Extracellular Matrices and Cancer-Associated Fibroblasts

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Solid cancer progression is dictated by neoplastic cell features and pro-tumoral crosstalks with their microenvironment. Stroma modifications, such as fibroblast activation into cancer-associated fibroblasts (CAFs) and extracellular matrix (ECM) remodeling, are now recognized as critical events for cancer progression and as potential therapeutic or diagnostic targets.

Keywords: cancer-associated fibroblasts ; extracellular matrix ; cancer ; therapeutic and diagnostic targets

1. Introduction

More than a century ago, the “seed and soil” theory was proposed by Paget [1], seed being cancer cells and soil the stroma. Molecular characteristics of “seed (cancer cells)” were analyzed in depth and many oncogenes/suppressor genes have been identified and characterized. However, the “soil”, microenvironment encompassing host stromal cells (vascular cells, fibroblasts, immune/inflammatory cells, etc.), as well as non-cellular components (soluble factors, extracellular matrix, etc.) generated by cancer cells themselves and stromal cells, is still under characterization because of its structural and functional complexity. Recent development of novel molecular technologies has revealed the biomedical significance of the “soil” that influences cancer cell biological behaviors and functions, such as proliferation, invasion and metastatic processes. It is now clear that not only the soil promotes the growth of the seed, but also that the seed “educates” the soil to support its needs. Indeed, stromal cells acquire a specific biological phenotype via direct or indirect interactions with cancer cells. As an example, fibroblasts, which are the major components of the tumor microenvironment in most of solid tumors, become activated into cancer-associated fibroblasts (CAFs) under cancer cell stimulation, and, in turn, favor cancer development [2] notably via their secretion of acellular component such as extracellular matrix (ECM) and soluble factors. This abnormal ECM is a key regulator of tumor survival, progression and chemoresistance and represents the “breeding ground” of cancer cells. Globally, as the soil promotes the acquisition and maintenance of each of the cancer hallmarks, over the years several approaches have been used to target it.

2. Cancer-Associated Fibroblasts: Main Actors of Matrix Remodeling

2.1. Cancer-Associated Fibroblasts (CAFs)

Cancer-associated fibroblasts, the major stromal cells of most solid cancers such as breast and pancreatic cancers, have been widely described as key actors in tumor progression through numerous mechanisms including their ability to secrete various exacerbated soluble and insoluble factors (such as ECM). CAFs are defined as all fibroblastic, non-neoplastic, non-vascular, non-epithelial and non-inflammatory cells, activated and found in tumors and metastatic niches [3][4]. As opposed to the physiological activation (observed during wound healing for example), the “activated” phenotype of CAFs is persistent [3].

CAFs have been proposed to be defined as a cellular state rather than a cell type [5] because CAF origin is diverse: whereas they mainly come from the activation of quiescent fibroblasts residing in the tumor host tissue, they also originate from bone marrow derived cells (BMDC), trans-differentiation of pericytes, endothelial and epithelial cells [6][7]. Although there are currently no specific markers defining completely and exclusively CAFs, vimentin, α-SMA (smooth muscle actin), FAP (Fibroblast activation protein), PDGFR-α (Platelet-derived growth factor receptor-α), PDGFR-β, FSP-1 (also known as S100A4) and PDPN (podoplanin) are markers [3][4][8].

During tumorigenesis, quiescent fibroblasts are activated in response to various stimuli such as hypoxia [9], oxidative stress [10], chemokines and cytokines and growth factors such as transforming growth factor superfamily (TGFβ) [11], platelet-derived growth factors (PDGF) [12], epidermal growth factors (EGF), fibroblast growth factors (FGF) [13] and sonic

