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Research Article

Ambiguity of Cancer Associated Fibroblasts: Protumorigenic or Antitumorigenic

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Abstract

Tumor microenvironment today has at least equally if not more than the tumor itself succeeded in garnering attention due to its key roles in affecting the cancer cells by the non-mutant cells. The cell-to-cell interactions by itself play a major role in the development and progression of cancer. Cancer associated fibroblasts (CAFs), a key component of the tumor microenvironment have sparked interest due to their herculean task of modulating cancer metastasis, also including matrix deposition and remodelling and tumor mechanistics, even though, till today, a lacuna exists in the understanding. CAFs have also been known to affect drug access and therapy responses. A possibility of counteracting CAFs can also prove as an armor in the fight against the dreaded disease cancer. However, there is an underlying hurdle as it is yet to be established whether its protumorigenic capabilities weigh down the antitumorigenic effects. This delinquent situation is largely affected by the inability to find the specific markers of these cell types. The present review deals with the identification, generation, functionality and challenges associated with the use of CAFs in depth.

Keywords: Tumor microenvironment; Cancer associated fibroblasts; Fibroblasts; Cancer

Introduction to CAFs

The tumor microenvironment is a multicellular system in which the cells in the extracellular matrix interact closely with the tumor cells [1,2]. This cross-talk may be having either a positive or a negative stimulus. These cells are mainly from the mesenchyme, endothelium, and hematopoietic origin influencing the process of tumorigenesis. One of the major components in the stromal environment are the CAFs. Conventionally, cells presenting with an elongated morphology and having a negative expression for epithelial, endothelial, and leukocyte markers qualify as CAFs. This is further potentiated by the lack of mutations found in the cancer cells [1]. However, cancer cells undergoing Epithelial-to-Mesenchymal Transition (EMT) have been excluded from this category. In the Banbury Center meeting at Cold Spring Harbor Laboratory, New York, USA in 2019, the experts discussed the current understanding of CAF biology and looked into the fundamental properties of CAFs and its applications [1]. Fibroblasts are generally quiescent which get activated in a wound-healing response and CAFs can be effectively put to use in anti-cancer immunotherapy [3-5]. It remains to be ascertained as to whether the common and specific traits of CAFs have been preserved across generations and lineages [6-8].

Origin, Evolution and Generation

The primitive mesenchyme developed from the mesoderm after the process of gastrulation along with a subset of fibroblasts derived from the neural crest, as part of the ectoderm [9]. There is mounting evidence which shows that the origin of CAFs lies in the resident fibroblasts, dedifferentiating mature cells, and also from the tumor cells [10]. This adds to the woes in establishing and characterizing the fibroblasts which are recognized on the basis of their morphology and position and lack of markers like epithelial cells, endothelial cells and leukocytes. However, markers for its subtypes are typically being used including fibroblast activation protein (FAP) and alpha-smooth muscle actin (alpha SMA) [11-

12]. Alpha SMA is typically expressed when the TGF beta through SMAD-dependent and independent pathways activates fibroblasts into CAFs [13]. Another important player secreted from the stromal and tumor cells is the transforming growth factor beta 1 (TGF- beta1) It has also been documented that the fibroblasts affect the local epithelial stem cell behavior, promote angiogenesis and harmonize the functioning of the immune system thereby promoting immune tolerance and also maintain the metabolic homeostasis. This prompts us in establishing the diverse roles of fibroblasts during key processes like normal tissue homeostasis and repair [14-19]. Additionally, CAFs can also be derived from the mesenchymal stromal cells expressing markers like alpha SMA.

In order to partially counter the problem, laboratories are increasingly and efficiently looking into the step-by-step changes leading to the formation of a cancer cell from a normal healthy cell and typically, the fibroblastic components involved in the transformation. In this context, the concept of stromatogenesis seems to have evolved in line with tumorigenesis. It is believed that the malignant transformation is also accompanied by the expansion of stromal fibroblasts. The varied areas of CAFs is being extensively studied with reference to the entire cancer spectrum. Figure 1 shows the pathology of CAFs in the different cancers.

