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Review

The cancer-inhibitory effects of proliferating tumor-residing fibroblasts

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A R T I C L E I N F O

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Initiation, local progression, and metastasis of cancer are associated with specific morphological, molecular, and functional changes in the extracellular matrix and the fibroblasts within the tumor microenvironment (TME). In the early stages of tumor development, fibroblasts are an obstacle that cancer cells must surpass or nullify to progress. Thus, in early tumor progression, specific signaling from cancer cells activates bio-pathways, which abolish the innate anticancer properties of fibroblasts and convert a high proportion of them to tumor-promoting cancer-associated fibroblasts (CAFs). Following this initial event, a wide spectrum of gene expression changes gradually leads to the development of a stromal fibroblast population with complex heterogeneity, creating fibroblast subtypes with characteristic profiles, which may alternate between being tumor-promotive and tumor-suppressive, topologically and chronologically in the TME. These fibroblast subtypes form the tumor's histological landscape comprising areas of cancer growth, inflammation, angiogenesis, invasion fronts, proliferating and non-proliferating fibroblasts, cancer-cell apoptosis, fibroblast apoptosis, and necrosis. These features reflect general deregulation of tissue homeostasis within the TME. This review discusses fundamental and current knowledge that has established the existence of anticancer fibroblasts within the various interacting elements of the TME. It is proposed that the maintenance of fibroblast proliferation is an essential parameter for the activation of their anticancer capacity, similar to that by which normal fibroblasts would be activated in wound repair, thus maintaining tissue homeostasis. Encouragement of research in this direction may render new means of cancer therapy and a greater understanding of tumor progression.

1. Introduction

A fundamental role of the tumor microenvironment (TME) is promoting cancer growth, which has been attributed to a specific type of stromal fibroblast population, cancer-associated fibroblasts (CAFs). CAFs, originating from diverse groups of mesenchymal cells, generally called fibroblasts, exist in all tumor types [1,2,3,4,5].

Although distinct stromal reprogramming has been described in mature tumors [6,7,8], the initial time point of the appearance of CAFs in a tumor is still obscure [5]. Several authors have suggested that during the initiation stage of a tumor's development, fibroblasts in the TME may restrain cancer cells [9,10,11,12]. It may, therefore, be inferred that there is an essential time interval during which specific factors and microenvironmental conditions guide fibroblasts toward or against cancer development [13,14,15]. Alterations of fibroblasts occurring during this time interval are, therefore, crucial, albeit poorly understood [e.g. [16,13,17,18,19]]. Some studies have investigated the initial stages of carcinogenesis focusing on the basic processes of the opposition between the strength of carcinogenesis and homeostasis [20]. However, it should be emphasized that the plethora of both in vivo and in vitro studies which emphasized the cancer-promotive role of CAFs, were carried out using: (a) tissues of established growing tumors with an organized angiogenic system, which served their continuous feeding, and which developed desmoplasia; (b) stromal fibroblasts which had already been adapted ("activated CAFs") to support cancer growth and progression; (c) stromal fibroblasts of which low proportions or none were in the proliferation state, and (d) in vitro systems in which the parameters/conditions of availability of growth space for fibroblasts, the duration of fibroblast x cancer cell interactions and the frequency of the feeding of the co-cultures were not considered. Thus, most of these studies were related to cancer stages far advanced from the initial confrontation of the first cancer cell seeds with the normal tissue homeostatic environs.

Early and current investigations indicating that fibroblasts may

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develop anticancer properties in vitro have raised several questions:

- Is there always a type of fibroblast within the tumor, or a fibroblast population that inhibits cancer-cell proliferation at a specific cell-cycle point?
- Are there conditions within a tumor or its hosting organism that favor recruitment of fibroblasts with anticancer properties and at which stage of tumor growth (initial or/and advanced)?
- Are these conditions influenced (suppressed or sustained) by factors within the TME, or are they induced by the tumor-hosting organism as an immunological or inflammatory or as-yet unknown reaction against tumor growth?

A basic background for answering the above questions has already been established by two solid facts: (a) The fibroblast population within the TME of multiple tumor types is heterogeneous [1,5,21,22] and heterogeneous fibroblasts are also present during cancer progression [10,18,23,24,25], and (b) there is evidence indicating inhibitory or catastrophic effects of fibroblasts within tumors on cancer cells under certain conditions [e.g [18,26,27,28,29]]. Fibroblasts can exert harnessing effects on cancer cells in vivo as a result of their desmoplastic reaction [28,30,31]. Considering the above facts, it can be postulated that tumor-stromal heterogeneity may provide factors responsible for the suppression of malignant growth [32].

Although multiple mechanisms involved in the cancer-promoting effects of CAFs have been proposed and often reviewed [1,5,25], the restraining role of CAF-subtypes, or normal stromal fibroblasts, on cancer cells, is not well understood [4,16,33]. Furthermore, although single-cell analysis, including single-cell RNA (scRNA) sequencing, has revealed functionally-distinct categories of CAFs from breast cancer, the categories of CAFs thus far studied by single-cell analysis promote metastasis and resistance to immunotherapy [21].

The present review attempts to gather and re-analyze our knowledge describing the complex phenomenon of cancer-growth inhibition by fibroblasts within the TME and to promote research in this direction.