hedgehog (SHH) [14]. Such activation leads to an increase of CAF contractile capacities (with increased expression of α-SMA and vimentin), to a morphological modification (stellate shaped) [5], and to an exacerbated secretion of many factors (soluble and insoluble factors including ECM proteins). CAFs have been shown to first deposit fibronectin, generating intracellular tension involving actin cables. This creates, in the case of wound healing, a positive feedback loop that keeps the fibroblasts in an activated state in which YAP (Yes-associated protein) is translocated to the nucleus and α–SMA overexpressed [15]. Signals from the neo-synthesized ECM activate the Rho-ROCK-Myosin II signaling pathway and the incorporation of α-SMA into actin-myosin fibers leads to an increased contractility of activated fibroblasts [16][17]. These cells then generate tensile forces which, once transmitted to the matrix, trigger its remodeling at different levels. At the biochemical level, activated fibroblasts modify the matrix molecular composition by increasing the deposition of new matrix components, and by modulating the expression of matrix metalloproteinases (MMPs). Mechanically, these cells affect the physical properties of the matrix by modifying its organization and stiffness [18]. Such modifications induce the recruitment of new fibroblasts and their activation, and other components of ECM are produced thereby increasing the deposition of type I collagen, resulting in a decrease in fibronectin/collagen I ratio. While in a physiological context, when the collagen I network is crosslinked, fibronectin fibers are relaxed and fibroblasts resume their quiescence [15], in a tumor context, the ECM remodeling is continuous [19][20][21], altering the distribution of fibronectin zones by preventing the relaxation of fibronectin fibers [22].

Through these secretions, CAFs maintain their activated status, enhance their number and install a dialogue not only with tumor cells but also with the other stromal cells (endothelial cells, immune cells, for example) leading to complex and finely regulated tumor modifications. Indeed, while in the past researchers believed that CAFs had exclusively pro-tumoral functions (promoting tumor cell proliferation, survival, chemoresistance, angiogenesis [23] and immunosuppression [24]), in the past seven years, several publications have shown that CAF deletion or ECM modifications could result, depending on the context, in enhanced tumor progression [25][26].

One CAF particularity to take into account when trying to understand their role in cancer, is the recent observation, based on single cell RNA seq analysis, that CAFs are heterogeneous, in terms of morphology, functions and markers. This emergent concept of CAF subpopulations is based on several recent publications reporting the presence of CAF subgroups in PDAC (pancreatic ductal adenocarcinoma), breast carcinoma, colon carcinoma, lung adenocarcinoma and high-grade serous ovarian cancers [27][28] (**Table 1**). In breast cancer, Costa et al. distinguished four different CAF subpopulations (referred to as CAF-S1 to -S4), that accumulate differentially depending on breast cancer subtypes (luminal, HER2, and triple-negative). Importantly, as authors identified that the CAF-S1 subset highly contributes to immunosuppression, they suggest that patients with CAF-S1 rich tumors may benefit from specific immunotherapeutic strategy [29]. In non-small cell lung cancer, CAF subgrouping, either based on the collagen aspect or on fibroblast density, has prognosis significance [30][31][32]. In PDAC, David Tuveson's team was the first to report the presence of diverse CAF subtypes: a CAF subpopulation with elevated expression of αSMA located immediately adjacent to neoplastic cells called "myofibroblastic CAFs" (myCAF), and another CAF subpopulation located more distantly from neoplastic cells (lacking elevated αSMA expression) which secreted IL6 and additional inflammatory mediators called "inflammatory CAFs" (iCAF) [33]. Later on, by performing single cell analysis, this same team also identified a third subpopulation named "antigen-presenting CAFs" (ApCAFs) capable of activating CD4+ T cells in an antigen-specific manner, thus with putative immune-modulatory capacity [34].

