Cancer Associated Fibroblasts (CAFS) and their Indispensable Role in Tumor Microenvironment: An Update

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Abstract

Cancer-associated fibroblasts commonly known as CAFs which have a modified phenotype as compared to normal fibroblasts are exclusively present in the tumor microenvironment surrounding the tumor mass. They play inevitable roles in tumor initiation, progression, invasion, and metastasis. The constant cross-talk present in between the cancer cells and CAFs is responsible for the maintenance of such a malignant environment. Thus,they may prove to be efficient targets in the field of cancer therapeutics which may yield excellent results. This review throws light upon their much evident roles in carcinogenesis as well as how the mechanisms driven by them may be targeted in therapeutic interventions.

Keywords: *Cancer-associated fibroblasts, CAFs, tumor microenvironment, tumor stroma.*

Introduction

A tumor mass is composed of malignant epithelial cells as well as groups of nonmalignant cells. These non-malignant or non-cancerous groups of cells include fibroblasts and myofibroblasts, endothelial cells and lymphatic networks, pericytes, immune regulatory cells, and cytokines in the extracellular matrix (ECM) (1). This mass of stromal cells along with the ECM constitutes the tumor microenvironment. Tumor microenvironment, in turn, governs the tumor progression through stages of initiation, progression, and metastasis (2).

One such subpopulation of cells is of the cancer-associated fibroblasts (CAFs) which is a group of fibroblasts having a modified phenotype of myofibroblasts. These are the same as the myofibroblasts which are transiently present during fibrosis and wound healing, the only distinguishing characteristic feature is that they are present and remain almost activated throughout, at the site of the tumor (2). An ideal microenvironment is maintained by these CAFs and they also undergo the required biological and morphological changes for tumorigenesis and its progression. These can serve as essential therapeutic targets for the treatment of cancer.(3, 4)

This review highlights the recent trends associated with CAFs and aims towards a better understanding of their role in the advancement of tumors. Additionally, the interaction between the malignant cells and tumor microenvironment for the scope of identification and development of potential anti-cancer therapy has also been analyzed.

Distinguishing Nature of CAFs: "The origin of CAFs comes from a variety of cells, majorly from fibroblasts while other sources include epithelial cells, endothelial cells, adipocytes, pericytes, or mesenchymal stem cells[1-5] CAFs are identified in the stroma using specific molecular markers and also distinguished easily as large spindle-shaped cells often showing resemblance to myofilaments of smooth muscle.[6] The biomarker most commonly used is α-smooth muscle actin.[7] Some

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of the other biomarkers less commonly expressed by these activated fibroblasts that have been detected with the help of immunohistochemistry includes FAPα (fibroblast activation protein α) a cytomembrane protein, vimentin, PDGF receptors α and β, podoplanin-a, S-100, FSP-1 (fibroblast specific protein), and IGFBP7 (Insulin-like growth factor-binding protein).[8,9]. Moreover, with techniques like microarray gene-expression analysis, there has been a better understanding of the nature of CAFs and more knowledge about their role in oncology has been gained. Many studies done on paired CAFs and normal fibroblast cell lines have identified a total of 46 differentially expressed genes which further encoded for paracrine factors released in the tumor microenvironment. The genes expressed were regulated by the TGF-β signaling pathway, and some of them include intercellular-adhesion molecule 1 (ICAM1), THBS2, MME, OXTR, PDE3B, B3GALT2, EVI2B, COL14A1, GAL, MCTP2 and Integrin α11 which were used to form a prognostic signature of CAFs in non-small cell lung cancer (NSCLC).[10,11]

Fibroblast Activation Induced by Tumor: Whenever there is metastasis of tumor cells to a different organ, natural fibroblasts are reinforced by them into the tumor mass. Once reinforced, they undergo phenotypic activation into cancer-associated fibroblasts under the influence of genetic as well as epigenetic changes that are either self-regulated or regulated by tumor cells themselves. Nonetheless, the precise mechanism of this activation is still not clear.[12]

"TGF-β, EGF, PDGF, FGF2, CXCL12(C-X-C motif chemokine ligand 12) are some of the chemokines involved in the activation of these fibroblasts which are secreted by the cancer cells and other stromal cellswhile other factors involved in their activation comprises of cell-cell communication with adhesion molecules like ICAM1 and vascular-cell adhesion molecule 1.[13,14]"

"A large group of miRNAs often regulate the conversion of natural fibroblasts into CAFs by undergoing upregulation or down regulation. Various differentially expressed CAFs have been listed in figure 1.[15-18]"