2. From desmoplasia to cancer-associated fibroblast heterogeneity

The growth of fibroblasts in parallel with cancer cells within a tumor has been characterized as a “stromal reaction” or “desmoplasia” and from early on was considered as an expression of immune surveillance [34] and a host response to neoplasia [12]. Although immune surveillance of cancer is becoming an intense area of study, desmoplasia and the related ECM remodeling processes concerning tumor initiation and progression are not well understood and almost surely involve non-immune mechanisms as well [24,35].

The presence of desmoplasia in a progressing tumor has been described by some as indicative of a highly malignant level and poor prognosis [e.g. [36,37,38,39,40]], but by others as an indication of good prognosis [23,31,41,42,43]. However, the supportive or restraining functions on neoplasia may also be subject to reversible processes [44,45,46]. Indeed, pathways to reverse or inactivate the tumor-promoting properties of CAFs have been identified [1,5,44,47,48,49]. Nevertheless, the detailed conditions which modulate desmoplasia to have a negative or positive impact on tumor development are still not well understood.

CAFs have been characterized as distinct entities by numerous specific gene-expression profiles and phenotypic properties [1] of which several seem to be associated with the stage of tumor progression [18,22,24,40,50,51], immunomodulation and immunosuppression [48,52,53,54,55,56], distant metastasis [57,58,59], angiogenesis [60], as well as with the response to chemotherapy [5,8,61], immunotherapy [21,52,62], or radiotherapy [63]. These studies also support the fact that fibroblasts within the TME consist of highly heterogeneous populations, each possibly having a different role during the initiation, progression, and metastatic stages of a tumor [1,5,25,64]. Table 1 provides a comparison of properties between human normal fibroblasts and CAFs with

Table 1
Comparison of functional properties of normal human fibroblasts and cancer-associated fibroblasts (CAFs) regarding their role in the promotion or suppression of cancer cell growth.

Normal human fibroblasts (including mesenchymal-stem and stromal-cells)	Human CAFs
Force-dependent activity in tissue integrity/homeostasis (Kaukonen et al., 2016 [132]; Papalazarou et al., 2018 [133]).	Force-dependent activity/mechanical stress in the support of cancer growth and invasion (Barbazan and Vignjevic, 2019 [13]; Gerarducci et al., 2020 [134]; Hadden et al., 2020 [135]).
Tropism/affinity for cancer cells (Delinassios and Kottaridis, 1984 [92]; Kidd et al., 2009 [136]; Klopp et al., 2011 [137]; Vegh et al., 2013 [104]).	Tropism/affinity for cancer cells (Delinasios et al., 2015 [26]; Klopp et al., 2011 [137]; Ling et al., 2010 [138]). Circulating cancer cells form clusters with CAFs (Ortiz-Otero et al., 2020 [87]; Satake et al., 2018 [139]).
Secretion of matricellular proteins (Gerarducci et al., 2020 [134]). Organization of ECM with collagens as major components (Barrett and Puré 2020 [52]; Nissen et al., 2019 [105]) contributing to tissue integrity (Papalazarou et al., 2018 [133]; Zeltz et al., 2020 [89]) and tissue repair (Desmouliere et al., 2005 [140]; Gabbiani, and Rungger-Bradle, 1981 [98]; Sabatini et al., 2005 [97]). Orchestration of the development and morphogenesis of tissues and organs (Chang et al., 2002 [141]).	Secretion of matricellular proteins and cancer-promoting factors to ECM (Huang and Brekken, 2020 [24]). Disorganization of ECM with disturbed ratios and synthesis of collagens (Zeltz et al., 2020 [89]). Remodeling and deposition of ECM (Huang and Brekken, 2020 [24]). Deregulation of glucose metabolism (Becker et al., 2020 [7]). Proteolytic activity (Barbazan and Vignjevic, 2019 [13]).
Absence of abnormal morphological features (Delinassios and Kottaridis, 1984 [92]; Lynch and Watt, 2018 [142]; Philippeos et al., 2018 [143]).	Presence of abnormal morphological features (Delinassios and Kottaridis, 1984 [92]; Delinassios et al., 1983 [77]; Olumi et al., 1999 [78]; Rønnov-Jensen et al., 1996 [11]).
Crosstalk of fibroblasts with epithelial cells to maintain homeostasis (Brügger et al., 2020 [20]; Buechler and Turley, 2018 [144]; Corn, 2012 [145]; Zhao et al., 2019 [81]).	Crosstalk of CAFs with cancer cells in the support of cancer growth, invasion and metastasis (Biffi and Tuveson, 2021 [1]; Pelon et al., 2020 [25]).
Regulatory control over epithelial proliferation and differentiation (Cunha, 1994 [115]; Schauer and Rowley, 2011 [146]).	Immunomodulating and immunosuppressive activities (Barrett and Puré, 2020 [52]; Davidson et al., 2021 [53]; Ho et al., 2020 [147]; Suzuki et al., 2021 [54]; Zadka et al., 2021 [56]).
Susceptibility to epigenetic reprogramming which may convert stromal naïve fibroblasts to CAFs (Lamprecht et al., 2017 [148]; Mishra et al., 2019 [149]; Pidsley et al., 2018 [150]).	Susceptibility to epigenetic reprogramming in the support of cancer growth, invasion and metastasis (Becker et al., 2020 [7]; Mishra et al., 2019 [149]; Pidsley et al., 2018 [150]).
Reciprocal signaling and changes in gene-expression profiles following interactions between normal fibroblasts and cancer cells (Delinassios et al., 2015 [26]; Kaukonen et al., 2016 [132]; Patel et al., 2018 [151]).	Proneness to a variety of gene-expression changes leading to abolishment of homeostatic control, metabolic reprogramming and heterogeneous populations (Berdiel-Acer et al., 2021 [23]; Eckert et al., 2019 [152]; Hesterberg et al., 2021 [22]; Neuwirt et al., 2020 [153]; Satake et al., 2018 [139]).
Antitumor and antiproliferative effects (Delinassios et al., 2015 [26]; Jones et al., 2007 [80]; Kidd et al., 2010 [154]; Maman and Witz, 2018 [4]; Miyai et al., 2020 [18]; Roberts et al., 2017 [33]; Rønnov-Jensen et al., 1996 [11]).	Support of cancer growth, angiogenesis, invasion and metastasis (Barbazan and Vignjevic, 2019 [13]; Biffi and Tuveson, 2021 [1]; De Palma et al., 2017 [60]; Drexler et al., 2021 [107]; Sahai et al., 2020 [5]; Zeltz et al., 2020 [89]).

