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*Review*

# The Role of Recruited Adipose Stromal Cells and Their Fibroblastic Differentiation in Cancer

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**Abstract**

Adipose stromal cells (ASCs) are perivascular mesenchymal progenitors of adipose tissue. In cancer patients, ASCs can mobilize and migrate to the tumor, where they subsequently play an important role in cancer progression. This biological process involves the conversion of recruited ASCs into cancer-associated fibroblasts (CAFs). ASC-derived CAFs influence the tumor microenvironment through extracellular matrix remodeling, vascularization, and immunomodulation. These and other processes mediated by secreted paracrine factors also affect gene expression in carcinoma cells to promote the epithelial-mesenchymal transition (EMT), metabolic adaptation, survival, and invasiveness of cancer cells. ASC-derived CAFs can enhance tumor aggressiveness, accounting in part for the link between obesity and mortality observed in many cancer types that are surrounded by adipose tissue. In this review, we highlight recent findings on the characteristics and functions of ASCs in cancer and discuss their potential as therapeutic targets.

**Keywords:** adipose stromal cells; adipose-derived fibroblasts; cancer-associated fibroblasts; tumor microenvironment

## 1. Introduction: Overview of Adipose Stromal Cells

The cells in adipose tissue can be separated by enzymatic digestion into the stromal vascular fraction (SVF) and the buoyant fraction [1,2]. The SVF contains a heterogeneous population of cells that includes adipose stromal cells (ASCs), immune cells and endothelial cells, while the buoyant fraction contains adipocytes and some preadipocytes [2]. The immunophenotypes of individual ASC sub-populations have been studied previously [1,3], but are still not completely understood.

Single-cell RNA sequencing (scRNA-seq) has helped to delineate populations within white adipose tissue (WAT), including ASCs and their subpopulations [4,5]. ASCs reside in the perivascular niche and support endothelial function, as well as differentiating into adipocytes or fibroblasts depending on the cues they receive [5,6]. A subpopulation of mesenchymal stromal cells (MSCs) is comprised of preadipocytes with high adipogenic potential and expression of Platelet Derived Growth Factor Receptor Alpha (PDGFR$\alpha$) and Platelet Derived Growth Factor Receptor Beta (PDGFR$\beta$). The transient signaling balance of these receptors determines whether MSCs differentiate into beige or white adipocytes [7]. Another major subpopulation, referred to as fibro-inflammatory precursors or interstitial progenitor cells, is characterized by a gene expression profile that has been associated with modeling of the extracellular matrix (ECM) and with inflammation [8]. Age-related subpopulations, such as aging-dependent regulatory cells, have also been identified. These secrete cytokines that may contribute to the reduced subcutaneous adipose tissue and tissue plasticity observed in human aging [9].

One particular ASC subpopulation has a characteristic signature containing several co-expressed genes, such as Apolipoprotein D (*APOD*), Decorin (*DCN*), Lumican (*LUM*), Complement Factor D (*CFD*), C-X-C Motif Chemokine Ligand 14 (*CXCL14*), and Prostaglandin D2 Synthase (*PTGDS*). This signature has been identified in several studies, indicating consistency across different tissues. For example, it was found among adipocyte progenitors in subcutaneous WAT from the dataset used in study [10], as shown in cluster visceral adipose tissue-derived progenitor cells 4 (VP4) of Supplementary Table 20. Moreover, the abundance of this population in the SVF was demonstrated by analyzing the same dataset in Supplementary Fig. 1 of the paper by Cai *et al.* [11].

