Cancer-associated Fibroblasts (CAFs): Come from Where and Where to Go?

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Abstract

Cancer-associated fibroblasts (CAFs) are the major and significant component of tumor stroma and play a crucial role in tumor initiation, progression, invasion and metastasis by modulating the tumor microenvironment and influencing the behavior of neoplastic cells. Such CAFs may provide new thought and approach to understanding and intervention againstmalignancies. We discuss the markers, origin and biological characteristics of CAF in the context of tumorigenesis.

Keywords: Cancer-Associated Fibroblasts (CAFs), Markers, Origin, Biological Characteristics, Tumorigenesis

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Introduction

Cancer-associated fibroblasts (CAFs) play an essential role in promoting tumor initiation, progression, invasion and metastasis [1-4]. Tumor proliferation, angiogenesis, invasion, and metastasis are dependent on the cancer-associated fibroblasts secretion of various cytokines, chemokines, growth factors and degradation of extracellular matrix (ECM) proteins for platform [5-7]. Based on previous studies of various source of CAFs, the cancer-associated fibroblasts (CAFs) and normal fibroblasts (NFs) differ in biological characteristics and gene expression profile [8, 9]. Cancer-associated fibroblasts are responsible for the generating of cytokines and growth factors which can affect tumor cells growth and metastasis, and the production and reconstruction of most extracellular matrix in tumor stroma [10]. The study of the mechanism of the development of cancer-associated fibroblasts plays a major role for tumor diagnosis and therapy.

The Origin of CAFs

Numerous cell types have been reported to

transdifferentiate to CAFs. The most direct source of CAFs is resident tissue fibroblasts and mesenchymal stem cells [11-15]. The stellate cell is a vitamin A-storing and lipid droplet-containing cell that can be found in the liver, pancreas, kidney, intestine, lung, spleen, uterus, and skin [16]. Although the stellate is a quite different cell type, it shares some same functions with CAFs, for instance, stellate cells express α-smooth muscle actin (α-SMA) and acquire a myofibroblast-like phenotype. Stellate cells acted like categorized CAFs, which are responsible for the majority of the desmoplastic reaction were found in many types of inflammation and malignancy, like chronic pancreatitis, pancreatic cancer [17] and liver fibrosis [18]. In addition, bone marrow-derived cells termed fibrocytes that are recruited to the tumor also are the other sources of CAFs and differentiated into myofibroblasts and fibroblasts [19-22]. α-SMA-expressing myofibroblasts have also been found to originate from neighboring adipose tissue [22]. Endothelial-mesenchymal transition (EndMT) and epithelial-mesenchymal transition (EMT) are another two potential sources of CAFs, indicating that endothelial cells and no transformed epithelial cells induce expression of FSP-1 to be an additional source of CAFs in response to stimuli from surrounding cells [23]. Therefore, the richness of the source of CAFs determines the complexity of the classification of them.

Various Markers of CAFs

The markers of CAFs not only act like identification of them, but also have the functions of support many different aspects of tumor initiation, growth and progressionby secretion of growth stimulatory, pro-survival and angiogenic factors [24, 25]. At the beginning, widespread expression of α-smooth muscle actin (α-SMA) [26] seemed to be a label of CAFs. However, it is now becoming evident that α-SMA expression in itself is neither sufficient to identify all subsets of CAF, nor able to clearly distinguish CAF from other cell types [27-30]. Here, we will focus on the functional aspects of CAF expressing some of the more widely used markers.

Fibroblast activation protein α

At first, in the stroma of various epithelial cancers, including breast, pancreas and colon carcinomas, fibroblast activation protein α (FAP) was only considered to be a tumor-specific antigen produced by cells [31]. However, recent studies found that FAP as a member of the serine protease subfamily of dipeptidyl peptidases is obtaining further characterization and selectively expressed by stromal cells and mesenchymal stem cells during embryogenesis, wound healing, fibrotic reactions and inflammatory conditions [32-35]. A recent study found that modulation of the composition and organization of the substrate by CAF^{FAP}, resulting in enhanced invasiveness of pancreatic adenocarcinoma cells [36], according to this work, CAF^{FAP} in the stroma of solid tumors was correlated to a poor prognosis in colon carcinoma and pancreatic adenocarcinoma [37, 38]. This indicates that FAP is part of stromal profile and can be considered as a prediction for advanced stages and poor outcome of invasive esophageal carcinomas [39]. What's more, CAF^{FAP}, through immunomodulation, represents a functional subset of mesenchymal cells within the tumor stroma with a diverse repertoire of tumor-promoting abilities.

