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Stromal reprogramming: A target for tumor therapy

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ABSTRACT

Cancer associated fibroblasts (CAFs) as the dominant, long-lived and highly plastic cells within the tumor microenvironment (TME) with multi-faceted roles that are endowed with tumor aggressive features. They can instruct and shape the stroma of tumor into being a highly qualified bed for cellular recruitment, differentiation and plasticity in the host tissue or secondary organ/s. In this Review, we have a discussion over CAF reprogramming as a general concept, inducers and outcomes, pursued by suggesting potential strategies to combat this key promoter of tumor.

1. Introduction

Cancer associated fibroblasts (CAFs) (also called peritumoral fibroblasts or reactive stromal fibroblasts) are the most frequent cell population of mesenchymal lineage within the tumor microenvironment (TME) of the majority of cancers [14,59,73], and their stromal presence depicts poor clinical outcomes [2]. CAFs are frequently found in breast, prostate and pancreas cancers, while their presence in renal and brain tumors is less common [3]. CAFs can occupy about 80% of breast and pancreatic tumor mass (volume) developed by widespread desmoplastic aggregations [5]. From cellular views, CAFs take about 40–50% of all tumoral cell population within cancers [78]. Fibroblasts are considered as cockroaches of human body in which they are able to survive upon exposure to severe stresses, even after culturing post-mortem tissue samples [41,76], and within a tumor they can sculpt the growth-permissive TME [84]. CAFs are referred to the architects of tumor pathogenesis [72], and their presence in the stroma take part of the role for the long-held notion about tumors that are 'wounds that never heal' [14,19,71,84], inferring that tumors and wounds have many similarities including fibroblast activation, and enhanced extracellular matrix (ECM) synthesis and remodeling [51], and that therapy is applicable by CAF harness [15]. CAFs are synthetic machines producing a plethora of chemokines and cytokines for sustaining their active state and implementing tumor progressive roles exerted in a multi-faceted way. CAFs create ECM structure, and are account for immune and metabolic reprogramming within the TME [41]. CAFs promote cancer cell intravasation, colonization and growth in the metastatic sites [41]. Compared to the normal tissue fibroblasts, CAFs exhibit robust proliferation and migration, and impose higher influence on cancer cells, determined mainly by the TME [41]. CAFs have higher levels of cytokines and other factors and enhanced capability for ECM remodeling [23]. In addition, CAFs have multiple cytoplasmic branches, indented nuclei, well-developed Golgi apparatus, higher endoplasmic reticulum and free ribosomes, and are enriched in stress fibers causing cell polarity [14]. Diverse influence from TME along with miscellaneous tissue and cell type origin has made CAFs a heterogeneous population [4] with no specific marker exclusively expressed by the cells [84].

Both cancer cells and cancer stem cells (CSCs) are able to reprogram into CAFs [62]. Unlike CSCs, CAFs lack genetic alterations, and genetic mutations is less common in the cells [65]. The questions here are what tumoral factors induce stromal reprogramming? and how this is important in relation with tumor progression and therapy? In this review, we aimed to discuss stromal reprogramming in tumors, with a special focus over CAF reprograming (as the dominant cell type within the stroma of tumor) and its critical contribution in regard with tumor progression. Then, some strategies are illustrated for targeting this important promoter of tumor aggressiveness.

2. Stromal reprogramming

To our understanding, cellular reprogramming within the TME might be a clear example for tumors being a dynamic pack of cells that

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are continuously reshaping in order to promote adaptive mechanisms for tumor growth and metastasis. Stromal reprogramming is a critical contributor to the TME remodeling and cellular interactions within a tumor. CAFs direct these interactions to pave the path for tumor progression and metastasis. In fact, CAFs are being instructed to attract environmentally friendly cells so as to help tumor progression. A cell type with such capability must be abundance in number and versatile in activity to exert variable responses under exposure to the ever-changing conditions occurring in the TME. Cellular reprogramming into CAFs can both help surviving from hazard conditions and to guide other cells exhibiting appropriate responses to such conditions. Thus, stromal reprograming can be a key resistance promoter. It seems that almost all cells within the TME have such capacity. This characteristic infers that cells within the TME are highly plastic, able to change morphology in order to synchronize their activity with the constantly changing milieu. The phenotypic reprogramming involves three steps: cellular (normal fibroblasts and other cells of origin) recruitment (induced primarily by factors released from cancer cells), *trans*-differentiation into cells with a CAF-like morphology (mesenchymal-mesenchymal transition [MMT]) without acquiring genetic alterations, and, finally, maintenance of the newly formed CAF cells (by TME factors including ECM stiffness [72]) [10,66,68].

