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Perspective

Heterogeneity and function of cancer-associated fibroblasts in renal cell carcinoma

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ABSTRACT

With the advancement of anticancer therapy, there is increasing interest in understanding the tumor microenvironment (TME). Cancer-associated fibroblasts (CAFs) play a pivotal role in the TME and have been the focus of much research in recent years. CAFs play an active role in cancer progression through complex interactions with other cells in the TME, releasing regulatory factors, synthesizing and remodeling the extracellular matrix. However, research on the role of CAFs in renal cell carcinoma (RCC) is still in its nascent stages. Here, we describe the origins and subgroups of CAFs, the roles of CAFs in the development and progression of RCC, the impact of CAFs on RCC prognosis, and the potential of CAFs as treatment targets in RCC. By analyzing CAF subsets, biomarkers, and targeted therapies, we present the significance and contribution of CAFs in RCC research. Furthermore, we highlight the distinct contribution of CAFs in advanced RCC through horizontal comparison with other cancers. This paper provides a comprehensive perspective of recent and foundational studies on the role of CAFs in RCC and other types of cancers and new insights for further study of CAFs in RCC.

1. Introduction

1.1. Renal cell carcinoma

Renal cell carcinoma (RCC), with a steadily increasing incidence rate, is the seventh most prevalent cancer in men.[1] In 2020, RCC accounted for 431,000 new cases and 179,000 deaths worldwide, with 73,000 new cases and 43,000 deaths reported in China alone.[2] Despite the advancements in the diagnosis and treatment of RCC over the past two decades, it remains a highly lethal malignancy of the urinary system. Furthermore, RCC exhibits substantial heterogeneity, with patients presenting various degrees of metastasis and progression rates. This diversity in patient conditions necessitates tailored treatment approaches.[3] Additionally, the treatment and prognosis of RCC vary significantly among different pathological types. Currently, a lack of accurate biomarkers and effective models hinders the precise analysis and treatment of tumor development in RCC.

1.2. Cancer-associated fibroblasts

Fibroblasts comprise the majority of interstitial cells in the connective tissues. They protect the structural integrity of the connective tissues by producing and maintaining the extracellular matrix (ECM) through the synthesis and deposition of collagen, laminin, and fibronectin. Fibroblasts also play important roles in inflammation and wound healing. In the tumor microenvironment (TME), some mesenchymal cells can be re-educated to prevent tumor progression and induce effective cancer remission. Activated fibroblasts trained by cancer cells, called cancer-associated-fibroblasts (CAFs), have sustained activation properties. CAFs are elongated and spindle-shaped with abundant cytoplasm and centrally located nuclei. CAFs have a range of cell sizes and are generally arranged radially or in bundles. However, in some cases, they are disordered and non-polarized. The latency period of their growth is longer compared to that of tumor cells, and their growth rate is relatively slow.

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1.3. Role of CAFs in the tumor microenvironment

In normal tissues, fibroblasts play an important role[4] in healing and repair by releasing cytokines, angiogenic mediators, and growth factors in response to tissue injury or stress. However, in cancer, CAFs can shift from a physiological to a pro-tumor survival state.[5] CAFs can inhibit the function of immune cells by secreting various cytokines and metabolites, and can also create a barrier to drug or therapeutic immune cell infiltration by altering the tumor ECM[6] or influence tumor development by regulating tumor-associated signaling pathways. Additionally, CAFs can release large amounts of lactic acid and hydrogen ions through glycolysis, forming an acidic microenvironment, which inhibits immune cell activity. Multiple studies on CAFs in RCC have highlighted the value of CAFs as the new prognostic and therapeutic targets for RCC. A thorough understanding of CAFs is therefore crucial for advancing cancer research.

2. Heterogeneity of CAFs in RCC

2.1. Heterogeneous origins of CAFs

CAFs consist of populations of cells having distinct functions, which could be attributed to their origins. It is believed that most stromal fibroblasts are derived from local fibroblasts undergoing tissue dysfunction. While the initial fibroblast response could be tumor-suppressive, recent studies have revealed that stromal fibroblast hyperplasia could produce tumor-promoting fibroblasts.[7]

