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REVIEW

Hematopoietic stem cell-derived adipocytes and fibroblasts in the tumor microenvironment

Ying Xiong, Lindsay T McDonald, Dayvia L Russell, Ryan R Kelly, Katie R Wilson, Meenal Mehrotra, Adam C Soloff, Amanda C LaRue

Ying Xiong, Lindsay T McDonald, Dayvia L Russell, Ryan R Kelly, Katie R Wilson, Meenal Mehrotra, Adam C Soloff, Amanda C LaRue, Research Services, Ralph H Johnson Veterans Affairs Medical Center, Charleston, SC 29403, United States

Ying Xiong, Lindsay T McDonald, Dayvia L Russell, Ryan R Kelly, Katie R Wilson, Meenal Mehrotra, Amanda C LaRue, Department of Pathology and Laboratory Medicine, Ralph H Johnson Veterans Affairs Medical Center, Charleston, SC 29403, United States

Ying Xiong, Lindsay T McDonald, Meenal Mehrotra, Adam C Soloff, Amanda C LaRue, the Hollings Cancer Center, Medical University of South Carolina, Ralph H Johnson Veterans Affairs Medical Center, Charleston, SC 29403, United States

Adam C Soloff, Department of Microbiology and Immunology, Ralph H Johnson Veterans Affairs Medical Center, Charleston, SC 29403, United States

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Correspondence to: Amanda C LaRue, PhD, Research Health Scientist and Associate Professor, Research Services, Ralph H Johnson Veterans Affairs Medical Center, 109 Bee Street, Charleston, SC 29403, United States. laruerc@musc.edu
Telephone: +1-843-7896713
Fax: +1-843-8765381

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Abstract

The tumor microenvironment (TME) is complex and constantly evolving. This is due, in part, to the crosstalk between tumor cells and the multiple cell types that comprise the TME, which results in a heterogeneous population of tumor cells and TME cells. This review will focus on two stromal cell types, the cancer-associated adipocyte (CAA) and the cancer-associated fibroblast (CAF). In the clinic, the presence of CAAs and CAFs in the TME translates to poor prognosis in multiple tumor types. CAAs and CAFs have an activated phenotype and produce growth factors, inflammatory factors, cytokines, chemokines, extracellular matrix components, and proteases in an accelerated and aberrant fashion. Through this activated state, CAAs and CAFs remodel the TME, thereby driving all aspects of tumor progression, including tumor growth and survival, chemoresistance, tumor vascularization, tumor invasion, and tumor cell metastasis. Similarities in the tumor-promoting functions of CAAs and CAFs suggest that a multipronged therapeutic approach may be necessary to achieve maximal impact on disease. While CAAs and CAFs are thought to arise from tissues adjacent to the tumor, multiple alternative origins for CAAs and CAFs have recently been identified. Recent studies from our lab and others suggest that the hematopoietic stem cell, through the myeloid lineage, may serve as a progenitor for CAAs and CAFs. We hypothesize that the multiple origins of CAAs and CAFs may contribute to the heterogeneity seen in the TME. Thus, a better understanding of the origin of CAAs and CAFs, how this origin impacts their functions in the TME, and the

temporal participation of uniquely originating TME cells may lead to novel or improved anti-tumor therapeutics.

Key words: Hematopoietic stem cell; Cancer associated adipocyte; Mesenchymal stromal cell; Tumor progression; Cancer associated fibroblast; Plasticity; Metastasis; Fibrocyte

Core tip: This review examines the roles of cancer-associated adipocytes (CAAs) and cancer-associated fibroblasts (CAFs) in remodeling of the tumor microenvironment (TME), presents evidence for a unique hematopoietic stem cell origin for both CAAs and CAFs, and discusses potential therapeutic implications of this novel origin. Studies highlighted herein emphasize the necessity of developing an understanding of the origins of cells in the TME and the importance of multipronged therapeutic targets directed at preventing both the incorporation and effects of stromal remodeling by the cells of the TME.