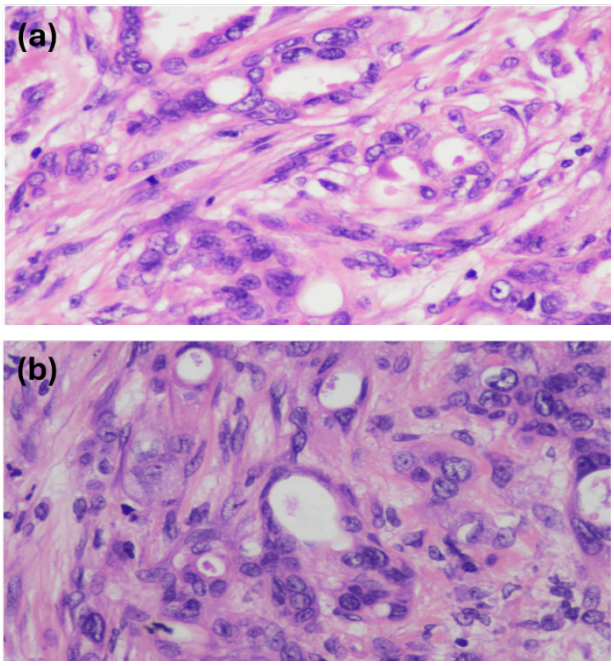

Figure 1: Representative images of cancer associated fibroblasts (CAFs) in (a) pancreas (b) breast.

Mechanisms of Activation

The routine physiological roles played by fibroblasts greatly impact the key behavior and functioning of the CAFs. The normal fibroblasts can lead to the activation of CAFs by a variety of mechanisms as shown in Figure 2. These include the contact signals (Notch and Eph-ephrins), extracellular matrix (stiffness and composition), DNA damage (chemotherapy and radiotherapy), Transforming Growth Factor- beta (TGF- beta), physiological stress (reactive oxygen species and disrupted metabolism), inflammatory signals [interleukins (IL) 1 & 6, Tumour Necrosis Factor (TNF), Receptor Tyrosine Kinase (RTK) ligands [platelet derived growth factor (PDGF) and Fibroblast Growth Factor (FGF). TGF- beta drives the expression of alpha SMA and increase the activity of contractile cytoskeletons [12,20-22]. In pancreatic cancer, the proliferation of CAFs is increased by vitamins A and D which increase the activation of CAFs into a pro-tumorigenic state [16,23,24]. This is achieved typically by the SMAD signaling pathway or the renin-angiotensin mechanism. Double-stranded breaks in DNA can stimulate the production of IL-6 and the TGFβ family ligand activin A [25,26]. Activation of signaling pathways including NF kappa B and ERK pathways help in the generation of CAFs from the resident fibroblasts along with the other factors secreted from the tumor cells [27-30]. Inflammatory modulators like interleukins (typically 1 and 6) also promote the activation of CAF working alongside NF kappa B and signal transducer and activator of STAT transcription factors [31,32]. CAF activation is also prompted by the involvement of JAK-STAT signaling and alterations in chromatin modification typically histone acetylation alterations [33,34]. Generation of reactive oxygen species and activation of hypoxia inducible factor (HIF 1alpha) also drive the activation of resident fibroblasts to CAFs [35-37].

Key Roles

Generation of CAFs and in turn its functioning is greatly dependent on its origin. Overall, they present as a very heterogenous population of cells [38]. A clear definition of CAF subpopulations and linkage with their functionality till today remains a challenge, chiefly due to the lack of specific biological markers. CAFs generated from the tumor itself or the tumor microenvironment in turn affect its functionality as being pro or ani-tumorigenic (Figure 2). In general, cancer therapies are also known to initiate the generation of CAFs which is an anti-tumorigenic property of CAFs. However, the catch remains that it can lead to therapy resistance. CAFs play a significant role in matrix remodeling which typically includes matrix crosslinking, proteolysis, and matrix production and remodeling. It also mediated the immune crosstalk by activation of TGF beta, IL-6 production, CXCL12, and CCL2 production. Metabolic effects which included lactate, alanine, and aspartate shuttling and amino acid depletion, and soluble secreted factors including VEGF, exosomes, and HGF and GAS6 production are also carried out by the CAFs. Matrix remodeling and immune crosstalk in turn regulate the cancer

cell invasion and the interference with T cell functioning, respectively. Macrophage and endothelial crosstalk are also delimited by the soluble secreted factors. Metabolic effects on the other hand, greatly regulate the growth of the tumor cells. CAFs also secrete large volumes of growth factors, cytokines, and exosomes. The functional heterogeneity of the CAFs has been greatly identified and defined in a variety of cancers. In the cancers of the breast and pancreas, CAFs are typically associated with angiogenesis, metastasis, immunosuppression, angiogenesis, migration, invasion, and chemoresistance whereas in oral squamous cell carcinoma, it is typically associated with invasion, immunosuppression, and migration [39-44].