Studies have shown that the precursors of CAFs in RCC come from a variety of sources (Fig. 1A). Resting fibroblasts are remnants of the intermediate mesenchymal cells involved in organ development and might be the precursors of activated fibroblasts. Other precursors include cells transdifferentiated from other cell types such as endothelial cells, epithelial cells, vascular smooth muscle cells, pericytes, adipocytes, and astrocytes, and tumor cells transdifferentiated into mesenchymal cells via epithelial-to-mesenchymal transition (EMT). Additionally, it has been demonstrated that whereas epithelial cells and endothelial cells transform into CAFs through EMT and endothelial-to-mesenchymal transition (EndMT), respectively, human adipose stem cells (hASCs) differentiate into CAFs upon exposure to transforming growth factor-β1 (TGFβ1). Moreover, pericyte-to-CAF transition has also been demonstrated.[8,9] Bone marrow-derived progenitor cells and mesenchymal stem cells (BM-MSCs) have been shown to transform into CAFs in cancers.[10] Due to their prevalence in the kidney, BM-MSCs have emerged as a promising area of research. However, there is currently insufficient evidence to support the notion that they can be converted to CAFs in RCC.[6]

2.2. CAF subgroups

The existing methods to classify pancarcinoma CAFs into subgroups implement single-cell RNA sequencing (scRNA-seq) analysis, using the spatial distribution of CAFs and the functions of expressed markers as the basis for classification. This classification system divides CAFs into four categories: (1) myofibroblast CAFs (myCAFs), which express high levels of fibroblast- and smooth- muscle cell markers, (2) desmoplastic CAF (dCAFs), which are characterized by the expression of genes associated with collagen and ECM remodeling, (3) inflammatory CAFs (iCAFs), which express high levels of genes associated with inflammation, and (4) proliferating CAFs (pCAFs), which express high levels of genes associated with the cell cycle.[11] Additionally, CAFs can also be classified into three functional subgroups: steady state-like (SSL), mechanical response (MR), and immunomodulatory (IM).[12] At present, there is no comprehensive classification system for CAFs in RCC; however, subtype classification in pancarcinoma could be used as a reference for further exploration.

Although the method using spatial distribution and gene expression as the basis for classification provides a useful framework, the categories myCAF, iCAF, dCAF, and pCAF are only used in one study at present and are not universally applicable. Furthermore, the nomenclature of CAFs can be misleading, as different types of CAFs are often labeled with the same name in various cancers, and conversely, similar CAFs may be given distinct names. This inconsistency hinders horizontal comparisons and makes it difficult to draw accurate conclusions about CAFs across different cancers. In contrast, functional subgroup classification is more general and is stable across multiple tissue types and species. Moreover, CAFs classified by this classification method can be easily assimilated into functional classes. Therefore, in RCC, functional CAF classification can be implemented to facilitate the comparison of CAFs across cancers. Alternatively, researchers can draw inspiration from the gene expression-based approach to undertake the novel and challenging task of producing a unique classification of CAFs in RCC. Furthermore, the use of scRNA-seq in RCC has shed light on the tumor immune microenvironment, cell origin, tumor markers, and therapeutic response. As such, employing the method of analyzing CAF subgroups in pancreatic cancer (PC) via scRNA-seq will be highly advantageous for further exploration of CAF classification in RCC.

CAF subgroups play distinct roles in the TME. Currently, CAF subgroup classification in RCC is primarily dependent on the evaluation of the expression-heterogeneity of specific biomarkers. Common CAF biomarkers include palladin (an early myofibroblast differentiation marker localized to fibroblast stress fibers), α-SMA, S100A4, FAP, PDGFRα/β, Vimentin, CD70, CD49e, CD10/GPR77, CD248, and MHCII/CD74 (Supplementary Table 1). While certain markers are expressed by multiple CAF subgroups, they are typically enriched in specific types of CAF, which may be due to the heterogeneity of their origins. Consequently, accurately identifying and classifying CAF subgroups in RCC remains an ongoing research focus. At present, the classification methods of CAFs in RCC mainly rely on simple and intuitive classification markers. For example, CAFs with significant accumulation of α-SMA are defined as α-SMA CAFs. Interestingly, we found that the expression of these biomarkers in CAFs is significantly correlated with the prognosis of RCC, suggesting that analyzing the heterogeneity of CAF subgroups may be a useful tool for predicting patient prognosis. However, we did not observe any significant differences in the prognostic effects among the CAF subgroups marked by different biomarkers. Therefore, we posit that the value of grouping CAFs for tracing their origin may outweigh the clinical significance of comparing the differences in their effects on prognosis.