Interestingly, a cell population with the same characteristic signature was found among fibro-adipogenic progenitors (FAPs) in skeletal muscle. For example, in the study by Rubenstein *et al.* [12] they were reported as LUM+ FAPs in Supplementary Table 1, and included the genes *APOD*, *PTGDS*, *LUM*, *DCN*, Matrix Gla Protein (*MGP*), *CFD*, *CXCL14*, Dermatopontin (*DPT*), and Serpin Family F Member 1 (*SERPINF1*). A similar population was found in Supplementary Fig. 3a of the study by Fitzgerald *et al.* [13], referred to as a Membrane Metalloendopeptidase (MME)+ FAP population, and which expressed the genes

*APOD*, *PTGDS*, *CXCL14*, *MGP* and Secreted Frizzled Related Protein 2 (*SFRP2*). These cells can differentiate into adipocytes. Cai *et al*. [11] referred to this subpopulation of ASCs as "the ASC/FAP population", with its progenitors having both adipogenic and fibroblastic differentiation potential. Consistent with these findings, Gao *et al*. [14] identified a fibroblast progenitor subtype in a multi-tissue fibroblast atlas. This was characterized by the expression of adipogenic genes such as *APOD*, and cluster "c03" shown in Supplementary Table 2 of the report by Gao *et al*. [14], which includes all ASC/FAP genes. Furthermore, the presence of this progenitor population in both adipose tissue and skeletal muscle is consistent with the finding that adipose tissue is a source of FAP-like cells recruited to the skeletal muscle during remodeling [15].

## 2. Recruitment of ASCs in Cancer

ASCs can be recruited into tumors to enhance the supportive properties of the tumor microenvironment (TME), as indicated by resistance to anti-cancer therapy in mouse models [16–19]. The recruitment and infiltration of ASCs into tumors is driven by specific molecular and signaling mechanisms that create a favorable environment for cancer progression. One such mechanism involves chemokine signaling, whereby chemokines such as C-X-C Motif Chemokine Ligand 1 (CXCL1) and C-X-C Motif Chemokine Ligand 8 (CXCL8) bind to receptors such as C-X-C Motif Chemokine Receptor 1 (CXCR1) and C-X-C Motif Chemokine Receptor 2 (CXCR2) on ASCs and guide their migration towards the tumor [17]. Mouse models have demonstrated the importance of the CXCL1 chemokine gradient for obesity-dependent tumor ASC recruitment that promotes the progression and metastatic potential of prostate cancer [17,20].

Once recruited, ASCs infiltrate the tumor and contribute to the stromal compartment by secreting agents that stimulate vascularization, immune modulation, and tissue remodeling [21]. ASC mobilization from WAT is initiated by molecular triggers such as the interaction between adipocyte-secreted proteins and integrins on the surface of ASCs [22]. Signaling pathways such as IL-22 also activate ASCs, thereby increasing their recruitment and integration into the tumor stroma where they produce ECM components and promote cancer cell survival [22,23]. These processes highlight the important role of chemokine-mediated recruitment and integrin signaling in ASC mobilization. In summary, ASCs are key contributors to the tumor-supportive stroma, and as such represent a potential target for therapeutic intervention [20].

We have previously studied the role of ASC-derived cancer-associated fibroblasts (CAFs) in epithelial-mesenchymal transition (EMT) induction and cancer aggressiveness [24–26]. C-X-C Motif Chemokine Ligand 12 (CXCL12 (alias, SDF1)) is a paracrine chemokine secreted by ASCs and adipose-derived CAFs and which signals via CXCR4 and CXCR7 to promote obesity-associated cancer progression via EMT. The SVF derived from WAT of obese mice shows significantly higher CXCL12 expression than the SVF from lean mice. Signaling by CXCL12 results in the activation of Signal Transducer and Activator of Transcription 3 (STAT3), Nuclear Factor Kappa-light-chain-enhancer of activated B cells (NF-$\kappa$B), and c-Jun N-terminal Kinases (JNK). Targeting of ASCs with a hunter-killer peptide D-CAN, which specifically depletes these cells, or with inhibitors of CXCR4 or CXCR7, leads to the suppression of cancer metastases and chemoresistance [27].