Fibroblast-specific protein-1

Within the tumor microenvironment, fibroblast-specific protein-1 (FSP1, S100A4) is expressed by a variety of cell types including CAF, macrophages and malignant cells [40]. Therefore, the functions of FSP1 are difficult to attribute to a particular type of cells. Nevertheless, in one study, CAF^{FSP1}

were found to significantly induce the infiltration of macrophages into the tumor microenvironment by secretion of monocyte chemotactic protein-1 [41]. It is worth noting that CAF^{FSP1} in this tumor model, and others, did not express α-SMA to a great degree, indicating that the myofibroblast phenotype is not a precondition for tumor-promoting CAF [41, 42]. Besides, in another tumor model, CAF^{FSP1} were found to limit the exposure of the carcinogen via collagen depositions, resulting in the formation of fibrosarcomas but no epithelial tumors [42]. When selective ablating CAF^{FSP1}, the carcinogen was no longer encapsulated and was thus able to transform surrounding epithelial cells, resulting in formation of overt carcinomas. However, FSP1 is not a specific marker of CAF, more work is needed to fully explain the specific functional and prognostic abilities of CAF^{FSP1}in malignancy.

Platelet derived growth factor receptor-α

Signaling by members of the platelet derived growth factor (PDGF) family is essential for a wide variety of functions performed by mesenchymal cells during embryonic development [43, 44]. In particular, activation of PDGFR-α seems to be involved in delivering mesenchymal-derived patterning information to forming epithelial structures in organs [43]. During tumorigenesis, PDGF-AA and PDGF-CC, both ligands of PDGFR-α, are abundantly expressed by the tumor epithelium and have been functionally implicated in a wide variety of malignancies [44]. In some studies, pharmacological blockade of PDGF signaling might delay tumor initiation and cause a diminished growth rate of squamous cell carcinoma of the cervix in a genetically engineered mouse model [45]. In addition, mechanistic studies found that PDGF-stimulation of $CAF^{PDGFR-α}$ supplied growth-promoting signals to malignant cells (keratinocyte growth factor), and pro-angiogenic factors that stimulated blood vessel formation (fibroblast growth factor (FGF)-2). Likewise, signaling by PDGF-CC has been reported to induce expression level of vascular endothelial growth factor (VEGF)-A by recruited $CAF^{PDGFR-α}$, thereby representing to recovery angiogenesis in tumors from VEGF-$A^{-/-}$malignant cells [26] and experimental melanoma [29]. $CAF^{PDGFR-α}$ was confirmed to experience an inflammatory program during the progression from quiescent to invasive tumors in genetically engineered mouse model of skin carcinoma. Through signaling of the NF-κB pathway, $CAF^{PDGFR-α}$ caused macrophage recruitment, angiogenesis and tumor growth [46]. Generally speaking, $CAF^{PDGFR-α}$ is commonly devided into paracrine interactions within the tumor microenvironment with various cell types that precisely regulate an enhanced angiogenesis and promote growth program in various malignancy.

Platelet derived growth factor receptor-β

Expression of PDGFR-β is mainly limited to vascular smooth muscle cells, perivascular cells (PC)$^{PDGFR-β}$ and $CAF^{PDGFR-β}$ in the tumor microenvironment and activated signaling pathway enhances tumor initiation by the formation of a functional stroma [47]. In rhabdomyosarcomas, existence of $CAF^{PDGFR-β}$ is related to the more aggressive alveolar subtype and metastatic spread [48]. Similarly, signaling through PDGFR-β in CAFs has been confirmed to induce metastasis of colorectal cancer [49, 50]. Functionally speaking, $CAF^{PDGFR-β}$ and $PC^{PDGFR-β}$ enhance a high interstitial fluid pressure in tumors, thus weakening the effects of therapeutic methods [51-53]. Furthermore, significant occurrence of $CAF^{PDGFR-β}$ is closely related to prognosis in breast cancer patients with shorter recurrence-free and disease-specific survival [54]. Thus, more work is needed to find out the functional effects of $CAF^{PDGFR-β}$ and $PC^{PDGFR-β}$ in the tumor stroma.