3. Role of CAFs in RCC development

3.1. CAFs contribute to RCC cell proliferation

One of the primary ways in which CAFs promote tumor growth is by stimulating tumor cell proliferation.[5] *In vitro* studies have established models of interaction between RCC cell lines and CAFs, and have shown that proliferation-related (Erks) and survival-related (Akt) pathways are activated in CAF-cocultured RCC cells. Moreover, the relationship of CAFs and hypoxia-inducing factor 1 (HIF-1) has been shown to play a crucial role in reprogramming energy metabolism of cancer cells. This leads to cancer cells becoming less dependent on glucose and increasing their production of lactic acid, which fuels the anabolic pathway that promotes cell growth.[13] These findings demonstrate that CAFs play an important role in supporting and driving RCC progression (Fig. 1B).

3.2. CAFs contribute to RCC cell stemness

CAFs are known to be enriched in the cancer stem cell (CSC) niche and have been shown to interact with CSCs to regulate their stem cell characteristics. CAFs have been reported to promote the stemness and progression of RCC through the exosome-mediated transfer of miR-181d-5p and TNF-α-induced EMT. Furthermore, CAF-specific surface markers such as CD10 and GPR77 have been shown to promote tumor

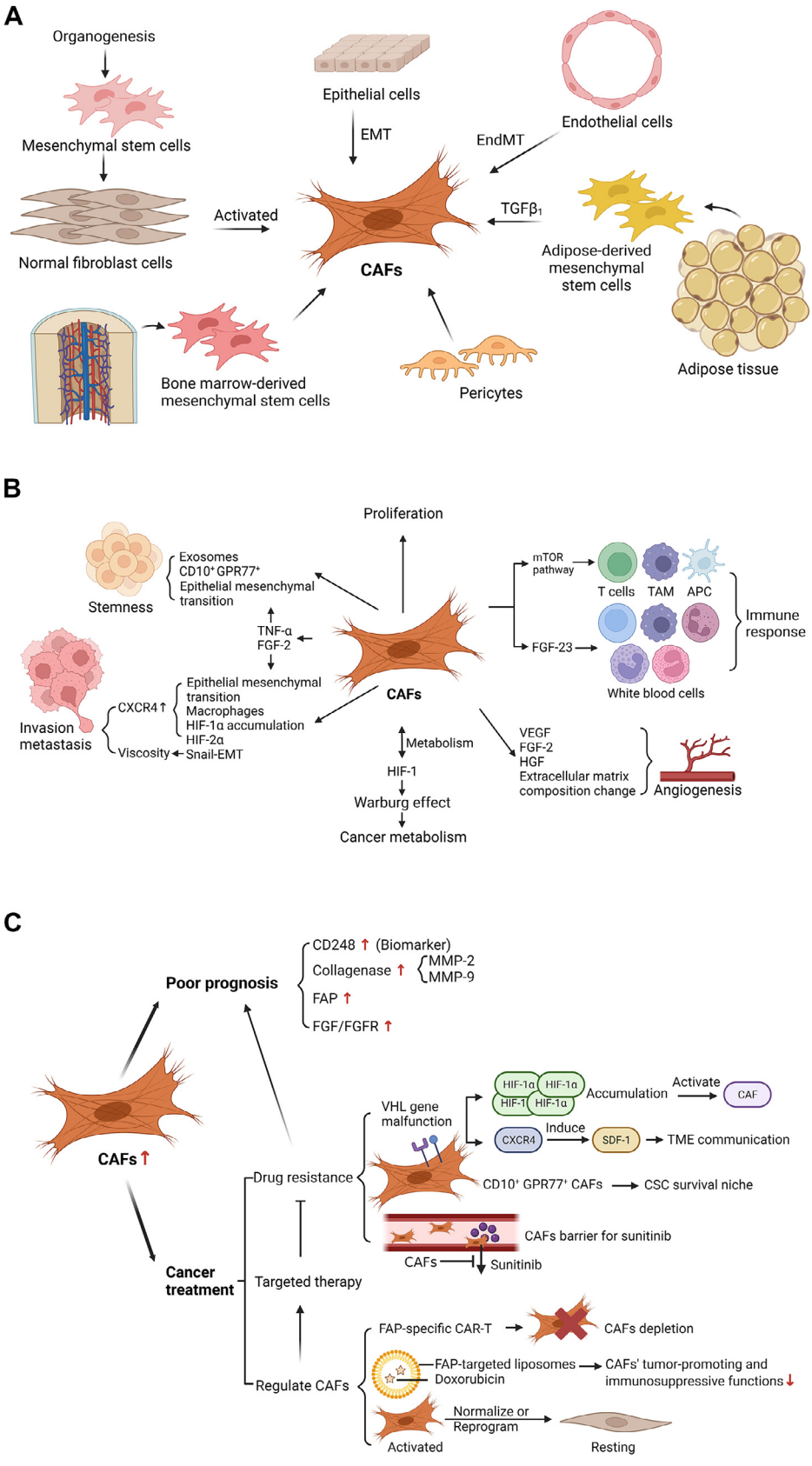

Fig. 1. Original, functional heterogeneity of CAFs, and its role in the prognosis and treatment of RCC. (A) There are many sources of CAF precursor cells in RCC. Resting fibroblasts exist as precursors to activated fibroblasts. Other precursors include (1) cells transdifferentiated from other cell types such as endothelial cells, epithelial cells, vascular smooth muscle cells, pericytes, adipocytes, and astrocytes, and (2) tumor cells transdifferentiated into mesenchymal cells via EMT. (B) CAFs play an essential role in the process of tumorigenesis and cancer progression such as RCC cell proliferation, stemness, evasion, migration, EMT, angiogenesis, immunosuppression, and metabolic changes. (C) CAF plays a decisive role in drug resistance in RCC patients. We can target the regulation of CAF by (1) directly or indirectly depleting CAF, (2) reducing or eliminating CAF's pro-tumor or immunosuppressive function, and (3) normalizing or recodifying CAF into a resting state. At the same time, we can develop new drugs and therapies. These characteristics make CAF, CAF-secreted factors, and their markers be used as prognostic markers of RCC. APC, antigen presenting cell; CAFs, cancer-associated-fibroblasts; CAR, chimeric antigen receptor; CSC, cancer stem cell; EMT, epithelial-to-mesenchymal transition; EndMT, endothelial-to-mesenchymal transition; RCC, renal cell carcinoma; TAM, tumor-associated macrophages; TME, tumor microenvironment.