2.1. Cellular recruitment

Fibroblasts are the key cells that reacts to tissue injuries and diseases, such as development of tumors. To promote a tumorigenic nature, the first step would be fibroblast recruitment toward the stroma of tumor. A number of factors are implicated in this recruitment. Hypoxia within the TME is an inducer. This condition may rise by the existing CAFs or from the cancer cells [3,68]. Platelet-derived growth factor (PDGF) plays a key role for recruitment of stromal fibroblasts [24,64]. Normal fibroblasts are not the sole origin of CAFs. In fact, there are a range of cells that have this capability, which includes mesenchymal stem cells (MSCs), pericytes, adipocytes, inflammatory, epithelial and endothelial cells (ECs) [80]. It seems that the multi-cellular origins for CAFs may indicate the utmost importance these cells take in cancer pathogenesis.

2.2. Cellular transitioning

When cells are recruited toward the TME, the next step is their *trans*-differentiation into attaining a CAF-like morphology with mesenchymal phenotype. Epithelial cells can undergo epithelial-mesenchymal transition (EMT), and ECs can take an endothelial-to-mesenchymal (EndMT) transition [80]. Fibroblasts upon transition into CAFs will lose caveolin-1 (Cav-1) and enhance expression of factors like monocarboxylate transporter 4 (MCT4, the main exporter of lactate and a marker of glycolysis) [49,56]. In the Table 1, a number of factors involved in induction of stromal reprogramming are presented.

2.2.1. Oxidative stress and stromal reprogramming

CAFs exhibit multiple distinct subtypes with specific markers co-existing in tumors. Proportion of these subtypes is modified deeply by chronic oxidative stress. This co-existence is for supporting metastatic dissemination [20]. Under exposure to oxidative stress, CAFs mostly exhibit a myofibroblast-like phenotype (α-SMA$^+$ subtype) that are highly reactive and have intense secretory profiling [29]. PDGFR-β^+ is another subtype of CAFs possibly affected by reactive oxygen species (ROS) exhibiting enhanced growth and motility [20]. Inducible effect of ROS on myofibroblast reprogramming is mediated partly through hypoxia inducible factor (HIF)-1α accumulation [65]. ROS are also potent promoters of metabolic reprogramming in CAFs, which is required for developing adaptation to oxidative crisis and thus promoting chemoresistance [20,21]. ROS enhance CAF glycolysis through induction of transforming growth factor (TGF)-β [21] and Cav-1 downregulation [55]. High TGF-β and low Cav-1 inducible effects on ROS generation in CAFs possibly reduce gap junctions between the cells; this reduction allows for attaining a myofibroblastic phenotype, as well as for enabling contacts between cancer cells and further tumor progression [18,19]. CAFs are also adapted to launch an antioxidative machinery to avoid cell death related to chemotherapy induced oxidative crisis [16]. Taken together, it is justifiable to assert that CAFs like CSCs [62] are equipped with a compatible reduction–oxidation (redox) system in order to habitat readily with the surrounding environment and thus resist therapy.

Table 1
Factors influencing reprogramming of normal fibroblasts into cancer associated fibroblasts (CAFs).

Factor name	Source	Enhancer or repressor	Tumor type	Ref
MiR-222		enhancer	breast	[11]
MiR-155	cancer cell	enhancer	pancreas	[67]
MiR-21	–	enhancer	breast	[69]
SNAI2	–	enhancer	ovary	[83]
TIMs	–	repressor	–	[71]
LPA	cancer cell	enhancer	–	[68]
TGF-β	fibroblast	enhancer	–	[43,57]
SDF-1	fibroblast	enhancer	–	[43]
NF-κB	–	enhancer	–	[49]
Cav-1	fibroblast	repressor	breast	[54]
BRCA1	fibroblast	repressor	breast	[54]
OPN	cancer cell	enhancer	breast	[74]
HIF-1α	–	enhancer	–	[65]
H_2O_2	cancer cell & CAF	enhancer	–	[3]
HTRA1	–	enhancer	gastric	[79]
HIPK2	cancer cell	repressor	colon	[31]

TIM, tissue inhibitor of metalloproteinase; LPA, lysophosphatidic acid; TGF, transforming growth factor; SDF, stromal derived factor; Cav-1, caveolin-1; BRCA1, breast cancer type 1 susceptibility; OPN, osteopontin; HIF, hypoxia inducible factor.