Single-cell analysis of biopsies from many cancer types has identified computationally-derived clusters that include cells with the same gene signature as the APOD+DCN+LUM+ ASC/FAP population mentioned previously. This indicates they are likely to be recruited ASCs. For example, Chen *et al*. [28] identified a fibroblastic population in esophageal cancer that was characterized by gene expression for *CFD*, *APOD*, Gelsolin (*GSN*), and Peptidase Inhibitor 16 (*PI16*). Zhang *et al*. [29] clustered stromal cells into nine subtypes, including one labeled as "normal activated fibroblasts" that was characterized by expression of *APOD*, *CFD*, *DPT*, *CXCL14*, *PTGDS*, and *MGP*. Other examples of the signature in breast cancer are found in Supplementary Table 9 (inflammatory CAF (iCAF) minor) of the study by Wu *et al*. [30], and Supplementary Table 3 (iCAF) of the study by Cords *et al*. [31], both of which feature the ASC markers *APOD* and *CFD* at the top.

The presence of recruited and infiltrated ASC/FAPs in cancer biopsies is in most cases thought to represent inflammatory CAFs, as described below. This is because computationally-derived clusters are typically labeled with one of several pre-assigned cell subtypes. To date, the ASC/FAP population has not been widely recognized as a stromal population in the TME, and as a consequence this population is usually assumed to be a type of CAF.

The TME reflects the progression to aggressive disease [32,33]. CAFs are a heterogeneous and plastic population of non-malignant mesenchymal cells within this microenvironment that modulate tumor vascularization and growth, EMT, chemotherapy resistance, ECM remodeling, metastatic dissemination, and immunosuppression [34]. They are recruited early in cancer development and evolve as the disease progresses [35,36]. Several major CAF subtypes are generally recognized, with the main ones being myofibroblastic CAFs (myCAFs) and inflammatory CAFs (iCAFs). MyCAFs exhibit a matrix-producing, contractile phenotype with high alpha-smooth muscle actin ($\alpha$SMA) (*ACTA2*) expression. They are associated with high TGF$\beta$ signaling levels and are observed adjacent to cancer cells. iCAFs are more distant and exhibit an immuno-modulatory phenotype that expresses a high level of interleukin 6 (*IL6*). Moreover, iCAFs display TGF$\beta$-mediated suppression of the IL1 receptor, which is responsible for driving NF-$\kappa$B signaling upstream of *IL6* induction [14,37–40]. In addition

to these subtypes, CAFs that express major histocompatibility complex class II (MHC II) and CD74 Molecule (*CD74*) are termed antigen-presenting CAFs (apCAFs) [39].

Tumor infiltrating ASCs in their original, undifferentiated progenitor state should not be classified as one of the three widely recognized CAF subtypes described above. However, they are often included within non-homogeneous, computationally-derived clusters. Since part of the cell population in such clusters expresses inflammatory markers, this has been thought to represent iCAFs in their original state, meaning that even genes such as *APOD* and *CFD* have been mischaracterized as iCAF markers. In reality, iCAFs are characterized by the signature previously reported by Elyada *et al*. [39], which includes the expression of *IL6*, C-C Motif Chemokine Ligand 2 (*CCL2*), and Hyaluronan Synthase 1 (*HAS1*). For example, "cluster 1" in Fig. 5D of the study by Dominguez *et al*. [41] is marked by the expression of *CFD*, *PTGDS*, and *C7*, all of which are expressed in ASCs. This cluster is distinct from "cluster 2" marked by *IL6*, *HAS1*, and *CCL2*, and which corresponds to the true iCAF population. Similarly, Chen *et al*. [28] identified iCAFs in esophageal cancer as a population that expressed inflammatory genes such as *CXCL1*, *CXCL8*, and Interleukin 24 (*IL24*). Ho *et al*. [42] found both iCAF and "adipose-like CAF" in head and neck squamous cell carcinoma (HNSCC), with iCAFs expressing *IL6* and *CXCL1*, while adipose-like CAFs expressed *APOD* and *CFD*, and clearly included recruited ASCs. The distinction between ASCs and iCAFs is further supported by the cross-tissue human fibroblast atlas. This identifies inflammatory fibroblasts as expressing *IL6*, *CXCL1* and *CXCL2*, whereas *APOD* and *PI16* expression is found in progenitor cells that are distinct from IL6-expressing cells [14]. Therefore, recruited ASCs in their original state should not be confused with IL6+ iCAFs, although some may independently transition to that state.