Others

CAF also expresses a variety of other markers, say, TGFBRII, SPARC and elements of the Hedgehog pathway, which have been confirmed to maintain both biologically and clinically valuable information [55-57]. More work is needed to identify and functionally explore the complex diversity of CAF subsets in the tumor stroma.

Therefore, it is significant to remember that there is currently no marker that accurately defines CAFs, and this should be kept in mind when explaining dues to different models. Furthermore, these proteins are often expressed or coexpressed CAFs subsets, probably reflecting different sources and stages of activation of CAFs (Fig. 1).

THE BIOLOGICAL CHARACTERISTICS OF CAFs (Fig. 2)

CAFs modulate the tumor microenvironment

CAFs play function by secreting soluble factors. CAFs carefully arrange critical pathophysiological processes in cancer occurrence and development by paracrine interactions, say, the secretion of various soluble factors. Growth factors such as insulin-like growth factor (IGF) , epidermal growth factor (EGF), connective tissue growth factor (CTGF) , nerve growth factor (NGF), basic fibroblast growth factor (bFGF), hepatocyte growth factor (HGF), and members of the Wnt family [25, 46, 55, 58-63]. Similarly, many cytokines have also been devided into this paracrine cross talk, for instance, chemokine C-X-C motif ligand 12 (CXCL12) and chemokine (C-C motif) ligand 7 (CCL7) [59, 64]. Furthermore, the CAF secreted proteins, e.g., vascular endothelial growth factor α (VEGF-α) , CXCL12, CXCL14, and CTGF [59, 65, 66], also modulate angiogenesis.

CXCL12 is significantly overexpressed in CAFs [60]. CXCL12 plays an essential role in the interaction between CAFs and CXCR4-expressing neoplastic cells, resulting in proliferation and migration [67]. CXCL12/CXCR4 signaling by no canonical Hedgehog pathway triggers EMT and invasion [68] and combines with activation of the canonical Wnt pathway to further enhance cancer progression [69]. Generally, HGF is hided in the ECM as part of a latent form. Proteolysis of HGF was able to affect signaling by the c-Met tyrosine kinase [70]. The activated c-Met signaling pathway leading to increased proliferation of neoplastic cells. In addition, co-cultures with $CAFs^{HGF}$ were found to enhance the invasion of preneoplastic cells by degrading the ECM of these cells in a three-dimensional model of ductal carcinoma in situ [71]. CTGF plays an essential role in fibrosis [72] and is also significantly overexpressed in various cancers [73, 74]. CTGF expression is elicited by hypoxia [75] and TGF-β in both activated neoplastic cells and stellate cells [76] and results in enhanced invasiveness of tumor cells [75]. In head and neck squamous cancer cells, CTGF increased stem-like characteristics and enhanced expression of various pluripotency genes [77].

CAFs remodel the ECM

One of the important characteristics of activated CAFs is their capability to synthesize and remodel the ECM in the tumor stroma. Unfavorable prognosis is correlated with severe desmoplasia in various tumors [78-82]. Changes in the component part and cross-linking of the ECM affect the hardness of the tissue, which plays a key role in tumorigenesis [83, 84]. CAFs play a key role in remodeling the ECM, like driving the recruitment of other cells into the tumor, promoting migration, and facilitating a metastatic phenotype of neoplastic cells.