2.2.2. Inflammation and stromal reprogramming

Activation of a pro-inflammatory gene signature is a characteristic developed upon CAF transitioning from normal fibroblasts under exposure to cancer cells [65]. The chronic inflammation primed by CAFs is considered as a main risk factor for many cancers. During the acute phase of inflammation, fibroblasts are reversibly activated, while irreversible activation of fibroblasts (pro-invasive CAFs) are formed during the chronic inflammation; these constantly activated cells act by influencing other cells within the TME. Activation of NF-κB in normal fibroblasts *trans*-differentiate them into CAFs, and its activation in the CAFs supports stemness and invasion [20,28,30,65,79,85].

2.2.3. Hypoxia and stromal reprogramming

Hypoxia is a key condition within the TME influencing cellular interactions and reprogramming. Metabolic reprogramming and adaptation of CAFs, and their metabolic symbiosis with cancer cells is under the strict control of hypoxia [29,41]. In fact, cancer cells induce a pseudo-hypoxic milieu for CAFs [85]. HIF-1α is a main actor for this aim. HIF-1α promotes a metabolic transition toward aerobic glycolysis in CAFs [17] and cancer cells [48]. In CAFs, this is mediated by HIF-1 regulatory effect on MCT4 gene [17,57]. Promotion of mtOXPHOS in cancer cells is mediated by HIF-2α [17]. HIPK2 downregulation by hypoxia in cancer cells contributes to fibroblast *trans*-differentiation into CAFs [31].

2.3. CAF maintenance

2.3.1. Metabolic symbiosis is a key for CAF maintenance

CAFs are known as the key fuel source within the TME. CAFs have metabolic symbiosis with cancer cells. Cancer cells in order to maintain

their survival and immortality are dependent on CAFs; the term 'fibroblastic addiction' is a concept used in this way, namely addiction of cancer cells to CAF-derived energy source. The contact between cancer cells and CAFs also educate CAFs to transform into a hyper-synthetic phenotype. This transformation is mediated possibly by ROS release from cancer cells [5]. CAFs shuttle lactate through which they influence tumor-stroma interplay [5,29,34,36,49]. Metabolic flexibility and adaptation is a characteristic that distinguishes CAFs from normal (quiescent) fibroblasts [82]. Being in contact with cancer cells, CAFs are induced to shift their metabolic demand toward glycolysis; enhanced glycolysis can also prime normal fibroblasts in order to attain a CAF phenotype. TGF-β and PDGF are known to induce this metabolic shifting in CAFs. An outcome of glycolysis reprogramming in CAFs is high lactate production and release into the TME, so increasing TME acidity [29,38,68,86]. Cancer cells through uptake of lactate can reduce the extreme acidity of the TME [20]. This is a protective mechanism for regulation of the acidity within the TME. Over uptake of lactate can possibly be destructive for tumor survival [29]. Proliferative cancer cells by being in contact with CAFs and further uptake of lactate, potentiate their mitochondrial mass and activity, and so undergo metabolic reprogramming toward oxidative phosphorylation (OXPHOS). The paracrine effect of aerobic glycolysis (Warburg) in CAFs for fueling mtOXPHOS in cancer cells (with lower dependence on glucose metabolism) is called 'reverse Warburg effect'. Oxidative stress (H_2O_2 release) is occurring as a secondary outcome of the OXPHOS metabolism, and high ROS production causes HIF-1 stabilization and chemotherapy resistance [29,36,37,62,65,81]. Metabolic shifting toward glycolysis in CAFs is partly due to the HIF1 stabilization [29,68]. Increased autophagy (possibly promoted by hypoxia) induced by factors like TGF-β is seemed to be responsible for metabolic differences between normal fibroblasts and CAFs [12,57,65]. Chaudhri and colleagues delineated no difference in the individual metabolites between CAFs and normal fibroblasts, but rather a considerable steady-state abundance of metabolites between the two cell phenotypes [12]. In fact, CAFs are equipped with a highly compatible autophagy system (compared to the normal fibroblasts) to transfer nutrients onto cancer cells continuously [53]. In addition, recovery and growth (so called relapse) of tumoral cells after radiotherapy is mediated by CAF-induced autophagy in the cells [78].