formation and resistance to chemotherapy by providing a survival niche for CSCs[14] (Fig. 1B).

3.3. CAFs facilitate evasion, migration, and EMT in RCC

CAFs play a key role in promoting RCC migration and evasion through interactions with other cells in the TME. The expression of FGF-2 in CAFs can promote the EMT of renal tubular epithelial cells, which is closely linked to the invasiveness of RCC. Additionally, the recruitment and activation of CAFs and macrophages can lead to ECM remodeling, which is a crucial process in tumor development and metastasis.[13] Moreover, elevated levels of CXCR4 and HIF1α have been observed in circulating RCC cells in patients with metastasized RCC, and have been shown to contribute to their metastatic potential. Furthermore, HIF-2α has been shown to promote tumor growth in RCC xenograft models in renal metastatic lung cancer through the promotion of cell cycle progression. Additionally, the EMT marker Snail has been shown to regulate CAFs to affect tumor viscosity and promote tumor migration.[15] CAFs can also regulate EMT in cancer cells and influence tumor progression through crosstalk, paracrine signaling, cancer cell proliferation, enhancement of tumor angiogenesis, and alteration of ECM hardness[16] (Fig. 1B).

3.4. CAFs control angiogenesis

The tumor vasculature is a vital component of the TME and is established primarily through hypoxia-induced angiogenesis. During tumor development, CAFs regulate the secretion of VEGF, FGF-2, and other cytokines, and increase the expression of HGF and the accumulation of MMP-9.[17] By modifying the composition of the extracellular matrix, CAFs can promote angiogenic phenotypes and regulate tumor growth[18] (Fig. 1B).

3.5. CAFs control immunosuppression

CAFs can influence the immune response directly through their ability to produce molecules with immunosuppressive effects on both innate and adaptive leukocytes, and indirectly through the regulation of ECM stiffness, angiogenesis, hypoxia, and metabolism. The relationship of mTOR pathway and CAFs can promote T cells, tumor-associated macrophages (TAMs), and antigen-presenting cells and participate in the regulation of immune cell function. Moreover, fibroblast growth factor-23 (FGF-23) can impair immune function through direct interaction with bone marrow cells such as macrophages and white blood cells. However, excess FGF-23 is associated with increased inflammation and adverse infection outcomes, as well as increased morbidity and mortality. Galectin-1 (Gal1), which is highly expressed by CAFs, can induce apoptosis of $CD8^+$ T cells and is significantly associated with adverse reactions of immunotherapy in papillary RCC and recurrent RCC[19] (Fig. 1B).