Specifically, CAFs contribute to production of hyaluronic acid, which is the most important and major part of non-structural component of the ECM and possesses biological functions, such as macrophage

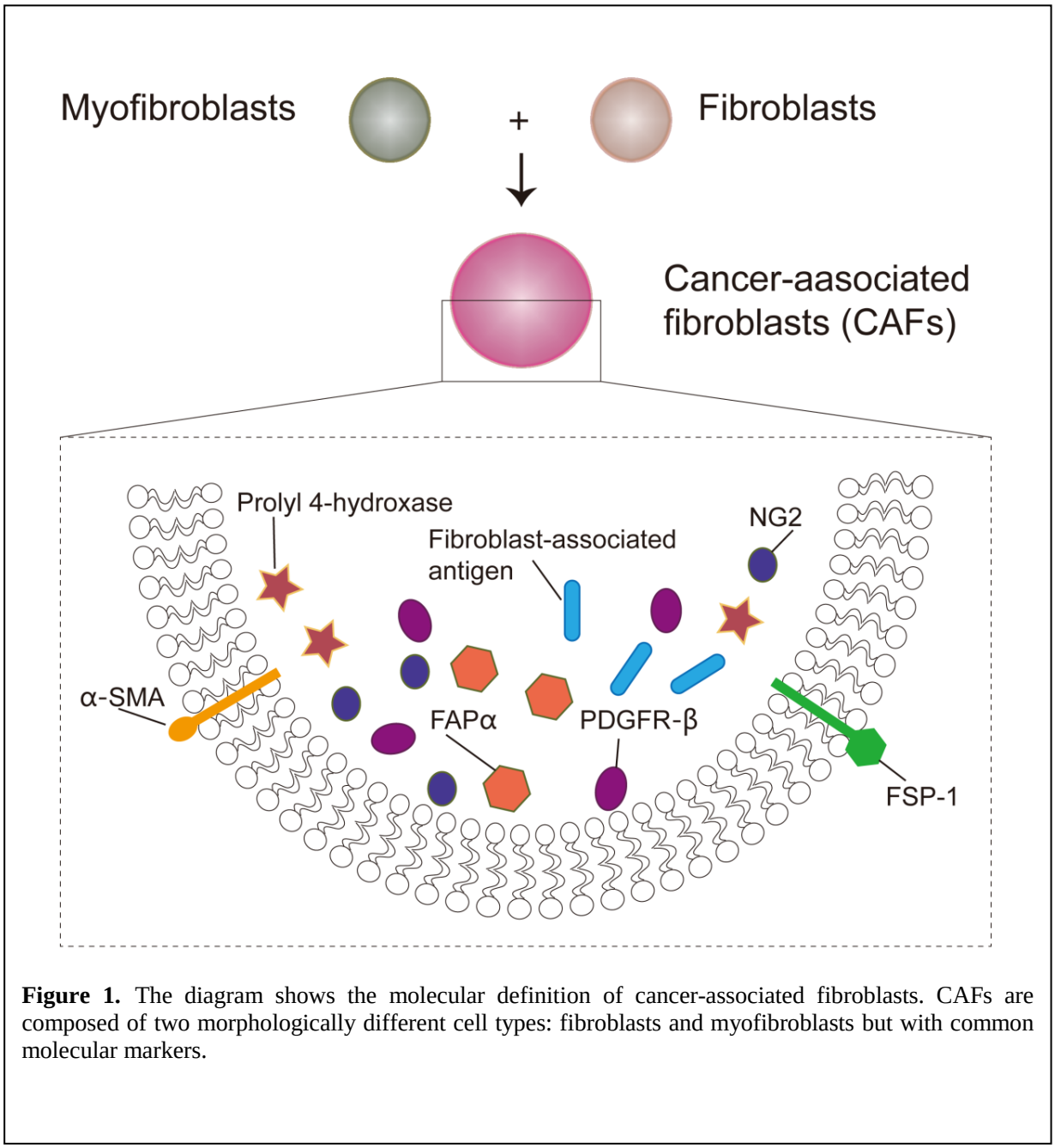

Figure 1. The diagram shows the molecular definition of cancer-associated fibroblasts. CAFs are composed of two morphologically different cell types: fibroblasts and myofibroblasts but with common molecular markers.