There are many examples in different cancer types where recruited ASCs with a consistent gene signature have been misclassified as iCAFs [43–51]. For example, transcriptomic analysis shown in Extended Data Fig. 7 of the study by Cui Zhou *et al*. [43] identified a stromal subpopulation in pancreatic ductal adenocarcinoma (PDAC) with a signature that included the marker genes *APOD*, *PTGDS*, *CXCL14*, *CFD*, *DCN*, and *LUM*. The study also identified 12 genes (*APOD*, *C3*, *PTGDS*, *C7*, *IGFBP3*, *SFRP4*, *CXCL14*, *CFD*, *SFRP2*, *DCN*, *FBLN1*, and *LUM*) that formed a "chemoresistance signature". Chemoresistant samples of pancreatic cancer showed a three-fold enrichment of this signature. Similarly, Supplementary Table 6-1 in the study by Wang *et al*. [49] identified the iCAF cluster C0, with high expression levels of *APOD*, *PTGDS*, *MGP*, *DCN*, *LUM*, *SERPINF1*, *CFD*, *CXCL14*, and *DPT*. Additionally, Zhao *et al*. [44] reported that iCAFs in obesity-associated breast cancer showed upregulation of genes including *CFD*, *APOD*, and *CXCL14*. Chen *et al*. [45] found a cluster labeled iCAF in bladder cancer that expressed genes such as *APOD*, *DCN*, *LUM*, *CFD*, *CXCL14*, *PTGDS*, *MGP*, *SERPINF1*, and *DPT*. Pu *et al*. [46] identified a cell population in thyroid carcinoma, labeled iCAF, that was characterized by high expression of ASC genes including *APOD*, *CFD*, *DCN*, and *CXCL14*. However, these authors noted a lack of key iCAF markers such as *IL6* and *IL8* (Supplementary Fig. 9e in study [46]). Finally, Thorlacius-Ussing *et al*. [47] suggested the existence of two separate populations of iCAFs in PDAC, with one being *IL6* positive and the other *IL6* negative. In fact, the IL6-negative cluster contained mostly the ASC population (Supplementary Fig. 4 in study [47]) without inflammatory gene markers.

## 3. Fibroblastic Differentiation of ASCs

Recruited ASCs have been found to undergo fibroblastic differentiation as part of a multi-faceted, cancer invasiveness-related biological mechanism [11] (Fig. 1). By analyzing datasets from multiple cancer types, including a particularly rich dataset from pancreatic cancer [52], Zhu *et al*. [53] identified a cell transition starting from APOD-expressing ASCs. The endpoint of this transition is an aggressive type of CAF with prominent expression of Collagen Type XI Alpha 1 Chain (*COL11A1*), referred to as "CAFs in aggressive tumors (aCAFs)". These also have a well-defined and characteristic gene expression signature that includes *THBS2*, *INHBA*, *POSTN*, *COL10A1*, and *MMP11*. First identified by Kim *et al*. [54], the aCAF gene signature was strongly associated with cancer invasiveness and poor prognosis. It was also found to be associated with tumor stage, consistent with the presence of adjacent adipose tissue. For example, in ovarian cancer the aCAF signature only occurs after the tumor cells have reached the omentum in stage III disease, whereas in breast cancer it occurs in stage I already. Following analysis of six cancer types, Ma *et al*. [51] reported a potential transition from an APOD+CFD+MGP+CXCL14+ population labeled as iCAF (Fig. 2b in study [51]), to a COL11A1+COL10A1+MMP11+POSTN+ population labeled mCAF (Fig. 2i in study [51]). In pleomorphic sarcoma, Lu *et al*. [55] identified *APOD* as a stem cell-related gene involved in cell transition, with decreased *APOD* expression accompanied by increased *COL11A1* expression.