3.6. CAFs support RCC progression through metabolic changes

CAFs can reprogram tumor cell metabolism. HIF-1 plays a key role in regulating energy metabolism of tumor cells, leading to decreased dependence on glucose and increased production of lactic acid to drive anabolic pathways.[20] The metabolic transition of renal fibroblasts from oxidative phosphorylation to aerobic glycolysis (Warburg effect) is a key feature of CAF activation in renal fibrosis.[21] Furthermore, the dynamic and heterogeneous TMEs in RCC are closely linked to several key metabolic enzymes in terms of carcinogenicity and therapy due to increased production of lactic acid, nitric oxide, and other novel metabolic byproducts, as well as alterations in glucose and lipid metabolism (Fig. 1B).

4. Role of CAFs in the prognosis and treatment of RCC

4.1. Effect of CAFs on the prognosis of RCC

CAFs and their secretions can affect the progression of RCC by regulating metabolism, immune inhibition, and chemical resistance. Tumor tissue typically has a higher proportion of stroma and immune evasion compared to normal tissue, and the proportion of CAFs increases with the progression of tumor stage and grade.[22] Currently, several interstitial collagenases that are mainly secreted by CAFs have been shown to have prognostic relevance (Fig. 1C). For example, the expression levels of MMP-2 and MMP-9 are correlated with the progression of RCC. The protein fibroblast activating protein-α (FAP) expressed by CAFs has been associated with tumor aggressiveness and shortened survival by immunohistochemical tests and can be used as a prognostic marker for RCC.[23] In particular, CD248 is specifically expressed in activated fibroblasts and contributes to their pro-tumor function. Current studies in hepatocellular carcinoma (HCC) and RCC have shown that CD248 can cause immunosuppressive TME by influencing the recruitment of immune cells, and its overexpression and CAF infiltration can predict a poor prognosis of RCC. Thus, CD248 is a promising molecule that requires further exploration and mechanistic verification. Additionally, activation of signaling pathways mediated by fibroblast growth factor and its receptor (FGF/FGFR) in CAFs has also been reported to influence the prognosis of RCC patients. Overexpression of FGF2, FGFR1, and FGFR2 is associated with poor morphological characteristics and advanced tumors and has a significant predictive value for RCC progression. A large number of studies have shown that higher CAF counts are associated with poor prognosis of RCC, thus CAF count may serve as a useful marker for evaluating patient prognosis.

4.2. Role of CAFs in RCC treatment

CAFs are the predominant cellular component of TME and play a key role in the acquisition of resistance to chemotherapy (Fig. 1C). Moreover, they are associated with poor prognosis and chemical resistance in RCC.[24] CAFs contribute to drug resistance through cell adhesion and secretion of soluble factors. In the TME, CAFs are activated upon the accumulation of HIF-1α, which is associated with the dysfunction of the Von Hippel-Lindau (VHL) gene in RCC cells.[25] In addition, the loss of function of the VHL gene induces stromal cell-derived factor-1 (SDF-1) signaling through its receptor CXCR4, thereby enhancing chemical resistance in patients by affecting the communication between tumor cells and TME. Therefore, the activation of CAFs is significantly correlated with the therapeutic resistance of RCC.[23] Moreover, CAFs with specific surface molecules, such as $CD10^+GPR77^+$ CAFs, promote tumor formation and chemical resistance by providing a survival niche for CSC.[14] Several indirect mechanisms of resistance have also been shown. For example, in clear cell RCC (ccRCC), intravascular CAFs constitute a barrier to prevent Sunitinib, a drug known to reduce the proliferation of ccRCC cells, from entering tumor cells.[26]

4.3. Therapeutic value of CAF-targeted strategies

Recent years have seen significant advancement in the development of therapies targeting CAFs for the treatment of RCC.[13] Current strategies include direct or indirect reduction of the CAFs population to minimize their overall presence, mitigation or elimination of the tumor-promoting and immunosuppressive functions of CAFs, and normalizing or reprogramming CAFs to a resting state.[27] These methods have been shown to effectively subdue the tumor-promoting effects of CAFs in RCC and improve therapeutic outcomes (Fig. 1C).

