, with MMP-14 in particular being closely associated with matrix remodeling and driving a high-stiffness stromal environment. Breast cancer shows a more complex protease landscape: in addition to MMP-9 and MMP-11, abnormal upregulation of MMP-3 and ADAM family members has been reported, with potential impacts on estrogen receptor signaling and cancer stem-like phenotypes. In CRC, co-expression of MMP-9 and MMP-13 is commonly associated with invasion and metastasis, and these programs are frequently driven by IL-6/STAT3 and NF-κB signaling.

4.3. Differences in signaling pathways and regulatory modes

Core regulatory pathways underlying the CAFs–MMPs axis also differ across tumors. In HCC, the TGF-β/Smad, HGF/c-Met, and HIF-1α pathways are particularly important, governing CAF activation, MMP transcriptional programs, and hypoxic adaptation, respectively. In pancreatic cancer, the IL-6/STAT3 and Sonic Hedgehog signaling pathways impel CAFs to secrete MMP-11 and facilitate immune exclusion. In breast cancer, the Wnt/β-catenin and NF-κB pathways predominantly regulate the expression of MMP-9 and MMP-3. The IL-6/STAT3 signal pervades colorectal cancer, where CAFs secrete IL-6 to upregulate MMP-13 and augment migration.

4.4. Differences in therapeutic sensitivity and translational potential

Disparities in the CAFs–MMPs axis directly influence the therapeutic responses of diverse cancer types. Owing to the dense extracellular matrix and suboptimal drug permeability, pancreatic cancer exhibits a poor response to MMP inhibitors and immunotherapy. The application of MMP inhibitors in breast cancer has been restricted by non - specific toxicity; however, novel selective inhibitors (e.g., the small-molecule inhibitor ND - 322 targeting MMP - 14) have demonstrated potential in suppressing metastasis in animal experiments. In colorectal cancer, the combination of MMP - 9 inhibitors with anti - VEGF therapy can optimize vascular architecture and enhance the delivery of chemotherapeutic agents.

In comparison to the aforementioned cancer types, hepatocellular carcinoma (HCC) features higher vascular permeability and active metabolic traits, rendering interventions based on the CAFs–MMPs axis more theoretically feasible. Firstly, CAF - specific targets such as fibroblast activation protein (FAP) and α - SMA can be utilized for drug or probe delivery. Secondly, nanocarrier strategies aimed at inhibiting MMP - 2/14 have shown efficacy in suppressing angiogenesis and metastasis in mouse HCC models [8]. Simultaneously, the efficacy of HCC immunotherapy (e.g., PD - 1 antibodies) is significantly augmented after the blockade of the CAFs–MMPs axis, indicating that targeting this axis can serve as a novel strategy to enhance immune sensitivity.

5. Clinical and translational prospects

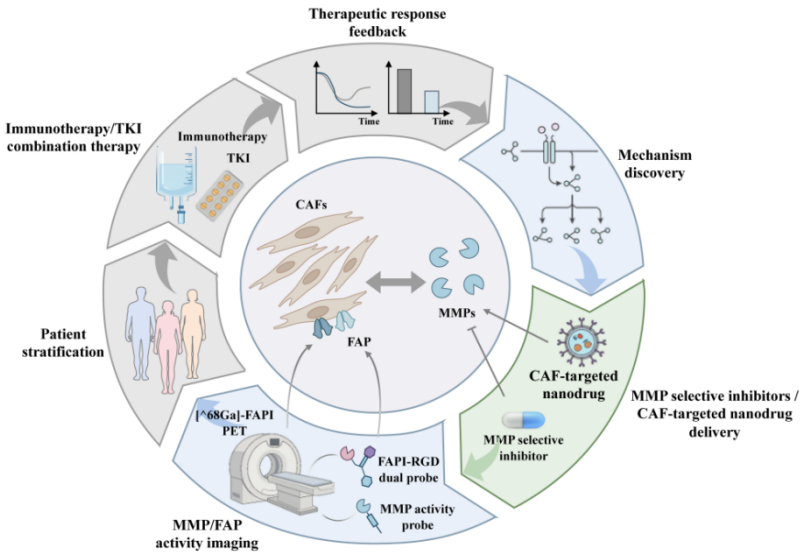

Figure 4. Clinical translation pathway targeting the CAFs–MMPs axis in HCC.

Mechanistic discovery of the CAFs–MMPs axis informs development of selective MMP inhibitors and CAF-targeted nano–drug delivery systems, alongside activity-readout tools such as FAPI-RGD dual probes and MMP activity probes (**Figure 4**). Axis activity can be assessed by MMP/FAP imaging (e.g., [^68Ga]-FAPI PET), enabling patient stratification and rational deployment of immunotherapy and/or tyrosine kinase inhibitor (TKI) combination strategies. Therapeutic efficacy feedback then iteratively refines axis-guided intervention design.

