Multifaceted Tumor Stromal Fibroblasts

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Abstract Tumors are highly complex tissues composed of neoplastic cells and different kinds of stromal cells. Tumor stromal cells, especially fibroblasts, play important roles during the multistep development of tumors. In this review, the two-faced characteristics of tumor stromal fibroblasts are discussed in the light of our current knowledge. For one thing, fibroblasts act as an “inflammation regulator” by secretion of cytokines and regulation of tumor immunity; for another, they act as a “damage healer” for cure of wounds by remodeling extracellular matrix or taking a part in the “foreign body reaction”. Since the properties of fibroblasts are complicated, both aspects of fibroblasts for tumor development should be considered carefully in clinical studies to target cancer-associated fibroblasts.

Keywords Tumor stroma · Fibroblasts · Inflammation · Tissue damage

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Introduction

The solid tumors are heterogeneous with a reactive stroma accompanying cancer cells. Similar to the stromal cells in normal epithelial tissue, the tumor stromal cells include a variety of cell types, including immune cells such as macrophages, granulocytes, and T cells, as well as endothelial cells and fibroblasts [1–3].

Fibroblasts are a type of cells that synthesizes the extracellular matrix (ECM), functions as an important regulator in inflammation, and also plays critical roles in wound healing [4–8]. As tumors are recognized as “wounds that do not heal” [9], it is possible that fibroblasts are activated and play an important role also during tumor development. The notion that fibroblasts within the tumor stroma acquire an activated phenotype, similar to fibroblasts in wound healing, has been studied since the 1970s [10–12].

In this review, the behaviors of cancer-associated fibroblasts (CAFs) are artificially divided into two parts: as an “*inflammation regulator*” by secretion of cytokines, which promote cancer-associated inflammation, facilitate premalignant cell proliferation and contribute to angiogenesis [1, 2, 13]; as a “*damage healer*” for cure of wounds, which contain the capability of remodeling ECM, producing collagen or collagenase [14–16] (Fig. 1).

Activation of Fibroblasts in Tumor Stroma

Activated fibroblasts express α -smooth-muscle actin and have more outstretched appearance, leading to the term ‘myofibroblasts’, are found in healing wounds, and are also associated with cancers [16]. Activated fibroblasts get the abilities of proliferation, migration, remodeling ECM and secreting cytokines. But how do they perceive the injury and

Fig. 1 Multifaceted tumor stromal fibroblasts. In tumor microenvironment, fibroblasts are activated by the inflammatory cytokines and mechanical forces. The two-faced characteristics of activated fibroblasts in tumor are shown. For one side, activated fibroblasts act as an “inflammation regulator” by secretion of cytokines, e.g. CCL-2 and

IL-6 to promote cancer-related inflammation, FGF and HGF to accelerate premalignant cell proliferation and VEGF to promote angiogenesis. For another, activated fibroblasts act as a “damage healer” who is responsible for ECM remodeling and foreign body reaction

get activated? One mechanism is that the injury causes inflammation [17], and various of inflammatory cytokines produced during this process will stimulate fibroblasts to a reactive status. Another is the mechanical stimulus, which is driven by the damage of tissue integrity, namely broken of intercellular adhesions, cell contractility, and forces generated within the microenvironment [18]. When the tissue integrity is impaired by injury, fibroblasts will sense the change of the mechanical force and be activated via integrins, which are specialized focal adhesion sites and physically link the ECM to the cytoskeleton [19–21] (Fig. 1).