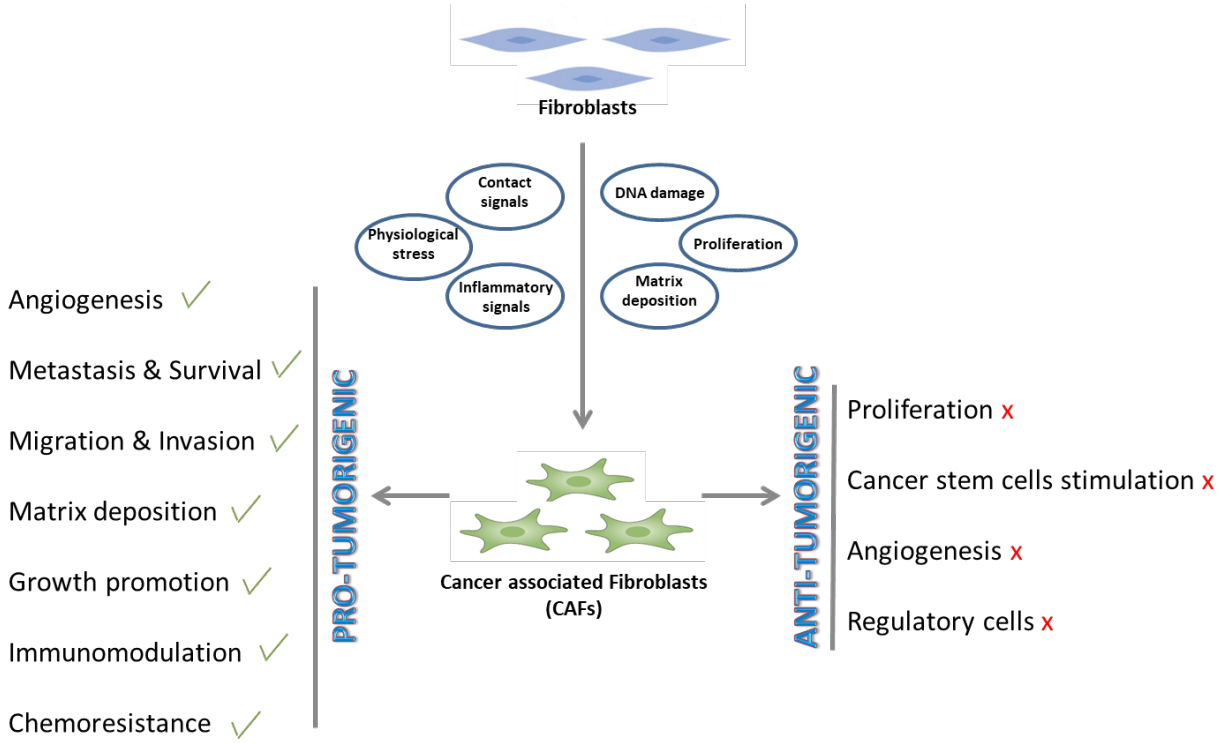

Figure 2: Mechanisms of activation of CAFs.

Also, in contrast to the pro-tumorigenic functions, CAFs are also involved in anti-tumorogenicity. An inhibition of factors including VEGF, CXCL-12, and IL-8 has been observed, hence inhibiting pathways affecting the growth of tumors, immunosuppression, and angiogenesis [45,46]. This is typically achieved by increased activation of Shh signaling by CAFs expressing alpha SMA. An inhibition of tumor cell proliferation has also been reported in prostatic adenocarcinomas and sarcomas due to increased production of TGF beta, and Tumor necrosis factor alpha [47-50]. In tumors of the intestine, tumor growth and angiogenesis is checked by NF kappa B signaling in CAFs [51].