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INTRODUCTION: THE TUMOR MICROENVIRONMENT

The "seed and soil" hypothesis suggests that an appropriate host microenvironment ("soil") must be present for the optimal growth of tumor cells ("seed")[1-3]. Although this paradigm was initially proposed by Stephen Paget in 1889, research efforts have predominantly focused on the epithelial component of solid tumors and tumor cell-intrinsic factors leading to tumorigenicity. However, in the last decade, Paget's hypothesis has again come to focus and it has been recognized that the epithelial "seed" and stromal "soil" components co-evolve and interact during tumor progression[4]. Seminal works from Weinberg's group have shown that this stromal compartment, often referred to as the reactive stroma or tumor microenvironment (TME), directly and indirectly supports tumor survival, growth, vascularization, escape from immune surveillance, drug resistance, and metastasis *via* extracellular matrix (ECM) remodeling and production of growth factors, cytokines, and chemokines (reviewed in[5-7]). The TME is comprised of a variety of cell types including endothelial cells, perivascular cells, immune cells, adipocytes, and fibroblasts/myofibroblasts. These cells interact with one another as well as with tumor cells to create an intricate network of cellular crosstalk and bidirectional regulation.

This crosstalk results in a heterogeneous population of tumor cells exhibiting varying degrees of differentiation, unregulated proliferation, the capacity to migrate and invade through surrounding tissue, and the ability to establish a dense irregular and leaky vascular network, all critical steps in metastatic tumor progression. Concomitantly, this crosstalk leads to changes in the local stromal populations, contributing to the heterogeneity of TME cells. The heterogeneity of the cells of the TME, the factors they contribute and their broad functional ability to promote all aspects of tumor progression make the "soil" a challenging and complex therapeutic target. Many factors contribute to the heterogeneity of these cell types, including exposure to the local tumor milieu, the plasticity between cells of the TME, and the multiple potential origins of each cellular population. Understanding the mechanisms behind this heterogeneity could lead to the identification of novel therapeutic targets for cancer. This review will focus on two stromal cell types, the cancer-associated adipocyte (CAA) and the cancer-associated fibroblast (CAF). The adipocyte is a stromal cell type that has recently been implicated in tumor initiation, growth, and metastasis (reviewed in[8]). Several epidemiologic studies have linked obesity with multiple types of cancer[9-11]. Recent clinical studies have reported a positive correlation between the presence of CAAs at the tumor margin and poor patient outcome, suggesting that CAAs contribute to the permissive pro-TME, particularly in adipocyte-rich tissues, such as the mammary gland[12,13] (and reviewed in[14]). CAFs, the most abundant cellular component of the TME in solid tumors, have a significant impact on tumor progression during multiple stages[5-7]. While more extensively studied than CAAs, the numerous roles of CAFs in tumor progression and metastasis are still under investigation. Like CAAs, CAFs have clinically been correlated with tumorigenesis and poor prognosis in many cancer types[15-18]. Similarities in the pro-tumorigenic functions of CAAs and CAFs suggest that these TME cell types may act in concert to promote tumor progression, indicating that therapeutic targeting of the TME may need to encompass both cell types. Herein, we will examine the phenotype and function of CAAs and CAFs in remodeling of the TME, present evidence for a unique hematopoietic stem cell origin for both CAAs and CAFs, and discuss potential therapeutic implications of this novel origin.