Inflammation and Fibroblast Activation

Chronic inflammation is a hallmark of cancer [22], a lot of factors in cancer-associated inflammation are reported to induce the activation of fibroblasts. Among them transforming growth factor beta (TGF- β) and platelet-derived growth factor (PDGF) are the most well investigated ones to activate fibroblasts. TGF- β has been reported to be capable of inducing fibroblasts to differentiate into activated smooth-muscle reactive fibroblasts, termed myofibroblasts; while PDGF is in favor of the proliferation of myofibroblasts [2, 23, 24]. Erez et al. have found that Interleukin (IL)-1 treatment on fibroblasts activated the nuclear factor (NF)- κ B signaling pathway and induced the expression of pro-inflammatory genes [25]. Similarly, hepatic stellate cells (HSCs), the main kind of fibroblasts in liver, were found sensitive to LPS derived from the intestinal tract, which resulted in the increased activation and survival rate of HSCs, and contributed to liver fibrosis and hepatocellular carcinoma [26, 27]. Surprisingly, cytokine signaling through JAK kinases is involved in generating actomyosin contractility in CAFs [28]. Except for cytokines, mitochondrial

oxidative stress can also facilitate cancer-associated fibroblasts to produce lactate and promote the tumor metabolism [29, 30].

Mechanical Forces and Fibroblast Activation

It was previously reported that primary cultured fibroblasts on petri dishes were activated “automatically” [31], and this phenomenon implies mechanical stimuli may acting as a driving force for myofibroblast differentiation. Recent studies have shown that mechanical force induces latent TGF- β activation and myofibroblast differentiation [20]. Fibroblasts were also reported to secrete higher levels of tumor necrosis factor (TNF)- α in response to compression [19]. Integrin-mediated activation of fibroblasts triggered by mechanical stress is also viewed as the major mechanism by several groups [20, 32]. It has been clearly reported that stiffened ECM, accompanied by collagen cross linking, facilitate epithelium invasion by promoting its focal adhesions and enhanced PI3 kinase (PI3K) activity [33]. However, it is still elusive about the exact mechanism for mechanically induced fibroblast activation in tumor microenvironment.

Stromal Fibroblasts in Tumor Initiation and Promotion

Many studies have demonstrated a direct involvement of activated fibroblasts in tumor initiation and promotion. By employing FSP-Cre; TGF- β RII^{flox/flox} mice, Bhowmick et al. have found that fibroblasts participated in tumor initiation by modulates the oncogenic potential of adjacent epithelia [34]. The loss of TGF- β responsiveness in fibroblasts resulted in intraepithelial neoplasia in prostate and invasive squamous cell carcinoma of the

forestomach in these mice, both associated with an increased abundance of stromal cells. The results show that TGF- β signaling in fibroblasts modulates the growth and oncogenic potential of adjacent epithelia in selected tissues. Other groups also found that genetic inactivation of Pten in stromal fibroblasts accelerated the initiation of mammary epithelial tumors [35, 36]. The characters of fibroblasts during tumor initiation and promotion are quite complicated and we will make some classifications in the following context, hoping this will be helpful to our understanding of the nature of this elusive stromal cell.

As an Inflammation Regulator

Fibroblasts are proved to promote tumor initiation, which relies on facilitating tumor-associated chronic inflammation. Our previous work has demonstrated that fibroblasts promoted skin carcinogenesis via maintaining chemokine (C-C motif) ligand (CCL)-2-mediated macrophage infiltration and chronic inflammation. The inflammatory reaction was impaired after the selective depletion of proliferating fibroblasts in the skin of FSP-TK transgenic mice. This led to reduced local CCL-2 concentration and impaired macrophage infiltration. As a result of down-regulated inflammation, the incidence of skin tumor was reduced [37]. In a spontaneous tumor model of K14-HPV16 mice, the inflammatory signature was already activated in CAFs isolated from the initial hyperplastic stage in multistep skin tumorigenesis. CAFs from this pathway promoted macrophage recruitment, neovascularization, and tumor growth in a NF- κ B signaling-dependent way [38]. It was also reported that overexpression of TGF- β and/or hepatocyte growth factor in mouse fibroblasts induced the initiation of breast cancer within the normal human epithelium [39].

CAFs helped tumor cells to escape from immune-mediated rejection by recruiting myeloid-derived suppressor cells (MDSCs), T regulatory cells (Tregs) and promoting Th2 polarization of the tumor microenvironment [40]. Haniffa et al. showed that IFN- γ -stimulated fibroblasts can also suppress allogeneic T cell proliferation by upregulated indoleamine 2,3-dioxygenase and accelerated tryptophan metabolism in fibroblasts. Kraman et al. found that ablation of fibroblasts in the established tumor aroused adaptive tumor immunity involving IFN- γ and TNF- α [41]. These indicate that fibroblasts may have the immunosuppressive properties [42].