Many other studies have also suggested that ASCs serve as precursors to CAFs within tumors, with some demonstrating their ability to transition into myofibroblast-like cells that contribute to tumor progression. For example, Kidd *et al*. [56] showed that adipose-derived cells could differentiate into $\alpha$SMA-positive myofibroblasts within the tumor stroma in a mouse model of breast cancer. Similarly, Jotzu *et al*. [57] found that a significant percentage of human ASCs differentiate into a CAF-like myofibroblastic phenotype with expression of $\alpha$SMA. Song *et al*. [58] reported that tumor extracellular vesicles can convert adipose stem cells into myofibroblasts.

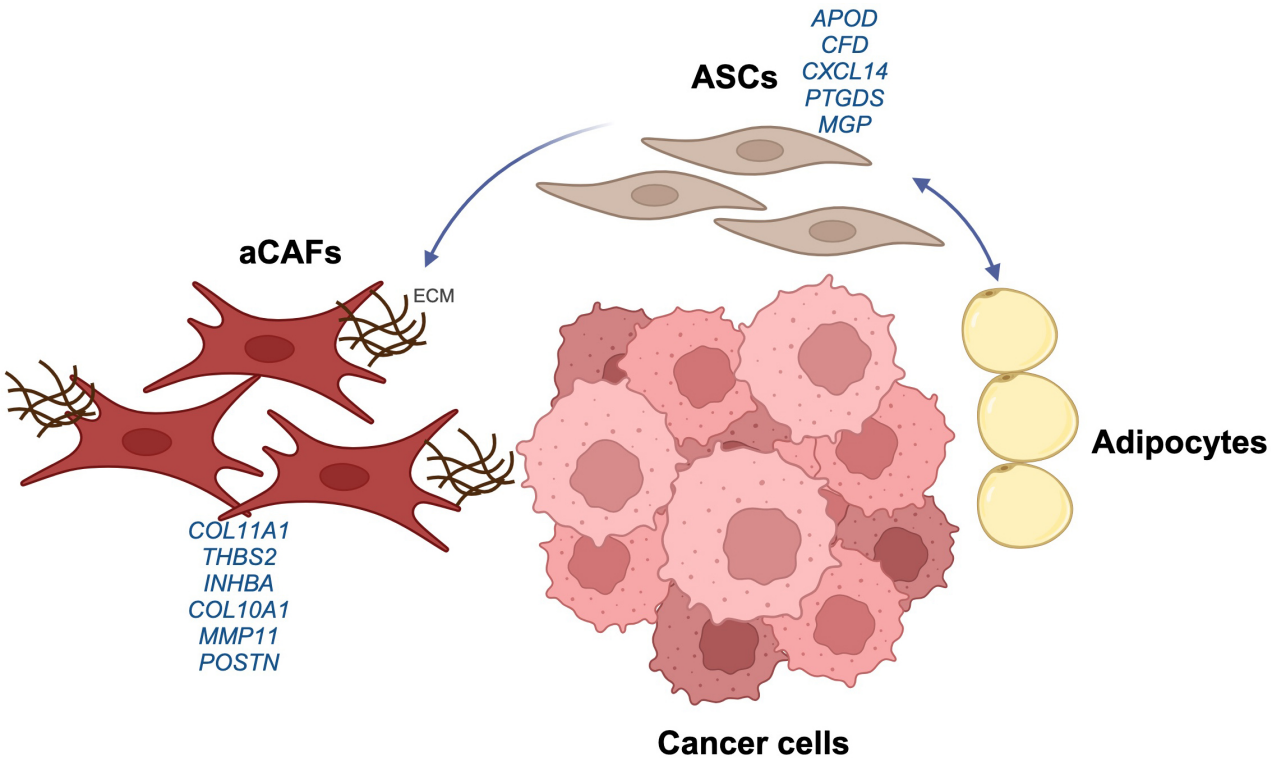


**Fig. 1. Adipose stromal cells (ASCs) as a source of aggressive cancer-associated fibroblasts (aCAFs) in tumors.** The diagram summarizes the transition of ASCs to aCAFs within the tumor microenvironment, showing some of the associated gene markers. The ASCs have both adipogenic and fibroblastic differentiation potential, and differentiate into aCAFs by interacting with cancer cells. Created with https://www.biorender.com. ECM, extracellular matrix; APOD, Apolipoprotein D; CFD, Complement Factor D; CXCL14, C-X-C Motif Chemokine Ligand 14; PTGDS, Prostaglandin D2 Synthase; MGP, Matrix Gla Protein; COL11A1, Collagen Type XI Alpha 1 Chain; THBS2, Thrombospondin 2; INHBA, Inhibin Subunit Beta A; COL10A1, Collagen Type X Alpha 1 Chain; MMP11, Matrix Metallopeptidase 11; POSTN, Periostin.