their roles in cancer-cell growth and inhibition.

Gene-expression changes associated with the functional heterogeneity within the tumor stromal-fibroblast populations indicate a plethora of biomolecules or/and activated signaling-pathways which are proposed as biomarkers of a promotive [e.g. [25,38,47,65,66,67,68,69,70] or a suppressive [28,71,72,73,74] action on tumor growth in various types of cancer. However, despite their extensive gene-expression changes, cultured CAFs or generally stromal fibroblasts have not been found to exhibit chromosomal abnormalities, thereby protecting their chromosomal integrity, and indicating they have not undergone oncogenic transformation, even when they are promoting cancer growth and progression and proliferating during tumor growth [75,76,77,78]. However, if gene-expression changes in the stromal fibroblasts do occur as a consequence of the continuously-altered genetic instability of cancer cells, as manifested by abnormal divisions and chromosomal rearrangements in the cancer cells, these changes might be random and unrelated, or they might indicate a specific response to the cancer cells. If gene-expression changes in a proportion of stromal fibroblasts lead them to a cancer-suppressive profile, then, we might be able to suggest that they were part of a pathway controlling innate fibroblastic tumor-suppressive, anti-proliferative and homeostatic properties. This aspect seems to be supported by past and emerging findings and discussions [18,20,33,79,80,81]. However, we should also consider that gene-expression changes in normal fibroblasts may enhance their malignancy-promoting properties. Consistent with this hypothesis is the induction of the differentiation of the fibroblasts into CAFs, with TGFβ signaling as the main factor within the TME [8,82,83,84,85]. It has also been suggested that stromal-p53 activity may convert fibroblasts from being tumor-inhibitive to tumor-promotive [86].

It has been found that the conversion of normal fibroblasts to CAFs proceeds from a proliferative to a quiescent state and these two states are characterized by a fluctuation of intensity of CAF markers [87,88]. These two states may exhibit different cell-cell adhesion properties due to ECM deregulation [24,89], as well as disrupted “contact inhibition of growth” [90,91] since tumor stromal fibroblasts in monolayer culture show areas of both morphologically normal fibroblasts, contact-inhibited confluency and uncontrolled overlapping or piled-up growth [26,77,78,91,92]. The in vitro growth-inhibitory heterogeneity of stromal fibroblasts may reflect their in-vivo heterogeneity within tumors.

3. The rationale for studying the anti-cancer properties of fibroblasts

Extensive evidence suggests that a high number of genes that are specifically expressed in distinct populations of stromal fibroblasts or CAFs, originating from various cancer types, affect each cancer developmental-stage, from initiation to invasion and metastasis [1,5,88,93,94]. The existence, however, of CAF subtypes that specifically express other genes attests to the plasticity, instability, or interconvertibility of CAFs within the TME [1,5,95]. The ease at which stromal fibroblasts and CAFs change by responding to factors existing in the TME, mirrors the multilineage potential of adult human mesenchymal stem cells [24,96,97], as well as the prompt response of normal-tissue fibroblasts to the needs of tissue repair and regeneration [3,98,99]. Thus, it may be reasonable to think that all human cells of connective origin carry an innate common property, the “ability to adapt”. This aspect is supported by the notable similarities among mesenchymal stem cells (MSCs), fibroblasts, and CAFs [100,101,102,103,104]. Additionally, during tumor development, MSCs, tissue fibroblasts, adipocytes, and stellate cells can give rise to CAFs [5] which express altered cell-surface and intracellular markers [1,105,106], including CAF-subtype-defining markers [1,106], to CAFs with altered immunologic properties [1,52,53] and CAFs that support cancer progression [5] and metastasis [25,107]. Therefore, the change of the tumor stromal-fibroblasts from the innately protective nature of normal fibroblasts in healthy tissues to CAFs may be an essential initial step, opposing homeostasis, leading toward cancer initiation and progression [108]. These concepts stimulate an interest in identifying the conditions involved in the expression of the transient fibroblast restraint of cancer cells.

4. Studies substantiating the anti-cancer properties of fibroblasts

In vitro co-culture procedures have combined isolated fibroblasts and cancer cells devoid of other tissue elements [26,91,109,110]. Such co-cultures are very useful for evaluating stromal-specific, as well as cancer-specific, drugs and for basic research on the interaction of the two isolated cell types.

Table 2 sets out in chronological order representative studies describing the inhibitory effects of fibroblasts against cancer cells. Table 2 also displays the results of experiments using fibroblasts and cancer cells of various origins and indicates conditions, correlative events, and the growth phase of the fibroblasts during co-culture, as well as studies of their conditioned media. The publications listed in Table 2 present evidence that fibroblasts may develop anti-cancer properties during their proliferative phase.