As a Damage Healer

Lots of tumor inducing agents, such as microorganisms or many kinds of carcinogens as well as growing tumors will produce tissue damage. Back to 80 years ago, G. Friedrich

[43] and R. Rössle [44] found in a series of patients (frequently smokers) that lung carcinomas grew at sites of scars. They suggested that scars predisposed to cancer be termed *Narbenkrebs* (scar cancer). Scars within the carcinomas had an immature phenotype (increased collagen type 3 content) indicative for an early stage of fibrotic process, whereas scars at some distance from the neoplasm revealed a mature, late stage of the fibrotic process (decreased type 3 and increased type 1 and 4 collagen) [45].

Polycyclic aromatic hydrocarbons (PAH) are a group of environmental pollutants some of which (e.g. Benzo(a)pyrene) have been shown to cause human cancers [46]. Methylcholanthrene (MCA), another PAH molecule, has been widely used in mice to study chemical induced carcinogenesis [47–49]. Injection of MCA/oil induced a series of local reactions against the carcinogen emulsion [50], including the infiltration of inflammatory cells, the recruitment and proliferation of fibroblasts and finally the encapsulation of MCA by ECM which is called “foreign body reaction” [51]. The “foreign body reaction” is characterized by encapsulation of foreign materials. It is phylogenetically one of the oldest defense mechanisms predating adaptive immunity, a major protective mechanism in invertebrates and usually observed as a pathological reaction in humans [14]. Further investigation shows that treatment with collagenase led to destruction of the MCA encapsulation and then a rapid tumor development in the long term “tumor free” mice. Fibroblasts protected epithelial cells from DNA damage, epithelial malignancy occurred in the absence of local activating fibroblasts (unpublished data). Besides chemical carcinogen, it appears that fibroblasts-derived fibrotic capsule is also able to enclose neoplasm. In clinical cases, mainly in hepatocellular carcinomas and mammary carcinomas, the presence of a capsule around neoplastic cells is recognized as an indication of good prognosis [52–54]. Encapsulated tumors have low growth rate, or none at all. Once the capsule is disrupted, growth of tumor resumes [55, 56].

Our results indicate that inflammation and scarring, both suspected to contribute to malignancy, prevent cancer in certain situations [14]. Whether scar cancer results from inefficient encapsulation of carcinogen is not yet known, however, benzo(a)pyrene was detected in substantial amounts in lung tissues of smokers [45, 57] and former smokers retain a substantial risk of developing lung cancer [58].

Stromal Fibroblasts in Tumor Progression

Co-injection of CAFs with tumor cells has already well demonstrated the tumor-promoting potential of fibroblasts nearly 20 years ago [59], and the refined mechanism of fibroblasts influence on tumor growth, angiogenesis, and metastasis has recently been investigated more intensively

[60–62]. As reviewing the CAF-associated proteins which were reported to influence the tumor development in the past 10 years, we found most of them could be divided into two parts: immune-derived, e.g. chemokine (C-X-C motif) ligand (CXCL)-14 [63], CXCL-12 [62], IL-1 [64], and IL-6 [65, 66], and conventional activated fibroblast-derived, e.g. hyaluronidases [67, 68] and matrix metalloproteinase (MMPs). So, in this section of tumor progression, we will also discuss the fibroblasts in two parts which mentioned above.