CONTRIBUTIONS OF CAAS AND CAFS TO TME REMODELING

Cancer has been likened to a perpetual wound

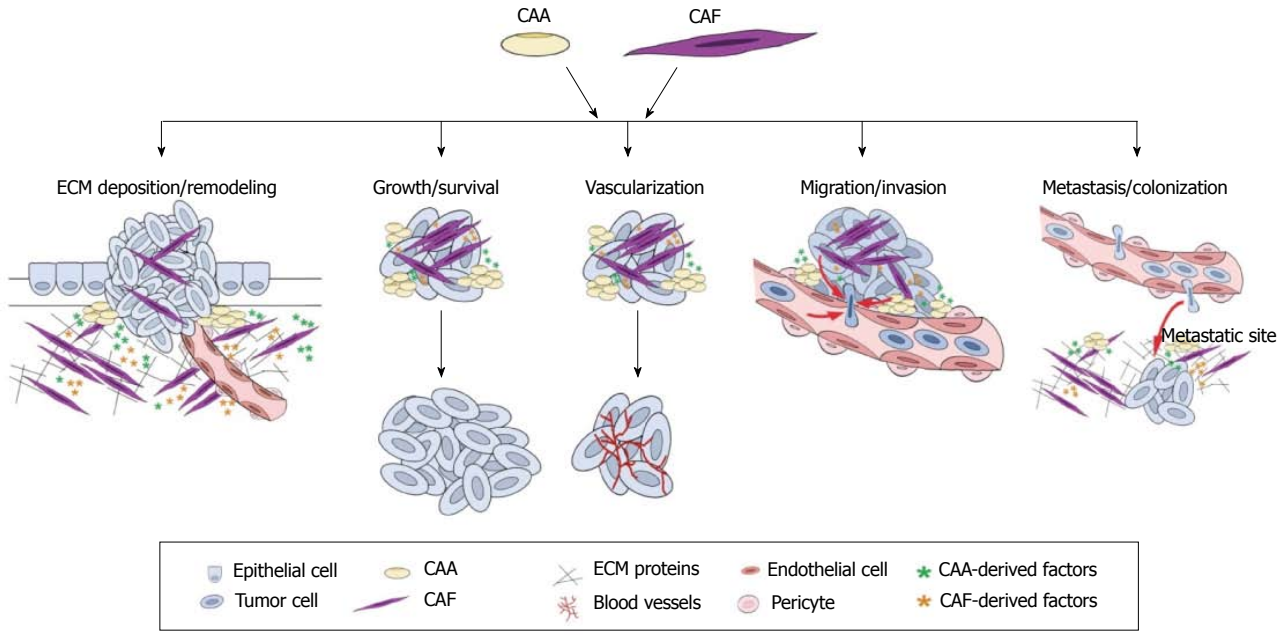

Figure 1 Multifactorial contributions of cancer-associated adipocytes and cancer-associated fibroblasts to tumor progression and metastasis. Research in the last decade has highlighted the importance of the tumor microenvironment in cancer progression. While there are numerous stromal cell types that contribute to the tumor microenvironment, this illustration depicts roles for cancer-associated adipocytes (CAAs) and cancer-associated fibroblasts (CAFs) in promoting the multiple stages of tumor progression and metastasis. ECM: Extracellular matrix.

healing process[19] since both processes begin with the formation of a reactive stroma. During wound healing the reactive stroma resolves rapidly, but, during cancer progression, this actively remodeling, inflammatory state is perpetuated. CAAs and CAFs have been shown to play a role in a variety of tumor promoting processes including ECM deposition/degradation, inflammation and immune surveillance, tumor growth and survival, angiogenesis, invasion, and metastasis[5,6,20-24], suggesting similarities in the pro-tumorigenic functions of these cells. As summarized in Figure 1, this section will discuss the CAA and CAF phenotypes and their roles in generating and maintaining the reactive stroma associated with cancer progression and metastasis.

The activated phenotype of CAAs and CAFs

Adipocytes, surrounded by fibroblasts, preadipocytes, pluripotent stem cells, endothelial cells, and immune cells, are the major components of the adipose tissue. Apart from their traditional function in energy storage, adipocytes are also considered endocrine cells, producing hormones, growth factors, cytokines and adipokines, including leptin, adiponectin, resistin, vascular endothelial growth factor (VEGF), tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6)[25]. During interaction with cancer cells, adipocytes acquire phenotypic changes and are reprogrammed to an activated state during which they are referred to as CAAs[26]. CAAs are generally located at the invasive front of tumors[21]. Several reports suggest that cancer cells can induce metabolic changes in adipocytes, resulting in enhanced lipolytic activity and an inability to properly store triglyceride[27]. Moreover, transforming growth factor-β (TGF-β), secreted by cancer cells or local stroma, is a potent inhibitor of adipocyte differentiation[28]. Thus, the associated morphological changes upon activation include loss of lipid content (delipidation) and acquisition of a fibroblast-like/preadipocyte phenotype (de-differentiation)[21]. Functional alterations in CAAs include loss of terminal adipocyte markers and products (adiponectin, resistin, fatty acid binding protein-4 (FABP4), hormone sensitive lipase (HSL), and CCAAT/enhancer binding protein-alpha (C/EBPα) and an increased production of pro-inflammatory cytokines IL-6, IL-1β, plasminogen activator inhibitor-1 (PAI-1)[21]. As detailed below, in this activated state, CAAs produce adipokines and inflammatory factors that have been shown to promote tumor progression in adipocyte-rich environments.