The phenomenon of “inhibition of heteroploid (cancer) cells by diploid fibroblasts” was first observed by Eagle and Levine who also showed that contact-inhibited fibroblasts were unable to inhibit the growth of cancer cells [91,111]. In these early experiments, the fibroblasts reached confluency before the 6th day of co-culture [111], thus, interactions in which both types of cells were proliferating could not be studied after 6 days, since contact-inhibited fibroblast layers were used as a feeding substratum by the cancer cells [26,110,112,113]. However, there were indications of early anticancer actions of fibroblasts before reaching contact inhibition, as shown later both in vitro [76,114], and in vivo [115]. Another phenomenon that has commonly been seen, since the first attempts to culture epithelial cancer cells from tumor specimens, is the fast appearance and overgrowth by fibroblasts in contrast to the absence, or very rare growth, of cancer cells in monolayer culture on a solid surface of glass or plastic. This experience may imply that fibroblasts take prompt advantage of the available space to leave behind their tissue of origin, expand and grow, while epithelial cancer cells, needing a long time to adapt to the culture conditions, die due to early deprivation of nutrients, or due to the expression of the antiproliferative properties of the fibroblasts or due to their culture in only two dimensions on a solid surface, instead of in three dimensions on a more in vivo-like flexible substrate [26,29,33,80,116,117].

Considering early observations, we aimed at modulating the in-vitro co-culture conditions in a way that would enable the study of the interactions between fibroblasts and cancer cells for a prolonged time whilst mimicking the incipient confrontation of cancer cells with fibroblasts. It was, thus, shown that three parameters including “space to grow, nutrients to support growth, and the initial fibroblast: cancer cell ratio” constituted sufficient conditions for this purpose [114,118]. The maintenance of the co-cultures under these conditions was facilitated for up to 20 days and demonstrated for the first time a sequence of events (Fig. 1), which led to a deeper understanding of the anti-cancer properties of fibroblasts in vitro [26]. In these experiments, since fibroblasts exhibit the phenomenon of contact-inhibition of movement and growth [119,120,121], availability of surface space and nutrients for the parallel proliferation of both cell types was found to be essential. Furthermore, considering the doubling time of the fibroblast strains used (fibroblasts; 53 ± 1 h) and that of HeLa cancer cells (cancer cells; 16 ± 1 h), an initial fibroblast:cancer cell ratio of 100:1 was implemented together with medium renewal every two days [26,114]. This 2D-culture model enabled the study of interactions at the interface between cancer cells and stromal or normal fibroblasts for as long as 20 days, as mentioned above. Interestingly, from the first hours of the fibroblast x cancer cell interaction, the fibroblasts developed a characteristic bent

Table 2
Events and conditions implicated in the development of the inhibitory activity of human fibroblasts against human cancer cells in vitro. Some parallel in-vivo studies were considered as critically important and were included.