A, Upregulated miRNAs			
Author, year	miRNA	Cancer type	Target gene
Mitra *et al*, 2012	miR-155	Ovarian	
Zhao *et al*, 2012	miR-266, miR-221-3p, miR-221-5p, miR-31-3p	Breast	ETS2
Enkelmann *et al*, 2011	miR-16, miR-320	Bladder	
Aprelikova *et al*, 2014	miR-29b, miR-146a miR-503	Endometrial	
Wang *et al*, 2013	miR-138, miR-210, miR-99a	Colorectal	
Bronisz *et al*, 2012	miR-320	Breast	
B, Downregulated miRNAs			
Mitra *et al*, 2012	miR-31	Ovarian	SATB2
Mitra *et al*, 2012	miR-214	Ovarian	CCL5
Zhao *et al*, 2012	miR-205, miR-200c, miR-200b, miR-141, miR-101, miR-342-3p, Let-7g	Breast	ZEB1/SIP1
Enkelmann *et al*, 2011	miR-143, miR-145	Bladder	
Yu *et al*, 2010	miR-17/20	Breast	IL-8, CXCL1, CK8, α-ENO
Aprelikova *et al*, 2014	miR-31	Endometrial	SATB2
Wang *et al*, 2013	miR-29b, miR-494, miR-126	Colorectal	
Verghese *et al*, 2013	miR-26b	Breast	TNKS1BP1, CPSF7, COL12A1
Mongiat *et al*, 2010	miR-15, miR-16	Prostate	

Figure 1: Regulation of miRNAs in CAFS

Initiation of Tumor Growth, Angiogenesis, Metastasis and Chemoresistance by CAFS:

(a) Tumor growth: Aconstant interplay between the abnormal increase in malignant cells and alterations in the tumor microenvironment is the probable cause for tumor growth and the induction signals for this neoplastic initiation are usually derived from CAFs.[19,20]

A variety of cytokines have been known to be produced by these CAFs that alter the malignant biological nature. These mostly include classical growth factors, EGF, hepatocyte growth factor (HGF), novel CAF-secreted proteins [secreted frizzled-related protein 1, and IGF like family member (IGF) 1 and 2], and membrane molecules (integrin α11 and syndecan-1) which possess either the ability to upgrade the migratory and invasive properties of tumors or directly and indirectly induce their growth as well as survival.[21]"

Previous studies have demonstrated that chemokines secreted by CAFs into the microenvironment allow for the recruitment of bone marrow-derived cells (BMCs) and immune cells. In oral squamous cell carcinoma (OSCC), CCL2 expression in CAFs is upregulated, promoting the production of endogenous reactive oxygen species (ROS) in oral cancer cells (OCCs). Subsequently, ROS induces the expression of cell cycle regulatory proteins in OCCs, and advocates OCC proliferation, migration, and invasion. Altogether, these chemokines and cytokines create a suitable microenvironment allowing for the proliferation and metastasis of cancer cells.[22-24]"

(b) Activation of tumor angiogenesis by CAFs: There is an increased production of vascular endothelial growth factor (VEGF) in the tumor microenvironment. The increased levels of VEGF are responsible for tumor angiogenesis and lymphangiogenesis. The main source of VEGF is the CAFs through the activation of the PDGF receptor pathway. Additionally, the induction of BMC's by PDGF leads to the formation of endothelial channels. Endothelial stability is then maintained by the entry of pericytes along the walls of the vessels by the action of subunit B of PDGF. Therefore, promoting angiogenesis.[25-27]

(c) Nagasaki *et al* reported that cancer cells stimulate the secretion of IL-6 from fibroblasts, subsequently inducing tumor angiogenesis. IL-6R neutralization antibody inhibited IL-6 signaling and tumor angiogenesis by inhibiting the interaction between the cancer, and stroma. This finding suggests that IL-6 is a novel target for anti-angiogenesis therapy.[28]

(d) Role of CAFs in mediating Tumor metastasis: There is much evidence about the metastatic role of CAFs in tumor genesis but their role in lymphatic and distant metastasis is still doubtful. The transformed phenotype (mesenchymal) of these CAFs is considered to increase the metastatic potential of the tumor cells as compared to the normal fibroblasts of epithelial origin which restrict metastasis.[29-31]

(e) YAP, regarded as the trademark feature of CAFs is a transcription factor that plays evident parts in matrix reinforcement, invasion as well as angiogenesis by controlling distinct cytoskeletal proteins (anillin, myosin, etc.) and also via the production of inflammatory cytokines (NF-KappaB) thus leading to carcinogenesis. Additionally, CXCL12 and IGF1 are also generated by CAFs which in turn initiate the AKT signaling pathway. Tumor cells in this CXCL-2 enriched microenvironment within bone marrow further initiate metastasis (34).Evidence about the reduced expression of miR-148a amongst CAFs and the resultant increase in the WNT10B gene because of activation of the Wnt activity leading to elevated migration of endometrial cancer cells has also been reported (40). Other miRNA's involved in migration and invasion includes reduced levels of miR-26b and miR-320 in human breast cancer, downregulated miR-15 and miR-16 in prostate cancer.[32-36]

(f) Resistance to anti-cancer therapy induced by CAFs: The development of chemoresistance is consideredto be a rare feature of CAFs and they can be easily targeted for potential anti-cancer therapies but a contradicting part is played by the fibroblasts in helping the tumor cells bypass these treatment modalities as explained under.[37]