In non-malignant tissues, fibroblasts provide structure and ECM scaffolding for tissues. In a wound environment, these fibroblasts become activated, produce increasing amounts of ECM proteins and migrate to wound interfaces to cause wound contraction and closure. In both wound healing and the TME, fibroblast activation is marked by increased α-smooth muscle actin (αSMA) protein expression, along with increased expression of vimentin, desmin, fibroblast specific protein, platelet-derived growth factor receptor α and β (PDGFRα and β), fibroblast activation protein (FAP), or a combination of these markers. TGF-β is present in both the wound and TMEs and has been shown to both induce and suppress differentiation and

tumorigenesis in a dose and context specific manner[29]. With respect to fibroblasts, TGF-β has been shown to upregulate αSMA expression[30,31], induce expression of FAP[32], and promote collagen synthesis[33], hallmarks of activated fibroblasts. Like CAAs, activated fibroblasts in the TME are also characterized by increased and altered production of inflammatory cytokines, chemokines, ECM components, and growth factors. The clinical importance of this activated phenotype is highlighted by molecular profiling studies of CAFs and matched normal fibroblasts. Studies in non-small cell lung cancer[16] and breast cancer[34] revealed that the cancer-associated gene signatures in CAFs correlated to disease outcome.

CAAs and CAFs in ECM remodeling and establishment of a reactive stroma

CAAs have been shown to play an important role in stromal remodeling during tumorigenesis. Type Ⅵ collagen, a soluble ECM protein, was reportedly up-regulated in peritumoral adipocytes during tumorigenesis[22] and was shown to promote early mammary tumor progression *in vivo*[23]. The α3 chain cleavage product of type Ⅵ collagen, endotrophin, augmented fibrosis, angiogenesis and inflammation through recruitment of macrophages and endothelial cells[23]. Rio and colleagues found that the native α3 chain of type Ⅵ collagen constituted a specific substrate for matrix metalloproteinase (MMP)-11, whose collagenolytic activity was functional in fat tissue ontogenesis as well as during cancer invasive steps[24]. Interestingly, they also reported that invasive breast cancer cells induced the expression of MMP-11 in the neighboring CAAs[20], suggesting that exposure to tumor cells promotes stromal remodeling abilities of CAAs.

CAFs function to generate and remodel ECM through production of collagens, fibronectin, and laminin[30,35], and proteases such as MMPs[36,37]. Collagens, fibronectin, and laminin contribute to the stiffness and density of the stroma, give structural support to the tumor cells, and provide important mechano-signals in the TME. Additionally, the expression of αSMA by activated fibroblasts was shown to promote matrix contraction[38-40], suggesting a direct effect on matrix stiffness. Like CAAs, CAFs also produce MMPs that degrade matrix collagens, fibronectins, and proteoglycans, profoundly contributing to structural remodeling of the TME. It has also been demonstrated *in vitro* that fibroblast overexpression of FAP, a serine protease selectively produced by CAFs, remodeled the ECM by increasing expression levels of αSMA, fibronectin, and collagen Ⅰ [41]. These data indicate that, orchestrated by the tumor-stroma crosstalk, CAAs and CAFs actively remodel the ECM to favor local tumor progression.

In addition to elaboration and remodeling of matrix, CAAs and CAFs may also promote changes in the local stroma by contributing to the inflammatory state of the TME. As described above, CAAs have been shown to produce a variety of inflammatory cytokines including IL-6, IL-8, IL1-β and TNF-α[8,26]. Through production of factors such as IL-1β, IL-23, TGF-β, IL-6, and IL-8[42-44], CAFs exert considerable influence over the inflammatory state of the TME. CAF production of ECM components such as hyaluronic acid further drive the inflammatory state by recruiting tumor-associated macrophages[45] that promote tumor vascularization and proliferation. While the interactions between CAAs, CAFs and immune cells are only beginning to be explored, it is clear that cellular cross-talk modulates the inflammatory state of the TME, potentially influencing tumor-specific immunity.

Tumor growth and survival

Both CAAs and CAFs aid the tumor in meeting requirements for rapid growth by providing structural matrix as described above as well as directly promoting tumor cell proliferation and survival. Rapid, unchecked proliferation is characteristic of tumor cells, and as the cells of the TME remodel the reactive stroma, tumor cell proliferation is further accelerated. In addition to proteases and ECM constituents, CAAs provide their high energy content lipids to cancer cells resulting in accelerated tumor progression[46]. In support of this, morphologically, CAAs at the tumor invasive front are smaller than those observed at a distance, which implies lipolysis. In the case of ovarian cancer, the cancer cell-adipocyte interaction initiated HSL-mediated lipolysis in the adipocytes, releasing fatty acids, which were then taken up by the ovarian cancer cells for energy production through β-oxidation[46]. In a PC-3 model of prostate cancer, the translocation of lipid from adipocytes to prostate cancer cells was visualized by Fourier transform infrared spectroscopy[47]. Together these studies suggest that in multiple cancer types, CAAs supply the TME with energy rich lipids that may act to promote tumor growth by supplying tumor cells with essential metabolites.