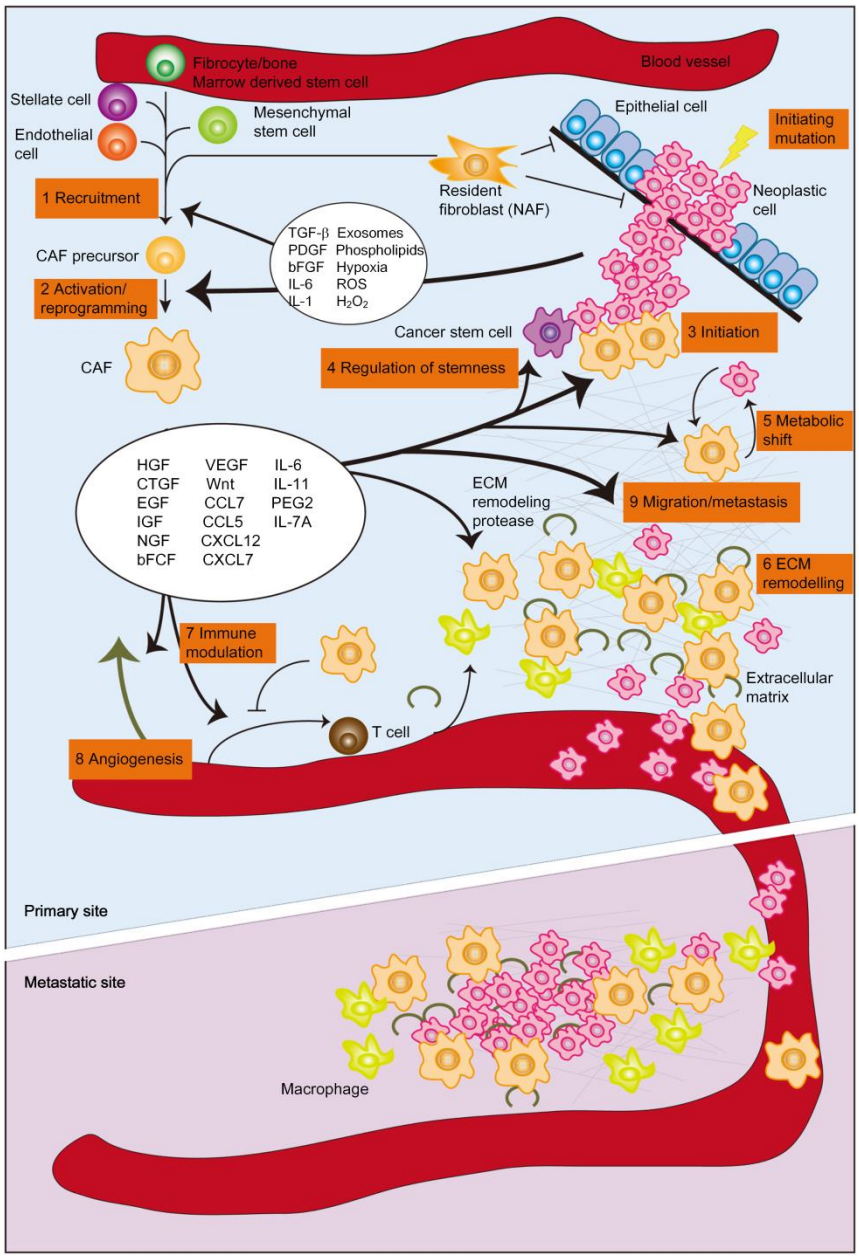

Figure 2. The progress of CAFs promoting tumorigenesis. By secreting soluble factors and lipid-based particles, transformed epithelium drives recruitment (1) and transforming (2) of many types of cells into CAFs, involving resident fibroblasts (NAFs), which are naturally tumor-suppressive. Then, CAFs are activated to promote tumor initiation (3), cancer cell stemness (4), and to modulate tumor metabolism (5) by paracrine function, communication of cell-cell contact, and remodeling the ECM (6). At the same time, CAFs help tumor cells escape host immune response (7) while balancing angiogenesis and inflammation (8). Finally, CAFs stimulate invasion and metastasis (9).