As an Inflammation Regulator

CAFs promote tumor progression through producing a cancer cell-favorable inflammatory microenvironment. Fibroblast-derived cytokines such as IL-1 and CXCL-14 also have been shown to play vital roles as immune modulators [63, 64]. CAF-derived CXCL-12 was shown to be responsible for recruiting endothelial progenitor cells to breast tumors, which stimulated tumor blood vessel growth [62]. Vascular endothelial growth factor (VEGF) has been reported as an important tumor angiogenesis factor in many studies, which can be secreted by tumor cells, macrophages, mast cells and fibroblasts [69]. Studies by Fukumura et al. have shown that VEGF promoter activity is high in stromal fibroblasts in the transplant and spontaneous mammary tumor models [70], indicating that fibroblasts may be the major producer of VEGF and therefore be crucial for tumor angiogenesis in specific tumor models. Consistent with that, our study also shows that stromal fibroblasts express VEGF at both the RNA and protein levels. Further studies showed that fibroblasts promoted tumor growth when coinjected with tumor cells. However, the presence of IFN- γ , well known to promote immunologically induced rejection of transplanted tumor cells [71], significantly impaired the ability of fibroblasts to promote tumor growth due to a reduced angiogenesis. The mechanism relied mainly on the IFN- γ -mediated down-regulation of VEGF production by fibroblasts [13]. Importantly, PDGF-C from fibroblast may rescue angiogenesis in some anti-VEGF resistant tumors [72]. Several factors secreted by fibroblasts, such as epidermal growth factor, hepatocyte growth factor, insulin-like growth factor and IL-6, can stimulate cancer cell proliferation, maintain their survival and enhance their invasive properties [24, 65].

As a Damage Healer

Fibroblasts decorate the tumor microenvironment through direct cell-to-cell contacts and secretion of MMPs, tissue inhibitors of metalloproteinase (TIMPs), and ECM components, such as collagen and hyaluronan [73]. It was reported that tumor cells can get signals from the former enzymes

and their targets, be stimulated to get epithelial–mesenchymal transition, migrate along tracks made of ECM collagen fibers, and then cross tissue boundaries and escape the primary tumor site, and finally achieve the metastasis with the help of fibroblasts to creating a niche [28, 74–78]. Actually, CAF derived MMP-1, 2, 3, 9, 11, 13, 14, 19, ADAMT-5 and TIMP-1, 2, 3 are reported involving in angiogenesis and the proliferation, adhesion, migration, differentiation and apoptosis of tumor cells or stromal cells [75].

The biomechanical remodeling of the microenvironment by fibroblasts is also important for the progression of tumor. Goetz et al. found Caveolin-1 positive fibroblasts are enriched in stroma of human breast, kidney and colon carcinoma and melanoma metastasis. Due to decreased CAF contractility, Caveolin-1-deficient mice got disorganized stromal tissue architecture [18]. It was also reported that cytokine signaling through the receptor subunit GP130-IL6ST generated contractile force in stromal fibroblasts to remodel the ECM and promote tumor invasion [28]. Similar to “foreign body reaction”, fibroblasts repressed the early stages of tumor progression by facilitating the formation of gap junctions between activated fibroblasts and thereby exerting contact inhibition on cancer cells [79, 80].

Further Discussion

Though the role of tumor stromal fibroblasts has been divided into two parts in this review artificially, to some extent, usually both sides of the dual characters of fibroblasts could influence each other and contribute to the final outcome of tumor in one given stroma. As discussed above, the “foreign body reaction” towards MCA is dependent on IFN- γ , a pleiotropic inflammatory cytokine [14]. For another example, ECM degradation will promote release of growth factors bound to the ECM [81].

It should be noticed that the specific roles of fibroblasts are microenvironment-dependent. It has been reported that normal human fibroblasts at different locations in the body should be considered as distinct differentiated cell types [82], which indicates the existence of different subsets of CAFs in different tumors. But whether different subsets of fibroblasts exist in one specific tumor type is still largely unknown. In conclusion, the role of fibroblasts during tumor development is doubtless but intricate. And many studies have shown their therapeutic opportunities by targeting CAF-derived pro-tumorigenic factors or interfering with the recruitment of CAFs [3, 72, 83, 84]. However, the ideal therapeutic methods should take account of the two-faced characteristics of fibroblasts in tumor stroma and remove cancer-promoting properties of fibroblasts but retain cancer-resistant ones.

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Conflict of interest The authors declare that they have no conflict of interest.

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