Over the years, several studies have looked for correlation between CAFs/ECM and PDAC patient prognosis. Erkan et al. showed in a cohort of 233 PDAC patients (who underwent surgical resection and received adjuvant therapy) that collagen deposition was an independent positive prognosis marker whereas the amount of α-SMA expression (CAF activity) was negatively correlated with patient survival, although statistically insignificant [35]. In this study, they defined four major patterns of collagen deposition with regard to PSC (pancreatic stellate cells), the main cell origin of CAFs in PDAC [3][36][37] activity, and they showed that the combination of high stromal activity and low collagen deposition was associated with worse prognosis, whereas the combination of high collagen deposition and low stromal activity was correlated with a better prognosis. Although these results are contradictory to the dogma that collagen-induced signals favor tumor aggressiveness [38][39], they have been confirmed in another publication. Indeed, Bever et al., using computer-aided quantitative method to correlate patient survival with stroma density and activity in pancreatic cancer, observed that high stromal density (ratio of the stroma area to total tumor area), but not stroma activity (measured by α-SMA expression), was significantly associated with longer disease-free survival (DFS) and overall survival (OS) in a cohort of 66 PDAC patients (who underwent pancreaticoduodenectomy and received adjuvant therapy) [40]. This year, R. Kalluri's group reported, by using a dual-recombinase (integrating the capacity to manipulate genes using both the Cre-loxP and Flp-FRT) genetic mouse model of spontaneous PDAC to delete type 1 collagen specifically in myofibroblasts, that reducing Col1 total stromal content accelerates PanINs (pancreatic intraepithelial neoplasia) and PDAC emergence and decreases mouse overall survival by the establishment of an immunosuppressive microenvironment (recruitment of myeloid-derived

suppressor cells) [41]. In contrary, Weaver's group observed no significant association between the levels of fibrillary collagens and patient survival. The authors demonstrated, using second harmonic generation (SHG) microscopy, that the diameter of the collagen fibers adjacent to the pancreatic lesions was significantly thicker in PDAC patients with the shortest survival suggesting that collagen thickness is indicative of poor prognosis [42]. Following these findings, another group showed, using a SHG-based quantitative approach, that PDAC patients with high collagen alignment (induced by collagen crosslinking) had significantly reduced overall survival compared to patients with low alignment [43]. Then, according to these publications, collagen quality (thickness, alignment) rather than quantity is predictive of poor prognosis; therefore, not only CAF activation is important but also ECM modifications. This concept is supported by Moffitt's studies that defined, based on PDAC virtual microdissection, "normal" and "activated" stromal subtypes with prognostic and biological relevance; "activated" subtype, corresponding to a stroma encompassing activated CAFs and highly remodeled ECM, has the worse prognosis [44].

Table 1. CAF subgrouping in breast, ovarian, pancreatic, lung and colorectal cancers associated with identified secretions, main tumoral characteristics and markers. Italic refers to genes. Abbreviations: Acta2: Actin Alpha 2, Smooth Muscle; C7: Complement C7; CAV: Caveolin; CCL: C-C Motif Chemokine Ligand; CD74: Cluster of Differentiation 74; Cdh11: Cadherin 11; Clec3b: C-Type Lectin Domain Family 3 Member B; CMH: major histocompatibility complex; Col: collagen; CXCL: chemokine (C-X-C motif) ligand; ENG: Endoglin; FAP: Fibroblast Activation Protein Alpha; FSP1: Fibroblast-Specific Protein-1 = S100A4: S100 Calcium Binding Protein A4; Gas6: Growth Arrest Specific 6; Gpm6a: Glycoprotein M6A; Gsn: Gelsolin; H2-Ab1: histocompatibility 2, class II antigen A, beta 1; HAS1: Hyaluronan Synthase 1; HLA-DRA: Major Histocompatibility Complex, Class II, DR Alpha; Igf: Insulin Like Growth Factor; Irf5: Interferon regulatory factor 5; ITGA11: Integrin Subunit Alpha 11; Lgals7: Galectin 7; LRRC15: Leucine Rich Repeat Containing 15; Lrrn4: Leucine Rich Repeat Neuronal 4; Ly6c1: Lymphocyte antigen 6C1 precursor; Msln: Mesothelin; MYH11: myosin heavy chain 11; MYL9: myosin light chain 9; Nkain4: Sodium/Potassium Transporting ATPase Interacting 4; PDGFR: Platelet Derived Growth Factor Receptor Alpha; PDPN: Podoplanin; POSTN: Periostin; Ptn: Pleiotrophin; Saa3: Serum Amyloid A3Slpi; Tagln: Transgelin; TGFb: Transforming Growth Factor Beta 1; Thy1: Thy-1 Cell Surface Antigen; TIMP1: Tissue Inhibitor of Metalloproteinase 1; Tnc: Tenascin C.