Stromal TGF-β acts for linking metabolic reprogramming in CAFs (through induction of Warburg effect) with the nearby cancer cells (by increasing mitochondrial activity) [33]. Proliferating cancer cells utilize lactate released from CAFs for mitochondrial OXPHOS [23]. In a report by Zhao and colleagues, positive relation between CAF-derived exosomes and enhanced tumor cell glycolysis under nutritional stress has been highlighted [87]. Shifting toward glycolytic metabolism would help tumor cells to acquire an EMT phenotype and to colonize in distant organs. OXPHOS in tumoral cells also promotes metastasis [81]. Of high importance, most glycolytic cancer cells maintain their functional OXPHOS, so they are able to restore OXPHOS when glycolysis in suppressed in the cells [5]. In addition, like CAFs, glycolytic cancer cells can utilize lactate taken up by CAFs to serve as a fuel source [35]. Taken all into consideration, it is reasonable to declare that CAFs act for promoting metabolic flexibility in cancer cells and vice versa (called symbiotic metabolic sharing), which, in part, is determined by conditions within the TME. This flexibility promotes cellular resistance and adaptation to hyponutrient and hypoxic conditions [5] (Fig. 1).

2.3.2. ECM stiffness

ECM stiffness is a hallmark of many cancers [60]. Fibroblasts are highly sensitive to the ECM mechanics. ECM stiffness is produced by CAFs, and it acts to maintain a CAF phenotype by activation of Yes-associated protein 1 (YAP) (via nuclear import) in these cells [46,60]. YAP activation in CAFs regulates their contractibility (maintaining their active state) and ECM remodeling (reinforcing ECM stiffness for providing a permissive environment for invasion of tumoral cells) [6].

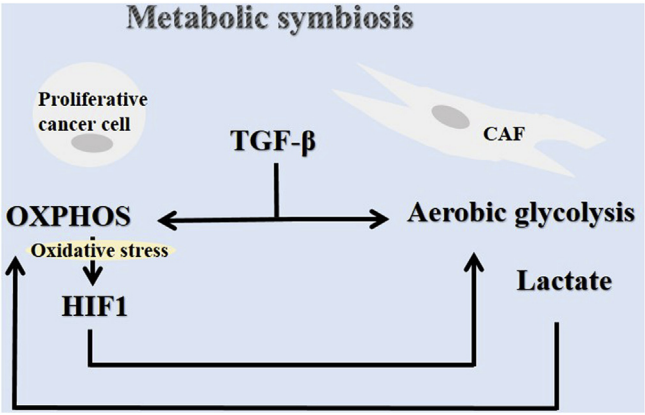

Fig. 1. Metabolic symbiosis between cancer associated fibroblasts (CAFs) with cancer cells. CAFs and cancer cells are co-evolved metabolically. Lactate release by glycolytic CAFs promotes mitochondrial oxidative phosphorylation (mtOXPHOS) in cancer cells (reverse Warburg); stabilization of hypoxia inducible factor 1 (HIF1) by mtOXPHOS cancer cells in an oxidative stress setting further induces glycolysis in CAFs for further release of lactate into the tumor stroma.

Aerobic glycolysis is required for sustaining YAP activity [27]. ECM stiffness through YAP activation induces metabolic rewiring in both CAFs and cancer cells [8].