Furthermore, adipocytes secrete adipokines into the TME, such as TNFα, IL-6, IL-8, monocyte chemoattractant protein-1 (MCP-1/CCL2), and leptin which have been shown to enhance tumor growth locally and systemically in a variety of cancer types (reviewed in[8]) including prostate[48,49] and breast[14,21] cancers. Another aspect of adipocyte pro-tumorigenic activity is their contribution to chemo/radio-therapy resistance. The antitumor effect of vincristine, daunorubicin and dexamethasone to acute lymphoblastic leukemia (ALL) was impaired under the influence of adipocytes, which augmented ALL cell survival due to increased expressions of Bcl-2 and Pim-2[50]. Likewise, breast tumor cells co-cultivated with adipocytes or recombinant IL-6 exhibited radioresistance, an increase in the effector

kinase Chk1, and a decrease in cell death[51]. Taking into account that CAAs secrete elevated levels of IL-6 in the TME, CAAs could promote chemoresistance *via* multiple mechanisms. These studies shed light on a new role of CAAs in fostering a chemo/radio-resistant phenotype in cancers and suggest targeting CAAs may increase effectiveness of conventional chemotherapy treatments.

CAFs also promote tumor growth through the production of factors that have been shown to be involved in proliferation of tumor cells, including TGF-α[52], TGF-β[53], hepatocyte growth factor (HGF)[54], and others (reviewed in[44,55]). Through production of MMPs, CAFs act to release stored growth factors from within the matrix, further contributing to an enriched host microenvironment and promoting proliferation of tumor cells (reviewed in[37]). Studies have identified a novel mechanism of cellular respiration, coined the "reverse Warburg effect" that involves an interplay and exchange between tumor cells and stromal cells whereby tumor cells take up energy-rich metabolites from CAAs[8] and CAFs[56] for use in the mitochondrial TCA cycle. This may contribute to the rapid proliferation of tumor cells by directing cellular energy towards cell division rather than cellular respiration. CAFs, like CAAs, have been implicated in promoting tumor chemoresistance. The expression and organization of collagen type I has been inversely correlated with intratumoral uptake of chemotherapeutic agents *in vivo* as it contributes to increased interstitial fluid pressure, forming a barrier to trans-capillary transport of agents[57]. DNA vaccine targeting of FAP on CAFs led to decreased deposition of a collagen Ⅰ rich matrix and improved chemotherapeutic drug uptake in pre-clinical animal studies[58]. Direct targeting of CAF-derived FAP also suppressed primary tumor cell growth in a pre-clinical murine model of multi-drug resistant breast cancer[58]; however, this finding has not held in Phase Ⅱ clinical trials. *In vitro* studies revealed that adherence of melanoma cells to fibroblast monolayers allowed for reduction of the cytotoxic effects of cisplatin, supporting a role for the CAF-induced ECM[59] in tumor cell survival. CAFs from melanoma and prostate cancer were found to be less sensitive to etoposide and vincristine due to expression of a non-mutated but functionally deficient form of p53[60]. Together, these findings suggest CAFs promote tumor growth and survival through multiple mechanisms and these effects may contribute to both the primary tumor and metastatic site.

Tumor vascularization

Angiogenesis is a critical step in tumor progression, without which tumors cannot maintain growth beyond 1-2 mm^3[61]. Many of the key factors required to initiate the angiogenic switch in solid tumors are produced by CAAs and CAFs. Adipocytes are known to produce multiple angiogenic factors [VEGF, fibroblast growth factor-2 (FGF2)], adipokines (leptin, adiponectin, resistin) and cytokines (IL-6), all of which stimulate angiogenesis and contribute to an overall pro-angiogenic microenvironment for tumor progression[62]. CAFs have been shown to produce angiogenic factors including stromal derived factor-1 (SDF-1)[63], TGF-β[64], IL-6[65] and VEGF[66,67], which support endothelial cell proliferation and tumor vascularization. In addition to their production of angiogenic cytokines, CAFs may play a more direct role in tumor vascularization through their ability to serve as vascular support cells. CAF and myofibroblast expression of αSMA closely links this cell type with the pericyte, a fibroblast-like cell, which plays a supportive role for endothelial cells in both normal and tumor systems. Thus, CAAs and CAFs are a source for critical angiogenic factors and may be involved in flipping the hypothetical switch to a vascularized tumor site, thereby acting to support an essential early step in tumorigenesis.