recruitment [85]. Moreover, CAFs express Lysyl oxidase (LOX), an enzyme responsible for cross-linking collagen I [86]. Some researchers have reported that the changes of collagen cross-linking were directly related to tumorigenesis, and decreased tumor incidence through reducing LOX-mediated collagen cross-linking and diminishing tumor tissue hardness in a xenograft mouse model [87]. On the contrary, CAFs also control the degradation of the ECM. CAFs facilitate tumor growth, invasion, and metastasis through expressing members of the matrix metalloproteinase (MMP) family [88-92]. ECM remodeling by MMP is essential for cancer angiogenesis by the regulation of VEGF. For example, CAFs express MMP13, which arouse the releasing of VEGF partly in the ECM, VEGF then plays a key role in promoting angiogenesis [93]. Furthermore, MMPs promote neoplastic cells growth and invasion by stimulating the surface protease-activated receptors (PARs) [94]. Other proteases are also involved in the degradation process of ECM. For example, urokinase-type plasminogen activator (uPA) activates the serine protease plasmin and has already been considered to enhance proliferation, migration, and invasion [95, 96]. Moreover, the CAF marker FAP a is a membrane-bound glycoprotein with both dipeptidyl peptidase (DPP) and collagenase activities that are significant for degrading the ECM [33] and stimulating tumor growth [97].

CAFs trigger tumor initiation and progression

A growing number of experiments showed that CAFs did play a crucial role in cancer initiation and progression through the ability of the CAFs to significantly change functions in neoplastic cells, like cell cycle regulation, migration, and death [98]. Interestingly, neoplastic cells of different origins differ in their responses upon stimulation from CAFs [99], illustrating the complexity of CAFs communication with tumor types.

Olumi et al. (1999) found that under specific tumor microenvironment, human prostatic CAFs could induce the initiation and proliferation of tumors from immortalized nontumorigenic human prostatic epithelial cells, which was not shown by normal fibroblasts, but under identical conditions, CAFs did not transform normal human prostatic epithelial cells [100].

Generally speaking, CAFs are believed to be responsible for this tumor-initiating potential by secretion. Although TGF-β signaling can help keep the CAF phenotypes, but removing TGFBR in fibroblasts resulted in spontaneous tumor in the prostate, which reveals TGF-β signaling exerts an inhibitory effect in the early stages of the tumor [55]. Fortunately, HGF can supplement the loss of TGF-β and mediate the tumor-initiating effect of CAFs. However, everything is a double-edged sword, HGF is not an exception. Over-expression of HGF in fibroblasts caused hyperproliferation of normal epithelium [101].

CAFs not only can promote tumor initiation, but also involve in tumor maintenance and progression. For example, co-implantation of breast cancer cells with CAFs was reported to enhance xenograft tumor growth [59]. Retinoic acid can be used to reduce paracrine cross talk, like Wnt/β-catenin signaling, and turn the activated stellate cells back to quiescent condition, by which delayed tumor progression by reducing neoplastic cell proliferation and migration in a three-dimensional co-culture system [101]. The $CAF^{FSP\text{-}1(negative)}$ mice also reported to have reduced engraftment of neoplastic cells and slowed tumor growth [102].

CAFs regulate cancer stemness

Cancer stem cells (CSCs) are the root cause of the diversity of tumor. Many factors secreted by CAFs, such as CXCL7, IL-17A, HGF, IL-6, and PGE2, were reported to trigger the Wnt-β-catenin pathway in neoplastic cells and increase the CSC population [68, 79, 103-106].

CD44, an outstanding CSC marker and receptor for hyaluronic acid, is up-regulated in various cancers by many cytokines secreted by CAFs and contributes to keeping CSC self-renewal characteristics and generic stemness ability [103, 105]. Interestingly, CD44 is also expressed on CAFs, which is essential for the existence of the nearby CSC population. Under hypoxia or low-nutrient conditions, CAFs up-regulate CD44 and maintain stem cell properties [107]. In various tumor types, the expression of other CSC markers can also be induced by CAFs, like ALDH1 and Nestin [105, 108, 109]. These markers are correlated with aggressive tumors, which display intensive invasiveness and metastatic capacities [68, 79, 110]. In general, these data explain that CAFs maintain stemness in neoplastic cells to further support tumor progression.