Ref.	Fibroblast (F)	x	Cancer cell (C)	Duration of co-culture	Culture procedure	Effects on cancer cells, factors involved and other remarks	Growth phase of fibroblasts
Kirk et al., 1980 [155], 1981 [156], 1983 [157]	Normal lung fibroblasts.	x	Prostatic-carcinoma cells (PC-3).	10 days	In vitro falcon dish; agar	Inhibition of the plating efficiency of cancer cells. High fibroblast:cancer cell ratio.	Proliferative
Delinassios & Kottaridis, 1981 [76]	Normal skin fibroblasts.	x	Lympho-blastoid cell lines	24 days	In vitro	Disintegration of lymphoblastoid cells.	Proliferative
Imanishi et al., 1983 [158]	Embryonic fibroblasts.	x	HeLa; PLC, hepatoma cells.	10–14 days	In vitro	Degeneration of cancer cells was enhanced by interferon.	Proliferative
Wu et al., 1985 [159]	Embryonic fibroblasts.	x	Burkitt's-lymphoma cell lines; Melanoma cell-lines.	3 days	In vitro	Inhibition of DNA synthesis and cell death induced by a diffusible factor in 2 Burkitt's lymphoma and 2 melanoma cell lines of those used.	Proliferative
Delinassios, 1987a [114],b [118] Delinassios et al., 2015 [26]	Normal skin-fibroblasts; stromal fibroblasts.	x	HeLa.	20 days	In vitro	Reciprocal influence of growth patterns, protein expression, chromatin features and cell survival. Apoptosis of HeLa cells. Cell–cell tropism and affinity. Refeeding every 2nd day. Lipid production by fibroblasts.	Proliferative
Shirasuna et al., 1988 [160]	WI-38 fibroblast cell line.	x	Salivary-gland cancer cell line; HeLa, KB cell lines.	24 hours	In vitro, agar	Inhibition of DNA synthesis and growth by a diffusible factor in the fibroblast-conditioned media with differentiation inducing activity.	Proliferative
Kooistra et al., 1991 [161], 1995 [162], 1997 [163]	Normal or tumor stromal fibroblasts.	x	Prostate-carcinoma cell lines, PC-3, LNCaP.		agar	Inhibition of growth by a diffusible factor (different from $TGF\beta_1$) in the fibroblast-conditioned medium.	Proliferative
Rossi et al., 1994 [164]	Human fetus, HFF fibroblasts.	x	MCF-7-cell line.	14 days	Collagen gel	Induction of necrosis in MCF-7 cells.	Proliferative
Hofland et al., 1995 [165]	Normal and breast-tumor-derived fibroblasts.	x	MCF-7-cell line.	4 days	In vitro	Reciprocal stimulation of growth (evaluated by ^{3}H-TdR uptake) between fibroblasts and breast-cancer cells. However, in one co-culture, fibroblasts were inhibitive.	Proliferative
Degeorges et al., 1996 [166]	Normal prostate fibroblasts; BPH and prostate-cancer fibroblasts.	x	Prostate-cancer cell lines, LNCaP, PC-3, DU145.		Double-diffusion co-culture chamber	Inhibition of cancer-cell growth (evaluated by ^{3}H-TdR uptake) by a diffusible factor identified to be IL-6. Fibroblast:cancer cell ratio: 10:1.	Proliferative
Donc-le-Bourhis et al., 1997 [167]	Normal breast-tissue fibroblasts.	x	MCF-7-cell line.	8 days	In vitro	Inhibition of cancer cell growth (evaluated by ^{3}H-TdR uptake) by normal fibroblasts, dependent on fibroblast:cancer cell ratio (10:1).	Proliferative
Javaherian et al., 1998 [168]	Normal keratino-cytes (NK).	x	Malignant keratinocytes (MK).	7 days	In vitro	Inhibition of growth of MKs at NK:MK ratio: 12:1.	Proliferative
Kawada et al., 1999 [169]	Embryonic fibroblasts, WI-38.	x	Prostate-cancer, cell lines, LNCaP, PC-3.	3 days	In vitro	Suppression of LNCaP cell growth by IL-1β or TNF-α and by conditioned medium.	Proliferative
Sadlonova et al., 2005 [170]	Normal fibroblasts (NAF), CAFs.	x	Breast-cancer cell lines.	14 days	In vitro 3D culture	Inhibition of proliferation and death of cancer cells. NAFs showed higher inhibitory activity than CAFs. Fibroblast:cancer cell ratio 1:2 to 3:1. Medium replacement every 4 days.	Proliferative
Qiao et al., 2008a [171], b [172]	MSCs.	x	Hepatoma cells, MCF-7 cell-line.	3 days	In vitro	Inhibition of hepatoma cell growth (reduced proliferation, increased apoptosis). Fibroblast:cancer cell ratio 1:1.	Proliferative
Postovit et al., 2008 [173]	Embryonic stem cells, hESC.	x	Melanoma and breast carcinoma.	14 days in vitro	In vitro and in vivo mouse orthotopic tumor model.	Tumor-suppressive effects (decreased proliferation, increased apoptosis) by factors produced by hESC in vitro and in vivo.	Proliferative
Trimboli et al., 2009 [94]	Human breast-cancer fibroblasts and mouse stromal-fibroblasts.	x	Human and mouse breast-cancer tissue.		In vivo (mouse model); transplantation and orthotopic model.	Identification of the tumor-suppressive activity of the PTEN-ETS2 axis in human and mouse-tumor stromal fibroblasts.	Proliferative
Cousin et al., 2009 [174]	Stromal cells derived from human adipose-tissue (ADSC).	x	Pancreatic- and other- cancer cell lines.	48 h in vitro; 28 days in vivo	In vitro and in vivo (athymic mice).	ADSC induced contact-dependent cancer-cell death (necrosis) following G_1 phase arrest, in vitro and in vivo.	Proliferative
Paland et al., 2009 [175]	Normal fibroblasts (NAFs), CAFs.	x	Epithelial cells; Metastatic-prostate-cancer cells (PC-3).	8 days	In vitro	NAFs inhibited, while CAFs promoted the growth of immortalized epithelial cells, but this activity was reversed for PC-3 cells.	Proliferative

(continued on next page)

Table 2 (*continued*)