Cancer	CAF Subpopulations	Secretion	Main Characteristics	Markers/Key Genes
Breast cancer [29][45] and high-grade serous ovarian cancers [28]	**CAF-S1**	**CXCL12, CCL2, CCL11, CXCL14 [28][29][45]**	**- Attract $CD4^+CD25^+$ T lymphocytes, promote their differentiation into Tregs and subsequent pro-tumoral functions [29] - Enhance cancer cell migration [45] - Initiate an epithelial-to-mesenchymal transition (EMT) [45]**	**$CD29^{Med}FAP^{Hi}$ $FSP1^{Low-Hi}\alpha SMA^{Hi}$ $PDGFR\beta^{Med-Hi}$ $CAV1^{Low}$ [28][29]**
	CAF-S2	**ND**	**Inactivated CAF [45]**	**$CD29^{Low}FAP^{Neg}$ $FSP1^{Neg-Low}\alpha SMA^{Neg}$ $PDGFR\beta^{Neg}$ $CAV1^{Neg}$ [28][29]**
	CAF-S3	**ND**	**Inactivated CAF [45]**	**$CD29^{Med}FAP^{Neg}$ $FSP1^{Med-Hi}\alpha SMA^{Neg-Low}$ $PDGFR\beta^{Med}$ $CAV1^{Neg-Low}$ [28][29]**
	CAF-S4	**CCL2, CCL11, CXCL12, CXCL13, CXCL14 [28][29][45]**	**Induce cancer cell invasion via NOTCH signaling [45]**	**$CD29^{Hi}FAP^{Neg}$ $FSP1^{Low-Med}\alpha SMA^{Hi}$ $PDGFR\beta^{Low-Med}$ $CAV1^{Neg-Low}$ [28][29]**

Cancer	CAF Subpopulations	Secretion	Main Characteristics	Markers/Key Genes
PDAC [8] [33][34][46] [47]	Myofibroblastic CAFs (myCAFs) [33][34]	ECM proteins	Anti-tumor, contractile, stroma-remodeling	FAP^{+} αSMA^{high} IL-6^{low} *Tnc*, *Tgfb1*, *Thy1*, *Tagln*, *Col12a1*, *Pdgfrb*
	Inflammatory CAFs (iCAFs) [33] [34]	IL-6, IL-11, LIF *IL-8, CXCL1-2-12, CXCL2, CCL2*	Pro-tumor, secrete cytokines and chemokines involved in cancer progression	αSMA^{low} IL-6^{high} *Clec3b*, *Col14a1*, *Gsn*, *Ly6c1*, *Cxcl12*
	Antigen-presenting CAFs (ApCAFs) [34]	ND	Present antigen to T cells	*CD74*, *Saa3*, *Slpi*, *H2-Ab1, Nkain4*, *Irf5*, *CMH class II*
	FB1 = iCAF like [46]	*Il-6, CXCL12, CCL2, CCL7*	Secretory phenotype	*Cxcl14, Ptn*, and genes mediating insulin-like growth factor signaling (*Igf1*, *Igfbp7*, *Igfbp4*), *Pdgfrα*
	FB3 = myCAF like [46]		Contractile phenotype	mesothelial markers (*Lrrn4*, *Gpm6a*, *Nkain4*, *Lgals7*, and *Msln*); fibroblast markers (*Cav1*, *Cdh11*, and *Gas6*), *Acta2* and *Tagln*, *MHC-II–associated genes*
	CAF-c1 [47]	Collagen I, SPARC, ECM proteins	Early tumors	CD74^{+}/*HLA-DRA^{lo}*/*Col1a1*$^{+}$/*Col3a1*$^{+}$/*TIMP1*$^{+}$/*FAP*$^{+}$, *C7*$^{+}$/*ENG*$^{+}$
	CAF-c2 = IL1-CAF [47]	Il1	Established tumors	*HAS1*$^{+}$/*CXCL1*$^{+}$/*CCL2*$^{+}$/*FAP*$^{+}$/*CD74^{hi}*/*HLA-DRA*$^{+}$
	CAF-c0 = TGFβ-CAF [47]	TGFβ	Established tumors	LRRC15^{+}/*TAGLN*$^{+}$/*Col11a*$^{+}$/*ACTA2*$^{+}$/*FAP*$^{+}$/*CD74^{hi}*/*HLA-DRA*$^{+}$
	Subtype A [8]	*ECM proteins*	Associated with poor/intermediate prognosis	POSTN^{high}/MYH11^{low}/PDPN^{low}/αSMA ^{low}/PDGFRα/Vimentin^{low}
	Subtype B [8]	*ECM proteins*	Associated with intermediate prognosis and with cancer cell protection against gemcitabine	MYH11^{high}/POSTN$^{low/high}$/PDGFRα/ αSMA^{high}/Vimentin^{high}
	Subtype C [8]	*Inflammatory mediators and ECM proteins*	Associated with “good” prognostic but with cancer cell protection against gemcitabine	PDPN^{high}/POSTN$^{low-high}$/PDGFRα
	Subtype D [8]	*ECM proteins*	Associated with bad prognosis and with cancer cell protection against gemcitabine	αSMA^{high}/Vimentin^{high}
Non-small cell lung carcinoma [32]	High desmoplastic CAFs	ND	Enhance collagen matrix remodeling, invasion and tumor growth	αSMA^{+}ITGA11^{+}
	Low desmoplastic CAFs	ND	Pro-tumoral functions limited compared to HD-CAFs	αSMA^{+}ITGA11^{+}