3. CAF mediated cellular recruitment and plasticity

CAFs are inherently plastic and are known to influence plasticity of other cells recruited toward the TME. CAFs through release of lactate into the TME promote monocyte recruitment and transition into pro-tumor M2 phenotype, while normal fibroblasts would shift the cells into anti-tumor M1 phenotype [34,84]. CAFs are also involved in bone marrow cell recruitment and differentiation into ECs for promotion of neoangiogenesis [20]. Recruited bone marrow cells can also attain a CAF like morphology [25]. CAFs also induce regulatory T (Treg)/cytotoxic T lymphocyte (CTL) ratio, causing increased accumulation of immunosuppressor Tregs [42]. CAFs exclude cancer cell exposure to CTLs through CXCL12 biosynthesis and ECM stiffness [39]. Cross-talking between CAFs and cancer cells promotes cancer cell plasticity through which cancer cells acquire an EMT phenotype; the EMT cells can either differentiate into CAFs [7,25,28] or dedifferentiate into CSCs [32,71] (Fig. 2).

4. How stromal reprogramming is related to metastasis?

Reprogramming between cancer cells, CSCs and CAFs is vital for tumor metastasis. Recruitment and reprogramming of normal stromal cells toward the pre-metastatic niche is possibly facilitated by tumor cells. Here, the reprogrammed cells can help metastatic dissemination and tumor growth [52]. Autocrine secretomes of fibroblasts including TGF-β and stromal-derived factor-1 (SDF-1) can change the cells into CAFs [73]. In addition, CSCs have the capacity to reprogram into CAF-like cells; this reprogramming is mediated by release of TGF-β from CAFs, and it would help formation of niches for maintaining CSC survival in the sites of metastasis [61]. In concise, co-traveling CAFs toward the site/s of metastasis would provide early growth advantage for active (non-quiescent) tumoral cells, while they form niches for maintaining survival of cells (namely CSCs) undergo dormancy in these niches [18,61].

5. How to target stromal reprogramming?

CAFs are conspicuous stromal targets in almost all solid tumors

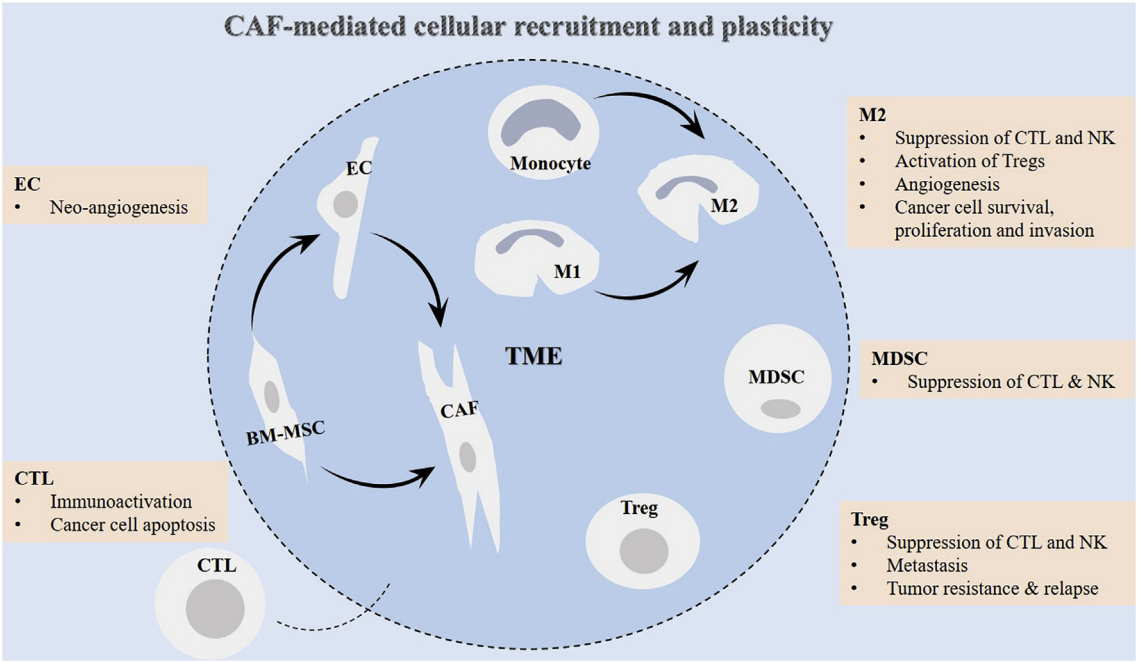

Fig. 2. The effects of cancer associated fibroblasts (CAFs) on cellular recruitment and plasticity within the tumor microenvironment (TME). CAFs promote recruitment of monocytes and their differentiation into macrophage type 2 (M2) cells. Recruitment of bone marrow mesenchymal stem cells (BM-MSCs) and their differentiation into endothelial cells (ECs), CAFs or both is also mediated by CAFs. In addition, CAFs increase the regulatory T (Treg)-to-cytotoxic T lymphocyte (CTL) ratio in the TME, thus along with enhanced infiltration of myeloid derived suppressive cells (MDSCs) represses anti-tumor immunity, causing tumor growth and metastasis.