Ref.	Fibroblast (F)	x	Cancer cell (C)	Duration of co-culture	Culture procedure	Effects on cancer cells, factors involved and other remarks	Growth phase of fibroblasts
Shao et al., 2011 [176]	Normal neonatal foreskin fibroblasts.	x	Melanoma cell lines.	2 days	In vitro	Fibroblasts inhibited melanoma cell growth by NOTCH1 signaling and WISP-1 upregulation.	Proliferative
Franses et al., 2011 [177]	Umbilical-vein endothelial cells (EC); Lung fibroblasts.	x	Breast cancer cell lines.	4 days in vitro; 22 days in vivo.	In vitro and in vivo xenograft tumor mouse model.	Reduction of cancer-cell proliferation and invasiveness by EC-conditioned medium in vitro and in vivo.	Proliferative
Sun et al., 2011 [178]	Pancreatic-cancer MSCs.	x	HepG2.	3 days	In vitro	Inhibition of cancer cells by MSCs, enhanced by TRAIL-transfection and by increased MSC:cancer cell ratio.	Proliferative
Chang et al., 2012 [179]	Normal stromal fibroblasts; CAFs.	x	Breast-cancer cell lines.	21 days	Soft agar colony assay.	Promoting or restraining activity of fibroblasts was observed in different cancer cell lines. The restraining activity was attributed to blocking of the P13K/AKT/β-catenin pathway.	Proliferative
Li et al., 2013 [180]	Foreskin MSCs.	x	Gastric-cancer cells.	72 h in vitro; 27 days in vivo	In vitro transwell system; in vivo athymic nude mice.	Inhibition of cancer-cell proliferation and induction of apoptosis in vitro and in vivo. F:C Ratio 1:1, 1:5, 1:10.	Proliferative
Takahara et al., 2014 [181]	Adipose-tissue-derived stromal cells.	x	Prostate-cancer cells, LNCaP, PC-3.	48 or 72 h.	In vitro; in vivo (athymic nude mice).	Inhibition of proliferation of the cancer cells in vitro and in vivo.	Proliferative
Ryu et al., 2014 [182]; Jung et al., 2019 [183]	Adipose-tissue-derived MSCs (ASCs).	x	MCF-7 cell line H460 human lung-cancer cells.	5 days	In vitro transwell system.	Suppression of growth of MCF-7 cells by IFN-β produced by the ASCs via the JAK/STAT signaling pathways.	Proliferative
Ahn et al., 2015 [184]	Adipose-tissue-derived MSCs (AT-MSCs).	x	Melanoma cell lines.	72 h in vitro; 15 days in vivo.	In vitro; In vivo (athymic nude mice).	Inhibition of growth of the melanoma cell lines in vitro and in vivo. Arrest of the melanoma cells in the G_0/G_1 phase of the cell cycle and apoptosis.	Proliferative
Lathrop et al., 2015 [185]	hMSCs; TRAIL-expressing MSCs.	x	Mesothelioma cell lines.	24 h in vitro; 3 weeks in vivo.	In vitro; in vivo.	Inhibition of mesothelioma cells in vitro and in vivo by hMSC-TRAIL cells, reducing local inflammation and cell migration, and induction of apoptosis.	Proliferative
Kaukonen et al., 2016 [132]	Telomerase immortalized normal-fibroblast matrix.	x	HeLa, MDA-MB-231 breast-cancer cell lines.	5–6 days in vitro; 5 days in vivo.	In vitro transwell system; in vivo (athymic nude mice).	Normal stromal-fibroblasts suppress proliferation of cancer cells by generating an antitumor extracellular matrix, via mechanosensitive regulation of JMJD1a-mediated transcription.	Proliferative
Wang et al., 2017 [131]	Pancreatic-cancer CAFs.	x	Pancreatic-cancer cell lines.	24 h in vitro; in vivo until tumor reached 1.5 cm diam.	In vitro transwell system; in vivo xenograft mouse model.	Senescent CAFs supported, while inhibition of senescent-CAF stromal-cancer signaling pathways restrained cancer growth. IL8 overexpression in senescent CAFs promoted invasion and metastasis.	Proliferative

morphology and protracted long argyrophilic cytoplasmic-projections, with an obvious tendency to encircle small and large HeLa colonies (Fig. 1). It was observed that these encircling fibroblasts, showing a remarkable affinity for, and active communication with, HeLa cells, actively divided, forming a dense layer surrounding the HeLa colonies, limiting their outgrowth. This activity was maintained for the entire duration of the experiment [92]. The proliferation state of the fibroblasts was evident by their intense Ki-67 staining (Ref. [26], Figs. 30–33), as well as by their dense growth at the areas of their confrontation with the edge of cancer colonies (Fig. 1a,e,f), (Ref. [26], Figs. 23, 24; Ref. [114], Figs. 2, 5; Ref. [118], Figs. 3,4). Over time, a series of prominent changes were observed involving the growth patterns, protein expression, chromatin features, and cell survival in both cell types (Fig. 1). Specific changes in histological staining for Ki-67, esterases, DHFR, lipids, argyrophilic proteins, and E-cadherin indicated the effect of cell interactions on diverse biochemical pathways in both interacting cell types [26]. Finally, a catastrophic apoptotic disintegration of the HeLa colonies was seen (Fig. 1e, f, g, h). However, a morphologically variant HeLa cell type emerged forming new colonies (Fig. 1i), opening a plethora of new questions. All the above characteristic morphological and functional changes depended on fibroblast proliferation. Our previous experiments showed that the anticancer properties of fibroblasts diminished when their proliferation was temporarily interrupted by fresh-medium deprivation, giving rise to a growth spurt of the cancer cells (e.g. Ref. [26], Figs. 23, 25; Ref. [114], Figs. 6,7). These results are important evidence that it is the proliferating fibroblasts that inhibit cancer-growth, not the quiescent fibroblasts. These interactions were observed using human primary fibroblast strains obtained from normal skin, breast cancer, normal breast, and tonsillitis tissue [26].

Fig. 2 displays a schematic representation of the interaction steps between cancer cells and fibroblasts, leading to the development of the supportive or restrictive activity of the fibroblasts on cancer growth. Several studies and comprehensive reviews have provided detailed descriptions of numerous mechanisms and factors involved in these interactions [1,2,3,4,5,11,16]; however, the process guiding the anticancer activity of fibroblasts is still obscure [17,18,19,20,26].