Invasion and metastasis

One of the initial steps in metastasis of solid tumor is the migration and invasion of the tumor cell through the ECM and through the basement membrane. This is followed by intravasation of tumor cells into a local blood vessel and the extravasation of the tumor cell to colonize and proliferate at a distant site. CAAs secrete similar levels of MMP-2 and MMP-9 compared to normal adipocytes[21], whereas MMP-11 is highly expressed by CAAs in the proximity of invading cancer cells, but not in normal resting adipocytes[24]. The role of MMP-11 (stomelysin-3) in tumor biology is still unclear (reviewed in[37,68]). However, MMP-11 has been shown to promote tumorigenesis and function through its proteolytic activity[69,70], but only weakly degrades matrix molecules. CAFs have been shown to produce a variety of matrix metalloproteinasese (MMP), including MMP-1, MMP-2, MMP-3, MMP-9, MMP-11, MMP-13, and MMP-14 (reviewed in[36,37]). Degradation of ECM allows tumor cells to cross the structural barrier of the basement membrane, a key step in tumor metastasis (reviewed in[37]). In an elegant imaging study, Gaggioli[35], demonstrated that CAFs are able to degrade matrix to form tracks through the ECM that allow invading tumor cells to efficiently follow behind.

CAAs and CAFs also directly affect the migratory and invasive abilities of tumor cells through production of adipokines, cytokines, and chemokines. Adipocyte/CAA-secreted IL-6 has been shown to play a key role in mediating adipocyte-dependent invasive activity of both breast cancer cells and melanoma cells[21,71]. FAP production by fibroblasts was linked to the increased invasion of pancreatic cancer cells in a β_1-integrin/FAK mediated fashion[41]. In breast cancer, CAFs were shown to increase the invasive ability of DCIS epithelial cells and this was related to their production of MMP-9 and MMP-14[72,73]. In addition, these factors secreted by CAAs and CAFs may flood