[14]. By being the most populous cells (and persistent presence) in the tumor stroma, along with the genetic stability compared to cancer cells, CAFs are the desired target for effective tumor therapies bringing reduced chance of resistance and tumor relapse [44,69,82].

5.1. Conversion of CAFs into a quiescent or normalization state. Is that helpful?

In healthy tissues, the term 'resting' or 'quiescent' is used for fibroblast cells that are not engaged actively in turnover of ECM components [34,71]. Cells residing within the TME are able to acquire a quiescence state. For CSCs, this state can help acquiring a more invasive and resistant phenotype [62]. How does it work for CAFs? CAFs, as discussed, have subpopulations that share an active state. These activated fibroblasts can repress tumor progression at early stages. The cells through formation of gap junctions inhibit contacts between cancer cells [19]. However, for tumors at higher stages, CAFs undergo infrastructural development, promote multifaceted interactions, and are kept in a chronically (irreversibly) active state by continuous influx of factors derived from tumoral cells, and thus they are highly invasive and are intensely resistant against reversion into a normal quiescent state [19,44,63]. CAFs in an active form have higher recruitment, activation, proliferation and migration compared to the quiescent fibroblasts [14]. Phenotypically, CAFs are similar to that found in wound healing, but the difference is that pro-invasive CAFs are permanently activated that neither revert to normal fibroblasts nor undergo apoptosis or elimination [2,3,47,80]. Reactive senescent fibroblasts are formed upon tumor exposure to irradiation; these senescent cells have characteristics similar to CAFs except for not being able to transform into a quiescent state [25]. The senescent stromal cells are able to recruit immunosuppressive cells toward the TME [70]. So, senescence can be targeted as a strategy to breakdown active stromal cells within a tumor.

In situ reprogramming of CAFs is most effective for desmoplastic tumors such as pancreas and bladder; in such tumors, CAFs wrap around tumor vasculature, thus hampering infusion of drugs to the tumor site. Normalization into a non-myofibroblastic (i.e. inactive) phenotype is a tempting and promising strategy for targeting stromal reprogramming. The normalized fibroblasts (formed from reversion of CAFs) take tumor suppressive roles. By fibroblast normalization, the amount of fibrotic content is reduced with ensuing decompression over intratumoral vasculature, and thus creating a window permeable to the targeted therapy [58]. Fibroblast normalization can cause immunoactivation, and sensitizing cancer cells to therapeutics [65]. There is a report by Chauhan and colleagues who found that angiotensin receptor blocker (ARB) can switch CAFs into a quiescent state as well as alleviating immunosuppression, and the two effects were found to be interrelated [13]; this is possibly mediated by TGF-β silencing [1]. The evidence for this is that TGF-β is an important driver of CAF phenotype acquisition and maintenance [77]. CAFs through secretion of TGF-β are kept in an active state in an autocrine manner, and that this cytokine takes immunosuppressive roles in the TME [1]. Stimulators of all-trans retinoic acid [26], vitamin D receptor [14], and ARBs [13] were found to be useful for dedifferentiation of CAFs into a quiescence state and so enhancing anti-tumor immunity against tumor. Administration with the vitamin D analog calcipotriol is reported to reprise activated fibroblasts into the quiescence state and thus inducing stromal remodeling, and increasing the efficacy of chemotherapy in pancreatic cancer [75].

5.2. Antioxidants for targeting stromal reprogramming

As mentioned, oxidative stress is a key mediator of CAF reprogramming and a prominent inducer of metabolic symbiosis between CAFs (also called reactive glycolytic stroma) with cancer cells, and so shifting toward normal phenotypes using antioxidants can rise motivation among researchers for cancer prevention. Cigarette smoke is an enhancer for induction of this metabolic symbiosis [23]. Antioxidants are effective for repressing the effects exerted from cancer cells on fibroblast-to-myofibroblast transdifferentiation. As for example, cancer cell death induced by N-acetylcysteine (NAC) and Tempol can be

effective for reversing metabolic changes in breast myofibroblasts [10,54].