Strong *et al.* [59] proposed that obesity alters adipose-derived stromal/stem cells, making them more likely to convert into CAFs in the presence of tumor-derived factors. This in turn promotes the proliferation, invasiveness, and expression of pro-tumorigenic factors by breast cancer cells [59]. Okumura *et al.* [60] demonstrated that ASCs contribute to pancreatic tumor progression by being recruited to extra-pancreatic invasion sites, where they produce dense collagen matrices that enhance tumor growth. In ovarian cancer, Tang *et al.* [61] suggested that adipose-derived mesenchymal stem cells (ADSCs) from the omentum can differentiate into CAF-like cells via the TGF-$\beta$1 signaling pathway, thereby enhancing the proliferation and invasion of epithelial ovarian cancer cells and contributing to the formation of metastatic niches. In both *in vitro* and *in vivo* studies, ASCs were observed to migrate to extra-pancreatic invasive lesions, where they formed dense collagen matrices that promote tumor progression [60].

Importantly, both *in vitro* and *in vivo* experiments conducted by Miyazaki *et al.* [62] confirmed that adipose-derived stromal cells have the ability to differentiate into CAFs. Specifically, direct co-culture of ASCs with tumor cells resulted in the expression of genes such as *COL10A1*, *COMP*, and *INHBA* [62]. Using mouse xenografts derived from human tumor cell lines, the same authors subsequently demonstrated the ability of ASCs to differentiate into CAFs with strongly upregulated expression of *COL11A1* [63].

Pan-cancer single-cell transcriptomic analyses further support the above conclusions, as evidenced by the fact that clusters which include genes such as *APOD* and *CFD* are typically located adjacent to clusters that include *COL11A1*. For example, Fig. 4 in the study by Hornburg *et al.* [64] shows two clusters in ovarian cancer, with each being defined by characteristic genes for the two populations (*APOD*, *CFD*, *MGP*, *DPT*, *CXCL14* and *COL11A1* for the first cluster; *MMP11*, *POSTN*, and *INHBA* for the second cluster). Similarly, Fig. 2 in the study by Wang *et al.* [49] on pancreatic cancer shows adjacent clusters C0 and C3, characterized by marker genes including *APOD*, *PTGDS*, *MGP*, *DCN*, and *LUM* for C0, and *MMP11*, *POSTN*, *COL10A1*, *COL11A1*, *INHBA*, *THBS2*, *SULF1* for C3. Other workers have also demonstrated adjacent clusters characterized by ASC gene markers and CAFs expressing genes such as *COL11A1*, *COL10A1* and *MMP11*. In PDAC, these include cluster 1 and clusters 3, 4 and 6 [47], "iCAF" and "myCAF" in study [48], and C1 and C0 in study [41].

In breast cancer, similar marker profiles were observed for the adjacent CFD-expressing "iCAF1" and COL11A1-expressing "iCAF2" clusters [44]. In gastric cancer, Zhao *et al*. [65] observed a similar pattern in the "poor prognosis" CAF_0 cluster, wherein *POSTN* appears alongside *APOD*, *CFD*, and *CXCL14* with expansion of the cluster, consistent with a transition.

Gao *et al*. [14] analyzed 517 samples spanning 11 different tissues. Their RNA velocity results revealed a transition from cluster c03 expressing the ASC/FAP signature, to cluster c16 with *SFRP4* as the top differentially expressed gene, identified as marking the start of the transition in another study [53]. The final transition to c04 included the top marker genes *COL11A1*, *THBS2*, *INHBA*, *COL10A1*, *MMP11*, *POSTN*, and *SPARC*. It remains to be determined whether any of these genes play a role in the pro-carcinogenic properties of ASC-derived CAFs, and whether their targeting could have therapeutic value.