As a core driver of tumor microenvironment remodeling in HCC, the CAFs–MMPs axis integrates ECM reconstruction with signaling amplification, immune modulation, and therapy adaptation. Accordingly,

translational efforts have expanded from mechanistic studies to an emerging pipeline that spans selective inhibition and targeted delivery, molecular imaging and diagnosis, and synergy with immunotherapy and resistance control.

5.1. Repurposing of MMP inhibitors and combination strategies

Early clinical trials of broad-spectrum MMP inhibitors (e.g., batimastat and marimastat) did not yield meaningful clinical benefit, largely due to dose-limiting toxicity associated with non-selective inhibition. With improved understanding of MMP subtype function, current strategies emphasize selectivity and tumor-restricted delivery. For MMP-2, MMP-9, and MMP-14, frequently overexpressed in HCC, selective small-molecule inhibitors (e.g., ND-336 and NSC405020) and antibody-derived agents have shown the ability to suppress invasion and angiogenesis in preclinical models

Combination regimens are also increasingly prioritized. For example, co-inhibition of TGF-β signaling and MMP activity can simultaneously attenuate CAF activation and matrix degradation, thereby restraining HCC growth more effectively than either approach alone. Another direction is CAF-guided precision delivery, exploiting CAF-enriched markers such as FAP and α-SMA to concentrate MMP inhibitors within stroma-dense regions and reduce systemic exposure. In one representative strategy, FAP antibody–modified nanocarriers preferentially accumulate in CAF-rich niches and release MMP-14 inhibitors, limiting ECM remodeling and angiogenesis.

5.2. Applications in imaging and diagnosis

MMP activity–based molecular imaging provides a complementary route for early detection, boundary delineation, and treatment monitoring in HCC. Fluorescent and near-infrared (including NIR-II) probes incorporating MMP-cleavable sequences can achieve high-contrast visualization of tumor margins in HCC animal models. In parallel, CAF-oriented imaging has advanced rapidly: the CAF-targeting tracer [^{68}Ga]-FAPI has demonstrated strong performance in clinical PET/CT, and its signal intensity closely correlates with the extent of CAF infiltration [9].

5.3. Potential of the CAFs–MMPs axis in immunotherapy and drug resistance regulation

Immune checkpoint inhibitors (ICIs) are a key systemic therapy for HCC, yet clinical responses remain highly variable. Increasing evidence implicates the CAFs–MMPs axis as an important determinant of immune sensitivity. MMP-9–mediated chemokine processing, together with ECM densification, can restrict T-cell infiltration and promote an immune “cold tumor” phenotype. In preclinical studies, combining MMP-9 inhibition with PD-1 blockade significantly increases intratumoral $CD8^+$ T-cell infiltration and prolongs survival.

Beyond immune exclusion, the axis also contributes to adaptive resistance. CAF-derived IL-6 and MMP-14 can cooperatively activate the STAT3–YAP signaling axis, enabling tumor cells to acquire resistance to TKIs and immunotherapy [10]. Accordingly, disrupting the CAFs–MMPs–STAT3 pathway may help reverse TKI/ICI resistance. Bifunctional small molecules capable of simultaneously targeting MMP-14 and STAT3 have been developed and have shown initial synergistic antitumor effects in early studies [10].

6. Current challenges and future directions

Despite encouraging progress, several issues remain. First, CAF subtypes are highly heterogeneous: differences in cellular origin and spatial localization are accompanied by substantial divergence in MMP programs and signaling responsiveness, yet a high-resolution marker system that integrates spatial state and functional state is

still lacking. Second, because MMPs contribute to physiological repair and immune regulation, targeting safety and spatiotemporal control remain major translational bottlenecks. Third, clinical detection standards for CAF and MMP activity have not been unified, limiting cross-cohort comparability and constraining biomarker and imaging parameter validation.

Future work may focus on three directions: (1) integrating single-cell and spatial multi-omics to build dynamic maps of the CAFs–MMPs axis and clarify subtype-specific coupling logic; (2) developing multimodal, closed-loop platforms that combine FAPI imaging, MMP-activatable probes, and nano–drug delivery for integrated diagnosis, treatment, and monitoring; and (3) establishing rational combination frameworks that pair immunotherapy with microenvironment-directed interventions to reprogram CAF–MMP signaling and improve ICI responsiveness and durability.

7. Conclusion

In conclusion, the CAFs–MMPs axis is not only a key driver of microenvironmental imbalance in HCC but also a promising entry point for future precision diagnosis and therapy. With continued integration of multi-dimensional technologies and mechanism-driven intervention design, this field may accelerate the shift in HCC treatment from "cell targeting" to "ecosystem intervention."

Disclosure statement

The authors declare no conflict of interest.

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