Cancer	CAF Subpopulations	Secretion	Main Characteristics	Markers/Key Genes
Colorectal cancer [48]	PDPN^{+} CAFs	ND	Associated with prolonged disease-free survival	PDPN^{+}
	PDPN^{-}/α-SMA^{high} CAFs	ND	Associated with aggressive tumors	PDPN^{-}/α-SMA^{high}
	PDPN^{-}/S100A4^{high} CAFs	ND	Associated with tumor budding and lymphovascular invasion	PDPN^{-}/S100A4^{high}
Melanoma [49]	S1 CAFs	*CXCL12*, *CSF1*, *CCL8*	Regulate immune cell recruitment	PDPN^{high}/PDGFRα^{high}/CD34^{high}
	S2 CAFs	*ECM proteins*	Drive desmoplastic reaction	PDPN^{high}/PDGFRα^{high}/CD34^{low}
	S3 CAFs	ND	Regulate actin cytoskeleton and contractility	Acta2^{high}/CD34^{low}

2.2. Extracellular Matrix (ECM)

One of the major features of CAFs is their ability to produce large amounts of ECM proteins, such as collagens, glycoproteins and proteoglycans [50]. The development of new technologies, mainly the “matrisome” approach which is based on mass spectrometry analysis of in vivo samples and enables to characterize the ECM biochemical composition, have revolutionized our understanding of tumoral ECM components and roles [51][52]. ECM is a complex scaffold composed of hundreds of proteins that provide anchoring and support to environmental cells under physiological and pathological conditions [51]. Major ECM structural components are collagens, proteoglycans, and hyaluronic acid that provide supportive framework within which other ECM components (such as laminin or fibronectin for example) and cells interact [50][53]. In addition to this architectural role, ECM proteins provide signals that cells interpret and transduce via cell surface receptors such as integrins. These signals, named mechanotransduction, activate cellular pathways that impact cellular functions such as proliferation, survival, morphology, adhesion and motility [54][55][56]. ECM represents also a growth factor reservoir as matrix proteins can sequester them and modify their signaling properties [57]. ECM modifications (biochemical composition, mechanical properties, integrity) are often observed in diseases such as fibrosis, cardiovascular or musculoskeletal diseases [58][59][60] and cancer [61][62]. It has recently become evident that ECM has biomechanical and physical properties that impact all cancer hallmarks, including the cellular processes that contribute to cancer initiation, progression, spreading [20][63] and metastatic niche formation [64][65]. Moreover, the extraordinarily dense fibrotic stroma, found in PDAC (PDAC fibrotic area accounts for up to 90% of the tumor area [66]) and breast cancer, impedes tumor perfusion and delivery of anticancer drugs [67]. ECM modifications within tumor (quantity, stiffness, etc.) have been shown to correlate with more aggressive tumors and worse prognosis for the patient [68][69][70][71].