5.3. Targeting reprogramming inducers

Therapy can be directed for targeting signaling related to stromal reprogramming. TGF-β is a pleotropic, immunosuppressive cytokine deregulated in many tumors, and it acts on a variety of TME cells including CAFs. TGF-β is a strong inducer of stromal reprogramming and heterogeneity, so it can be a promising target [1,10,51]. Aerobic glycolysis, oxidative stress and autophagy/mitophagy in CAFs are all under the control of TGF-β [5]. Due to the key roles take by this cytokine for CAF reprogramming, reversion into a non-proliferative quiescence state is seemingly applicable by deregulation (or disruption) of TGF-β [1,22,40].

6. Concluding remarks

Intractable TME, tumor relapse and lethal metastasis are the main interrelated predicaments in tumor therapy [15], being spotlights of current cancer research. Stromal reprogramming within the TME is without a doubt a potent inducer of carcinogenesis, and that CAFs are placed at the top of this event. Rearrangement of fibroblasts in the shape and infrastructure enables them acquiring a constitutive active CAF morphology, and being highly efficient for promoting tumor initiation, progression and relapse in corroboration with other cells within the TME. This is understandable through intense bi-directional interactions exist between CAFs with other cells within a tumor. As for example, metabolic symbiosis with cancer cells would help satisfying energy demands in various situations, and the term ‘metabolic slave’ used for CAFs in this context [5] is now indicate the more advantage cancer cells taken from CAFs for promoting survival and growth. CAFs would take such actions for developing mechanisms of adaptation in cancer cells, so the cells upon exposure to unstable environments induced by targeted therapy or even mimicked upon migration toward the metastatic sites can effectively maintain their survival, resistance and growth. In fact, stromal cells (predominantly CAFs and their products) are acting as a ‘soil’ to ‘seed’ the tumoral cells in these versatile sites [9,14,52]. The Achilles' heel of current approaches is primarily for targeting the fast-proliferating tumor ‘seeds’, ignoring to a great extent the contribution of the tumor fertilizing ‘soil’, namely the TME [51]. Targeting CAF reprograming is thus a desired approach for dissociating cellular cross-interactions within the TME; this is due to that CAFs rarely harbor genetic alterations, and are less likely to acquire resistance after targeted therapy compared to that for cancer cells [85]. In fact, genetic stability would guarantee for maintaining CAFs sensitive to drugs [18]. Extensive control imposed by CAFs over cells belong to the immune system indicate that CAF targeting can be a desired approach for improving the efficacy of immunotherapy, particularly for desmoplastic cancers [50]. Among a number of strategies proposed so far, a special and promising approach is active-to-quiescence shifting of CAFs. Unlike CSCs that are more invasive when acquired a quiescent state, switching fibroblasts toward a dormant state is presumably an appropriate way to debilitate them for promoting a tumor, much like their normal counterpart found in healthy tissues that exist generally in a quiescent state [50]. Of note, transcriptomatic profiling of CAFs is different among organs of origin, and so marker-based targeting of CAFs may not only be less effective but it may also cause systemic side effects such as anemia, cachexia or other paraneoplastic syndromes [45]. Multi-origin of CAFs is another concern. Although resident fibroblasts are the major origins of CAFs, a number of cells are identified for their potential to transform into CAFs, which accounts for generation of multiple CAF subtypes hard to target for cancer therapy. The focus of current research is to target pre-existing CAFs, needing more investigations for identifying the behavior of cells in the stroma of tumor and possibly identification and combating markers that are more essential for tumor progression. For example, among different subtypes of CAFs recognized so far, the higher tumor-promoting activity is conferred to the fibroblast-specific protein-1 (FSP-1) + CAFs [25], so this marker can be a target when considering the tumor type, as mentioned above. Targeting major signaling related to CAF reprogramming is another appropriate strategy. Among various signaling identified so far, a special focus must be onto targeting TGF-β.

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