## 4. Prospects for ASC-derived CAF Targeting

CAFs have often been considered to represent a potential therapeutic target [36,66–69]. According to some studies, selective depletion of certain CAF subtypes can impede tumor growth and improve treatment outcomes. For example, conditional depletion of FAP+ stromal cells in transgenic mice led to slower PDAC growth [70]. Similarly, depletion of Leucine Rich Repeat Containing 15 (LRRC15)+ CAFs in pancreatic tumors reduced their overall CAF content, decreased tumor burden, and boosted the responsiveness to anti-programmed cell death ligand-1 (anti-PD-L1) immunotherapy [71]. Collectively, these findings indicate there may be therapeutic potential in modulating the aCAF population to improve cancer treatment. However, the general approach of targeting CAFs remains a subject of ongoing debate. Depletion of $\alpha$SMA-expressing CAFs [68] or Sonic Hedgehog (SHH)-dependent CAFs in mice was actually found to promote metastasis and reduce survival [69]. This effect may be due to the effect of CAFs in supporting endothelial cells, thereby reducing the hypoxia that drives cancer invasiveness. Additionally, inflammatory CAFs appear to facilitate cytotoxic T cell infiltration, thereby improving the efficacy of immunotherapy [72] and potentially meaning their inactivation is actually a disadvantage.

It remains to be determined whether selective inactivation of ASC-derived CAFs can provide a unique therapeutic benefit. A few studies have investigated the effects of ablating CAFs that express ASC markers [25,73,74]. Our group used the hunter-killer peptide D-CAN, which specifically targets ASCs and their non-glycanated decorin- and PDGFR$\beta$-expressing derivatives to induce apoptosis [25,73]. D-CAN was found to suppress tumor growth and metastasis in mouse models of breast cancer [25]. A recent study by our group also showed that D-CAN suppressed tumor growth in a mouse PDAC model, but induced metastasis [74]. This result is consistent with observations that genetic depletion of perivascular stromal cells can promote metastasis [68]. In both studies, depletion of stromal cells was shown to suppress ECM deposition and the vascularization of tumors. The balance between the anti-metastatic effect of ECM reduction and the pro-metastatic effect of tumor hypoxia varies between different cancer types, possibly explaining model-specific effects. The roles played by ASC-derived CAFs in regulating tumor progression are likely to be cancer type- and stage-specific, with further investigation required. Importantly, there is growing evidence that targeting of ASC-derived aCAFs may be effective in combination with other treatments [11]. In mouse models of breast cancer, the depletion of ASC/CAFs was found to synergize with chemotherapy to suppress cancer progression [25]. We also recently found that ASCs are involved in immune evasion by tumors, suggesting that targeting of ASC-derived CAFs could improve immune checkpoint blockade immunotherapy [74].

## 5. Conclusion

The recruitment of ASCs in cancer and their differentiation into CAFs is associated with invasiveness, poor prognosis, and resistance to therapy. Although the identification of viable therapeutic targets that play driver roles in the clinical setting show considerable promise, several challenges remain. Accumulating evidence suggests that blocking ASC-derived CAFs can help to suppress tumor growth and metastatic dissemination, as well as overcoming therapy resistance. The identification of specific markers expressed by adipose-derived CAFs, together with a better understanding of their function, may lead to targeted treatments against these cells that could transform cancer management with adjuvant therapies.

## Author Contributions

MGK and DA designed the study; LC and MGK contributed to the literature review; LC drew the figure; LC, MGK, and DA wrote, reviewed, and edited the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

## Ethics Approval and Consent to Participate

Not applicable.


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## Conflict of Interest

The authors declare no conflict of interest. Given his role as the Guest Editor, Mikhail G. Kolonin had no involvement in the peer-review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Sung Eun Kim.

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