Collagens are by far the most abundant and best characterized ECM components. Collagen I is responsible for the majority of the desmoplastic reaction [72][73][74], and high levels of its deposition have been associated with reduced survival in PDAC patients [38]. In breast cancer, as in PDAC, accumulation of fibrillary collagens I, III, and V occurs [39][75][76] and increased level of Col1a1 or Col3 is associated with a metastasis status [76] and correlates with shorter survival [77]. Mechanistically, fibrillary collagens regulate tumor cell functions via the integrin activation promoting tumor cell proliferation, migration and preventing apoptosis [78]. In contrast, type IV collagen, which is mainly present in the basement membrane (BM) that underlies epithelium and endothelial cells, is decreased in both PDAC and breast cancer [39]. In PDAC mouse model (KTC: *Tgfbr2*$^{flox/wt}$; *Kras*$^{LSL\text{-}G12D/+}$*Tgfbr2*$^{flox/wt}$*Ptf1a*-Cre) [79], as in human PDAC tumors [80], not only Col4 is decreased but also BM proteins in general. This BM destruction facilitates invasion and metastasis in many cancers [63][81]. Interestingly, the tumoral ECM remodeling, involving protease-mediated ECM cleavage, generates ECM fragments, named matrikines or matricryptins, capable of influencing tumor progression and dissemination [60]. Indeed, increased level of MMP-mediated degradation of type I, II, III, and IV collagens release C-terminal collagen domains named C1M, C3M C4M and C4M12a1, respectively, that are often found in PDAC patient serum and are associated with significantly shorter survival [82][83].

Glycoproteins are the second main ECM subgroup deregulated during cancer that encompasses fibronectin, laminins and many other proteins. Fibronectin (FN) is found to be overexpressed in several cancers and reported to participate in several steps of tumorigenesis including growth, invasion, and metastasis. When analyzed as a potential prognosis factor for cancer patients, FN's role in cancer progression appears to be complex, as FN deposited in tumor microenvironment (TME) or FN tumor cell endogenous expression have opposite correlations with patient prognosis [84][85]. A better understanding of such paradoxical role of FN in tumorigenesis is of high interest and has been recently extensively well reviewed by Tsung-Cheng Lin et al. [85]. In fibrotic solid tumors, FN expression is associated with poor clinical outcome [39], tumor aggressiveness [86], and participates in the resistance to radiotherapy via the FN-specific $\alpha_5\beta_1$-integrin pathway [87]. Other glycoproteins such as periostin and galectin-1 are upregulated in PDAC [88][89] and their expressions are negatively correlated to patient survival [88][89][90]. Numbers of glycoproteins are found to be enhanced in cancer patient serum and used as diagnostic and prognostic biomarkers: for example, CA125 and CA19-9 are two glycoproteins used as ovarian cancer and pancreatic cancer biomarkers, respectively [91].

Finally, proteoglycan expression is also modified during tumorigenesis and one major example is the hyaluronan (HA). HA is a negatively charged glycosaminoglycan found to be highly accumulated in solid cancers [38][92][93]. HA expression within tumor, through a mechanism involving its high hydrophobic properties, enhances interstitial tumor pressure, and its accumulation correlates with poor prognosis [38] and metastasis [94].

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