Challenges

Despite the benefits of the CAFs as reported in the trials, the key challenge still remains with its mode of usage in combating cancer. One way can be by using strategies to directly target the CAFs and eliminating them. There still remains a dearth of markers in identifying the CAFs and hence the delay exists in eliminating them. A protein, alpha FAP which is expressed in greater than 75% CAFs has been routinely targeted [52]. Chimeric antigen receptor T cells and monoclonal antibodies are being explored in tumors of breast, lung and colon. CAR-T cells are particularly being looked into with the advantage of increased efficacy and little/ no toxicity. Growth factors including platelet derived and tumor growth factors have been widely linked to the activation of CAFs. Its activation has also been linked to the epigenetic changes involving regulatory miRNAs. The identification of these strategies further provides the opportunity and evidence to directly target these CAFs [53]. Apart from this strategy, another way of targeting CAFs can be done by targeting the proteins secreted by CAFs or also by using the CAFs to deliver the anti-tumor molecules. Table 1 lists the drugs involved and their underlying mechanisms in directly targeting the CAFs.

Name of drug	Phase of trial	Cancer site	Mechanism	Reference
Sibrotuzumab	I	NSCLC, Melanoma, Pancreas	Monoclonal antibody against alphaFAP	[54-56]
TRC-105	II	Neuroblastoma	Monoclonal antibody against endoglin	[57]
Calcipotriol	II	Pancreas	Vitamin D receptor activation and stellate cell deactivation	[58]
Ruxolitinib	I & II	Pancreas, Lung	JAK inhibitor	[59-61]
Losartan	II	Pancreas, Melanoma	Angiotensin receptors blocker	[62,63]
Bevacizumab, FOLFIRINOX	II	Pancreas, Colorectum	Neutralization of VEGF	[64,65]
Abraxane, Gemcitabine	II	Pancreas	Decreases type I collagen production and secretion of CXCL10 and IL6	[60]
Nab-paclitaxel, Atezolizumab	III	Breast, Lung	Monoclonal antibody against PDL1	[66-68]
Plerixafor	Murine model	Prostate, Pancreas	Small molecule inhibitor for CXCR4	[69-71]
Galunisertib	Ib/ II	Pancreas	Small molecule targeting TGF beta receptor	[72]
Defactinib	I/II	Pancreas, Ovary	Small molecule inhibitor reducing signaling downstream of integrins	[73]
Saridegib, Vismodegib	I/II	Breast, Prostate, Ovary, Lung, Pancreas, Stomach, etc.	Small molecule inhibitor reducing CAF activation	[74,75]
Dasatinib	I/II	Breast, Prostate, Ovarian, Endometrium	Tyrosine kinase inhibitors	[76]
Tasisulam	I/II	Breast, Ovarian, Lung, Kidney	TGF beta receptor kinase inhibitors	[76]
Crenolanib	I/II	Gastrointestinal tumors	PDGFR tyrosine kinase inhibitors	[76]
Other drugs e.g. curcumin	I/II	Breast, Prostate, Lung, Head and Neck, Brain, etc.	Miscellaneous	[76]

NSCLC: Non-Small Cell Lung Cancer; FAP: Fibroblast Activation Protein; JAK: Janus Kinase; VEGF: Vascular Endothelial Growth Factor; CXCL: Chemokine (C-X-C motif) Ligand; IL: Interleukin; PDL1: Programmed Cell Death Ligand 1; CXCR: C-X-C Chemokine Receptor; TGF: Transforming Growth Factor; CAF: Cancer Associated Fibroblasts; PDGFR: Platelet-Derived Growth Factor Receptor

Table 1: Drugs involved in directly targeting the cancer associated fibroblasts.

Points to ponder

In the times to come, both the pro and anti-tumorigenic properties of the CAFs can be fully utilized for their use in cancer-directed therapies, especially with the improved understanding of their heterogeneity. Also, targeting CAFs and their secretome can also greatly help in targeting the tumor microenvironment without directly affecting the tumor cells as the tumors are residing in a typically fibroblast-rich microenvironment. Clinical trials evaluating the same should be very careful and vigilant in reporting the results especially taking into consideration the morphology, pathology, and functionality of these fibroblasts. How these fibroblasts depict themselves greatly drives the functionality and their possible usage in future therapies. A very comprehensive and robust nomenclature capturing these findings

should be adopted and put into practice universally and evolving a common nomenclature across the cancer types can greatly give the required impetus in this area. Spatial transcriptomics can be effectively put to use in order to address the problem adequately by integrating histopathological annotation and high-throughput sequencing in a unified framework with the objective of identifying the phenotypic heterogeneity and functional diversity of CAFs.

Statements and Declarations

Competing Interests: None to disclose

Author Contributions

RT: Conceptualization, Writing the review

AM: Conceptualization, Finalizing the review

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