CAFs modulate the immune response

An inflammatory environment with high-rate proliferation is known to promote error-prone, thereby facilitating tumorigenesis [111]. Indeed, chronic inflammation is a prominent risk factor for various cancers [112-114]. Tumor-enhancing inflammation, that mediated by CAFs by expressing a series of proinflammatory gene signatures to create a microenvironment, attract myeloid cells and support tumor growth and angiogenesis [46, 115]. These signatures were early identified via NF-κB-dependent signaling and initiated by IL-1β in skin cancer. Above all, in order to turn on these proinflammatory gene signatures, carcinoma cells must firstly transform normal fibroblasts into CAFs [46]. Cyclooxygenase 2 (COX2), an important target of the proinflammatory gene signature and closely related to NF-κB, is expressed by CAFs and cancer cells [46, 116], and has been reported to acting like a mediator of tumor progression [117-119]. Genetically, altered neoplastic cells with neoantigens should be easily recognized and destroyed by the immune system. However, tumor stroma and CAFs actively participate in modulating the immune response to help neoplastic cells escape detection, in other words, supporting tumor progression [120-124]. CAFs possess the ability to regulate the immune system mainly through secretion to affect the function of the T and NK cells in the aberrant inflammatory pro-tumorigenic microenvironment [123-127].

CAFs promote cancer cell migration and metastasis

Cancer cell metastasis inevitably presents to the mid-late tumor development and results in the death of most patients, sadly, CAFs play an essential role during this process [39], indicating that CAFs are often correlated with poor clinical outcomes [128]. The most basic part of invasion and metastasis process is effective cross talks between neoplastic cells and CAFs, for instance, TGF-β response in CAFs led to secretion of IL-11, which in turn induces GP130/STAT3 signaling in neoplastic cells to turn on tumor initiation and speed metastasis [129]. There are two pathways, classic CCL5/CCR5 and noncanonical Wnt-planar cell polarity (PCP) pathway can also promote the metastatic process of breast cancer in the body [130, 131]. Another important consequence of CAF-mediated signaling on neoplastic cells is EMT, which is identified as a key process in the extravasation of tumors [132]. For example, pancreatic stellate cells, one subset of CAFs, were shown to increase metastasis by triggering EMT in co-cultured neoplastic cells or not [132]. Notch and COX2/NF-κB signaling have also been found to take part in acquiring and

maintaining the EMT phenotype [68, 110, 133].

Conclusion and Prospect

More and more studies emphasize prognostic impact of CAF-derived markers and biological characteristics. Generally speaking, gene expression profiling seemingly generate more persuasive results, with many studies demonstrated that CAF signatures add independent prognostic information to established markers. Furthermore, these studies made clear the potential CAF-characteristics that could be markers in different cancer types, but also some cancer type-specific features. Given the diversity of concerned signals and the complexity of communication cell types, it still remains challenging to fully find out the clinical markers of CAF that strongly relates to human cancers.

All along, the tumor is seen as the result of clonal proliferation, where tumor cells constantly experience screening and cloning that make up late-stage tumors so as to be the best candidate to avoid the host immune response and give therapies. Indeed, preneoplastic cell is initiating in this way, however, great changes then occurs in the tumor microenvironment, where various cell types, like neoplastic cell, CAFs and other stromal cells, develop a symbiotic relationship that promotes tumor growth. Thus, a selected population of CAFs and neoplastic cells result in different types and prognosis of tumor, which can lead to diverse survival and mortality rate of patients. It is significant for a neoplastic cell to obtain the capability to transform normal stromal cells into CAFs and through this influence to modulate the microenvironment. Hence, the communication between neoplastic cells and their microenvironment is important and gaining accumulated evidences to be the new target of tumor. Further insights in this process have the potential to reveal relevant discoveries with following clinical implications.

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