3D organotypic in-vitro models, as well as differential staining of fibroblasts and cancer cells, may further elucidate the complex cell interactions in the TME, especially if they mimic human tumors and provide the appropriate conditions for studying tumor heterogeneity, cell-to-cell ratios, necrotic areas, and alterations in biochemical pathways [122,123,124,125,126,127,128,129]. Gelfoam sponge-matrix histoculture seems especially promising for these studies [117,130]. Gelfoam sponge-gel histoculture is a bridge to in vivo studies. Furthermore, the translation of the in vitro anticancer properties of fibroblasts to the complex in vivo environment may require novel methodologies, but they will indicate new ways to target tumor growth [186]. Until new in-vivo knowledge becomes applicable, caution should be exercised in

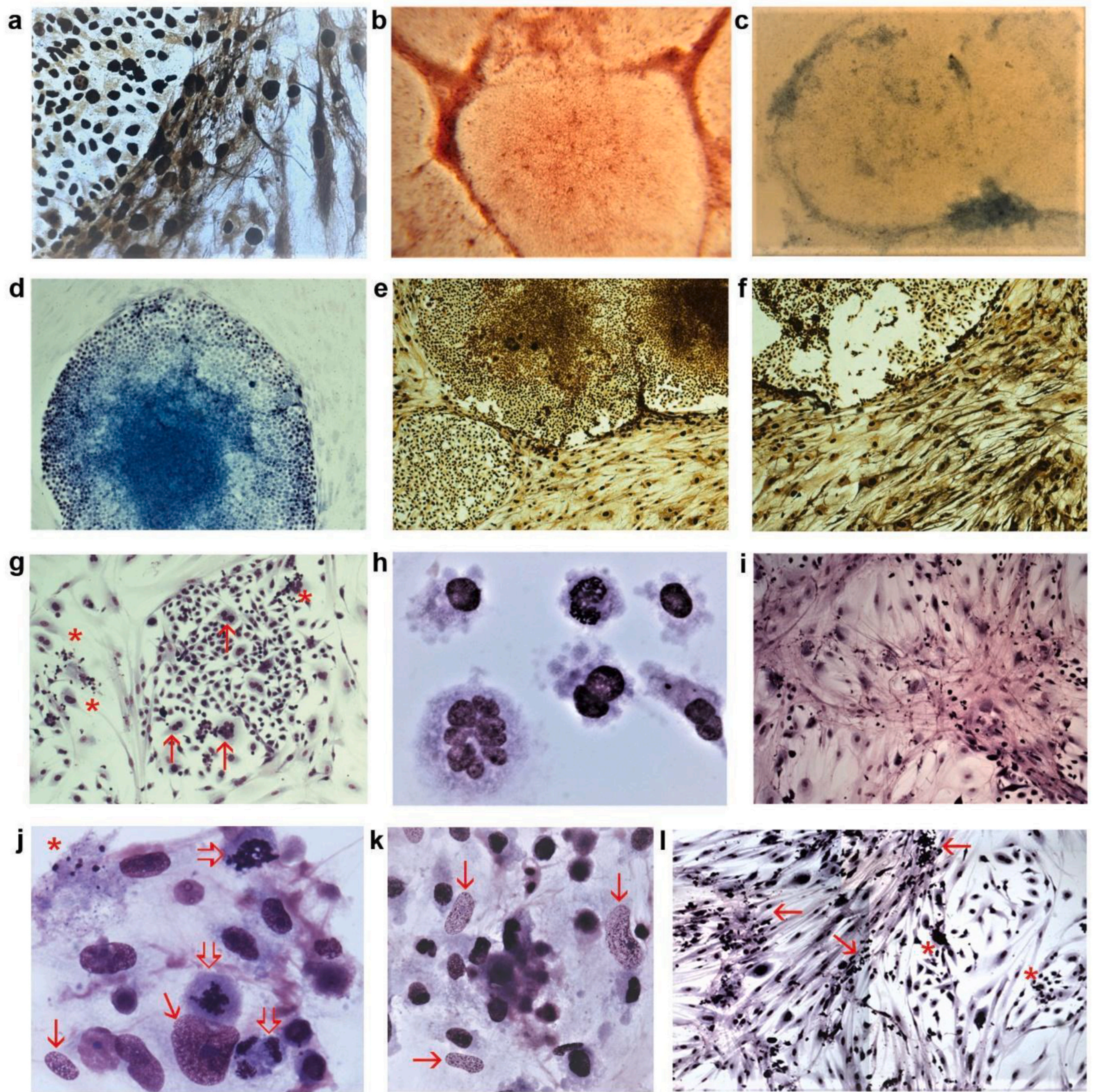

Fig. 1. Morphological and functional events observed during the in-vitro interactions between fibroblasts (F) and HeLa cancer cells (C) for 20 days. Culture conditions: F:C ratio, 100:1; 5–6 HeLa cells were allowed to form colonies of 8–16 cells on a 1 × 1 cm coverslip and then a suspension of fibroblasts was added (day 1); medium was replaced every second day (further details in Delinassios et al., 2015 [26]). a) Development of long argyrophilic cytoplasmic projections and formation of a dense layer of fibroblasts surrounding the HeLa colonies. b) Increased esterase activity in the dense layer of fibroblasts. c) Lipid production in the dense layer of fibroblasts. d) Induction of increased DHFR activity at the perimeter of the HeLa colonies. e-f) Gaps, due to HeLa-cell detachment, along the perimeter of HeLa colonies, which are gradually increased until HeLa colonies are disintegrated. g) Areas with abundant multinucleated (arrows) and apoptotic mini sub-cellular fragments (asterisks) of HeLa cells. h) Areas with apoptotic HeLa cells. i) Expansion and growth of fibroblasts in areas previously occupied by HeLa colonies. j-k) Blockade of fibroblasts in early-to-late prophase (G2-M) (arrows; double arrows show abnormal HeLa mitoses, and asterisks show mini sub-cellular fragments of HeLa cells). l) Emergence of foci of morphologically-different HeLa-cell growth (asterisks) within an environment of growing fibroblasts and apoptotic mini sub-cellular fragments of HeLa cells (arrows).