(i) "PDGF: Solid tumors exhibit the property of an elevated interstitial fluid pressure that is IFP in the centermost portion as compared to the remaining portion of the tumor tissue. As a result, the drug infiltration into the core of tumor tissue is cut down and the probability of survival of these malignant cells is increased. Thus, the chemotherapeutic regimens are designed to reduce this IFP and increase

the drug penetration up to the center of the tumor. One such regimen includes targeting the tyrosine kinase receptors and PDGF present in different malignancies like STI571 in anaplastic thyroid carcinoma, targeting of which causes a reduction in IFP and elevated Taxol intake and reduced tumor growth.[38-41]"

(ii) **"HGF:** Data demonstrates that the presence of fibroblasts secreting HGF confers resistance to therapy. Besides, HGF can activate MET, which is expressed on cancer-initiating cells (CICs) through paracrine signaling.[42] This can sustain typical CIC properties, including long-term self-renewal, ultimately leading to resistance to anti-EGFR therapy. Subsequently, there is the restoration of cell proliferation and rescuing of cells from G_1 phase arrest, and apoptosis through restimulation of the MAPK and AKT signaling pathways.[43] Notably, this effect is inhibited by suppressing MET activation with PHA-665752, a highly specific MET kinase inhibitor, or by knocking down MET expression using RNA interference."

(iii) **"Chemokines:** Many chemokines present in the tumor stroma play an evident role in the maintenance of chemoresistance. One such chemokine is CCL2, recruited by immune cells into the tumor microenvironment and is responsible for resistance against many drugs. Moreover on treatment with CCL2 inhibitor, there is enhancement of the anti-tumor potency of paclitaxel and carboplatin therapy. CAFs can induce CCL2 production through signal transducer and activator of transcription 3 (STAT3) phosphorylation, and in turn, CAF-derived CCL2 promotes cancer progression by regulating cancer stem cells through activation of the Notch signaling pathway (46). Hence, chemokines, including CXCL12, may act as promising targets for cancer therapy, alone or in combination with other cytotoxic drugs.[45,46]

(iv) **"Interleukin family:** An important inflammatory cytokine mainly secreted by CAFs is IL-6 which is involved in growth and invasion of tumor cells through activation of STAT3. Thus, IL-6 is responsible for the survival of tumor cells and also induces their relapse.[47]

(v) **"Other factors:** Some of the other fibroblast-derived proteins like WNT16B and B1 which are secreted in the tumor microenvironment are responsible for conferring chemoresistance against many drugs. WNT16B reduces apoptosis induced by chemotherapy drugs and thus targeting WNT16B may reverse chemoresistance. Group protein B1 present in the tumor microenvironment, performs paracrine signaling on neighboring cancer cells, which has been suggested to induce chemoresistance in breast cancer.[48]"

Loop of Interaction: A constant communication present between the malignant cells and CAFs in the tumor stroma is responsible for the development of a malignant microenvironment as well as the advancement of cancer. This interplay between the two components is initiated by a complementary signaling activity of stromal components such as cytokines and other factors of the extracellular matrix. Platelet-derived growth factor (PDGF) is secreted by neoplastic cells which in turn governs an increase in the population of fibroblasts and further production of IGF I and II. These IGFs initiate tumor cell proliferation as well as the production of more PDGF.[49](49).

Production of matrix metalloproteinases (MMPs) by CAFs further accelerates the invasive potential by destroying the ECM (50), further resulting in secretion of growth factors from fibroblasts like HGF, keratinocyte growth factor, IGF-1 and IGF-2 which also stimulate proliferation of tumor cells.[51-53] Thus, these positive feedback loops governed by signaling pathways result in boost up of signaling molecules, elevated numbers of tumor cells and as a consequence resistance to tumor therapy. A better understanding of these processes may prove to be helpful in the evolution of more targeted therapies that may inhibit such feedback looping mechanisms."

Suppression of the Feedback Loop: A Potential Target in Cancer Therapeutics: Such techniques targeting the association between fibroblasts and tumor cells are yet to be exploited practically, but apparently, their definite benefits cannot be ignored. This idea of targeting the loop mechanism can be implemented either by direct suppression of fibroblastic markers or by inhibition of CAF related paracrine growth factor signals.

(a) **"Direct suppression of fibroblastic markers:** Targeting the FAP membrane protein which is extensively expressed on CAFs can suppress the growth of tumor cells.[54] FAP protein induces tumor growth and division and therefore targeting the associated antibodies like FAP5-DM1 inhibits

tumor growth in xenograft models of head and neck cancer in vivo.[55]"

(b) "Inhibiting paracrine signaling of fibroblasts: This involves targeting the various pathways like PDGFR, VEGFR, FGFR which further inhibits MAPK and Akt signaling pathways in endothelial cells and prevents angiogenesis as well as initiates apoptosis. Additionally, targeting the HGF/MET signaling pathway has proven to be of therapeutic value in various cancers. Furthermore, suppressing the TGF-β pathway which is responsible for myofibroblast differentiation, has resulted in a considerable reduction of tumor growth and lastly the use of matrix metalloproteinase inhibitors (MMPIs) as anti-cancer drugs is still undergoing research.[56-60]"

Conclusion

One of the most important aspects in the field of carcinogenesis is the various roles played by cancer-associated fibroblasts which have much research and studies in their evidence. They promote carcinogenesis through their multifarious nature and mechanisms and can be exploited as promising marks in the field of cancer therapeutics.

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