There are also several promising strategies currently in early clinical trials.[28] For example, the use of liposomes as vectors to specifically deliver therapeutic drugs such as doxorubicin to CAFs targets FAP, which is a membrane-bound post-serine proline peptidase expressed by

a CAF subpopulation. This allows targeted regulation of CAFs to inhibit tumor growth. Moreover, chimeric antigen receptor (CAR) T cell therapy has been explored as an effective approach to directly target CAFs. FAP-specific CAR T cells can clear most FAP^+ cells, including CAFs, and inhibit the formation of tumor interstitium, thereby enhancing the uptake of chemotherapy agents. Overall, these recently developed CAFs-targeted therapies are expected to inhibit tumor progression and enhance anti-tumor immunity. Preclinical studies have demonstrated their efficacy and potential to provide clinical benefits to patients.

4.4. Development of CAF targeted therapy

There are two main approaches to CAF-targeting drug therapy: direct and indirect targeting (Fig. 1C). Direct targeting strategies include CAF-specific pathway targeting, CAF and TME dual targeting, implementation of non-coding RNAs, and CAF-targeted vaccines. Indirect targeting strategies primarily focus on the downstream effectors critical to CAFs function, targeting CAF-derived ECM proteins, restoring the phenotype of silent fibroblasts, making CAFs biased towards inhibitory phenotypes, and co-targeting CAFs with various cancer-targeting drugs.[29] Currently, several drugs have been developed for clinical use in PC and breast cancer, but relatively fewer have been implemented in RCC treatment. Examples include anti-FAP monoclonal antibodies bound with tubulin binding agents, anti-FAP antibodies labeled with β-emitting radionuclides, and FAP-targeted immunotoxins. Another promising approach that has been used to specifically eliminate the FAP^+ cells in the TME is near-infrared photoimmunotherapy (NIR-PIT). This is a new molecularly targeted cancer photo-therapy which has been shown to significantly inhibit tumor growth in human esophageal squamous cell carcinoma xenograft models without causing adverse effects.[30]

Future treatment strategies for cancer will likely target CAFs. In PC, iCAF is defined as an immunomodulatory CAF subgroup, which secretes inflammatory mediators such as IL-6 and IL-11. These mediators can activate cancer cells, and enhance tumor growth and survival. This is also true for breast cancer, ovarian cancer, and liver metastases. Moreover, scRNA-seq analysis of liver metastases and intrahepatic cholangiocarcinoma (ICC) revealed that a major subgroup of $CD146^+$ vascular CAFs (vCAFs) express inflammatory mediators such as IL-6 and CCL8.[31] These mediators may interact with cancer cells through IL-6 and/or IL-6 receptor (IL6R) to promote tumor growth and stemness. A common characteristic of inflammatory CAFs across various types of tumors is the up-regulation of IL-6-IL-6R signaling, suggesting that anti-IL6 therapies such as Siltuximab and Tocilizumab could potentially target these CAFs.

5. Conclusions and future prospects

In this paper, we discussed the characteristics of CAFs in RCC, focusing on their origin, heterogeneity, and mechanisms of action. We further explored the prognostic value of CAFs, with an emphasis on their origin heterogeneity and functional diversity. The subgroups and nomenclature of CAFs remain controversial; however, their origin heterogeneity and markers could be utilized as reliable classification criteria. These markers can be used for the identification of CAFs, and further analyzed using scRNA-seq and various immunofluorescence techniques. However, some markers expressed by CAFs might need contextual interpretation, owing to the functional diversity of CAFs.[13] For example, S100A4 promotes tumor metastasis by secreting VEGF-A and Tenascin-C,[32] while α-$SMA^+S100A4^+$CAFs activates tumor immune responses by promoting $CD8^+$T cell activation through fusion with dendritic cells. Overall, the classification of CAFs has several issues and further work is needed to refine it. Several RCC-specific CAF markers COL16A1, COL1A1, COL1A2, COL5A1, EMILIN1, LOXL1, and LUM have also been identified with good prognostic values in The Cancer Genome Atlas (TCGA). These markers could serve as a reliable source for studying CAF specificity in RCC and potential targets for the treatment of RCC. Given the important role of CAFs in the tumor immune system, targeting CAFs through therapeutic strategies like immunotherapies holds promise for RCC treatment. Therefore, the study of CAFs in RCC can provide new insights into the assessment and treatment of the disease.

Declaration of competing interest

The authors declare that they have no conflict of interests.

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Author contributions

H.T., W.X., and J.L. performed the study and drafted the manuscript. H.T., W.X., A.A. and H.Z. conceived the project and designed the outline. W.X., J.L., H.Z. and D.Y. revised the manuscript. All authors read and approved the final manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jncc.2023.04.001.

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