Figure 1	a	b	c	d	e	f	g	h	I	j	k	l
Fibroblast cell line used*	KR-BC	LA-BC	KR-BC	LA-BC	KR-BC	KR-BC	G-EP	G-EP	KR-BC	KR-BC	KR-BC	KR-BC
Co-culture day	8	13	10	9	11	13	15	15	18	18	18	18
Magnification (approx) x-	270	30	20	50	30	40	70	900	40	240	200	70
Staining**	A	E	L	D	A	A	G	G	G	G	G	G

*Details: Delinasios et al., 2015 [26]; **Stainings: A, silver; E, non-specific esterases; L, lipids; D, dihydrofolate reductase; G, giemsa.

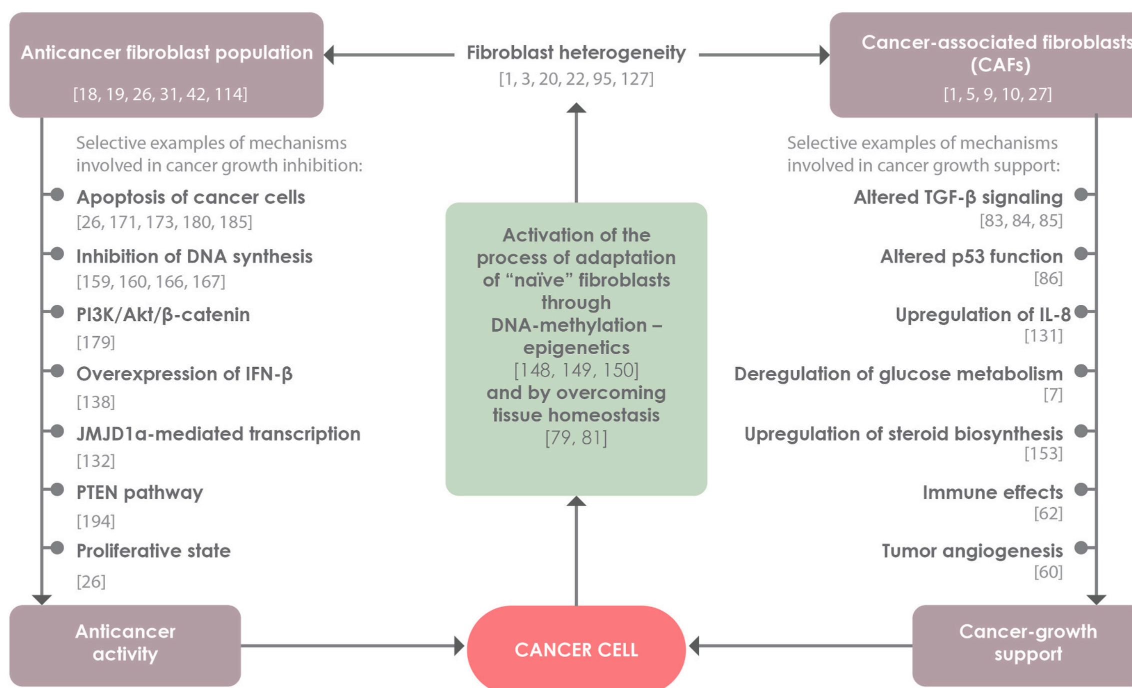

Fig. 2. Schematic representation of the interactions between cancer cells and fibroblasts showing the development of the supportive or restrictive activity of the fibroblasts on cancer cells. Selected key references are shown.

the extrapolation of in-vitro experiments to the in vivo situation. Considering that the proliferating-fibroblast population includes cells in different cell cycle phases, it should be interesting to study the effects of each cell's cell-cycle phase on cancer cell growth in vitro and in vivo. Cell-cycle phases can now be imaged in real time in Gelfoam histoculture, as well as in vivo, using FUCCI, which color codes each phase of the cell cycle in real time [187,188]. We have now developed technology to reveal tumor-residing fibroblasts with fluorescent genetic reporters by engrafting tumors, including patient tumors, in fluorescent-protein-expressing transgenic nude mice, whereby the growing tumors stably acquire fluorescent-protein-expressing fibroblasts from the murine host [189,190]. We demonstrated the specific targeting of stromal fibroblasts labeled with one-color fluorescent protein and cancer cells with another-color fluorescent protein, with TGF-β [191]. The transgenic FUCCI mouse [192] will be appropriate to determine the role of proliferation and cell-cycle phase, as well as gene expression of tumor-residing fibroblasts on implanted cancer cells also color-coded with a fluorescent protein.

Since 1976, many investigations have contributed to establishing that tumor-stromal fibroblast heterogeneity encompasses these cells with cancer-restraining as well cancer-promoting properties as discussed above. The categorization of CAFs into groups of senescent CAFs (cancer-promoting) and non-senescent (cancer-restraining) CAFs [131], also supports our hypothesis that the fibroblasts within the TME may be divided into two functional types regarding their behavior when challenged with cancer growth: ("a") those which are enabled to proliferate under conditions of availability of nutrients, time and space, and exert their innate antitumor action; and ("b") those which express senescence, suppress their innate anti-cancer traits and acquire cancer-promoting action. Consequently, further research in finding ways to increase the "a:b" ratio may need to pay attention to triggering and maintaining a high proliferation rate of fibroblasts within the TME.

Author contributions

JGD conceived and wrote the review. RMH made scientific and editing suggestions while reviewing and revising drafts of the manuscript.

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Consent for publication

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Declaration of Competing Interest

The authors declare no potential conflicts of interest.

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