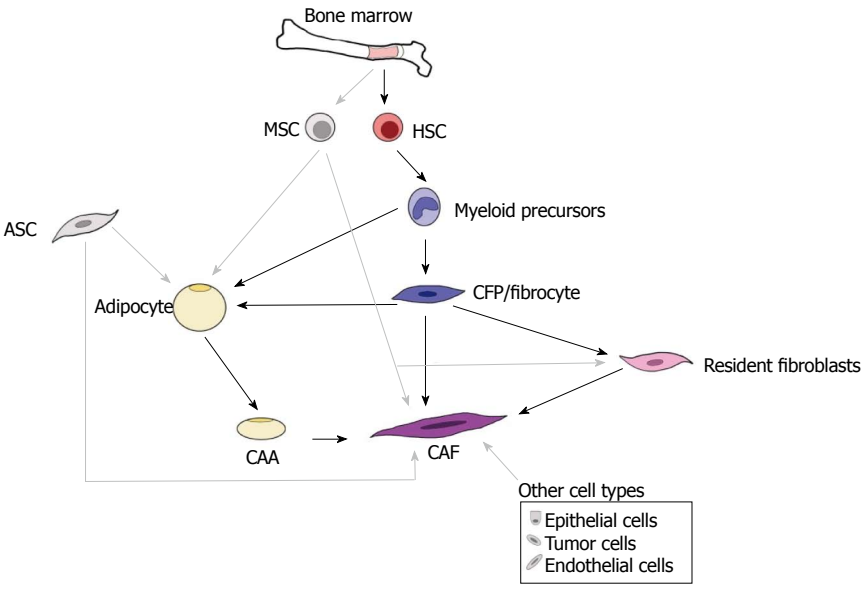

Figure 2 Origins of cancer-associated adipocytes and cancer-associated fibroblasts. This drawing illustrates the complex and ever-growing understanding of the origins for cancer-associated adipocytes (CAAs) and cancer-associated fibroblasts (CAFs). CAAs and CAFs are generally thought to arise from resident tissue cells, the adipose stem cell (ASC) and resident fibroblast, respectively. However, alternative sources for adipocytes and CAAs have been demonstrated including cells of the bone marrow, specifically those of the myeloid lineage (*e.g.*, macrophages, CFPs, and fibrocytes). In addition to resident fibroblasts, CAFs have been shown to be derived from myeloid progenitors (CFPs, fibrocytes), mesenchymal stromal cells (MSCs), ASCs, CAAs, epithelial cells, tumor cells, and endothelial cells. It is possible that these multiple sources are reflected in the morphological, phenotypic, and functional heterogeneity described for adipocytes and for CAFs. HSC: Hematopoietic stem cell; CFPs: Circulating fibroblast precursors.

the circulation with signals for distant metastatic sites to initiate their own expression of chemokines that will aid the tumor cell in homing to the metastatic site and preparing the site for colonization once the tumor cell arrives[74]. Research conducted on human omental adipocytes indicates they secrete IL-6 and IL-8 and that antibody-mediated inhibition of either factor resulted in reduced homing of ovarian cancer cells *in vitro* and *in vivo*, although inhibition of IL-8 was more efficient at reducing homing of cancer cells *in vivo*[46]. Once ovarian tumors are established on the omentum, they may convert adjacent adipocytes into CAAs, which results in a positive feedback loop leading to increased IL-6 production and further recruitment of cancer cells to the omentum. It has also been suggested that tumor cells do not metastasize alone, rather, they "travel" with stromal cells. Studies from Duda *et al*[75] demonstrated by cannulating primary tumor bearing mice, that tumor cells are shed with stromal cells in heterotypic "clumps" from the primary tumor. The stromal component, which included fibroblasts, acted to support the viability of the tumor cells while traveling through the circulation to the metastatic site. Together, these studies suggest that CAAs and CAFs promote the migratory and invasive phenotype in a variety of solid tumors and highlight the importance of elucidating mechanisms to target both CAAs and CAFs.

ORIGINS OF CAAS AND CAFS IN THE TME

Both CAAs and CAFs are generally thought to arise from tissues adjacent to the tumor; however, recent studies have begun to demonstrate alternative sources, including other resident stromal cells, epithelial cells, and bone marrow. This complex and ever-growing understanding of the origins for CAAs and CAFs can be appreciated in Figure 2. It is possible that these multiple sources are reflected in the morphological, phenotypic, and functional heterogeneity described for adipocytes from different fat depots[76] and for CAFs[77,78]. Given that this heterogeneity is a significant hurdle in therapeutically targeting the TME populations, it will be essential to elucidate the multiple origins for these cells as well as to examine the impact these origins may have on cellular function.

Origins of CAAs

The expansion of adipose tissue is achieved *via* increases in size (hypertrophy) and/or number (hyperplasia) of adipocytes. Mature adipocytes are postmitotic, therefore, adipocyte hyperplasia requires new adipocytes be produced from their adipogenic precursors. A long-standing paradigm of adipocyte generation is that all adipocytes are differentiated from mesenchymal progenitor cells resident in the vascular stroma, referred to as adipose stem cells (ASCs), where the regional fat depots eventually form[79,80]. However, these progenitor cells are found associated with adipose vessels[79], bringing up the possibility that circulating progenitors, such as those provided by bone marrow, home to adipose tissue through the bloodstream followed by extravasation across the endothelium of blood vessels, subsequently undergoing adipogenic conversion. To test this hypothesis, several groups transplanted GFP-labeled bone marrow into wild-type mice[81-83]. Two of these groups detected GFP-expressing adipocytes in the major adipose depots[81,82], while one failed to detect these cells[83], perhaps due to low marker expression or limited engraftment. When engrafted mice were treated with rosiglitazone or a high fat diet that stimulated adipogenesis, the number of GFP-expressing adipocytes was elevated, and cells were often found in clusters, suggesting clonal growth from bone marrow-derived progenitors[81]. While these studies support a bone marrow origin for CAAs, it is unclear which bone

marrow stem cell serves as the CAA progenitor.

It is commonly held that the bone marrow contains two types of stem cells, the mesenchymal stromal cell (MSC) and the hematopoietic stem cell (HSC). MSCs are defined by their adherence to plastic and potential to differentiate into mesenchymal tissue cells such as bone, fat, muscle, cartilage, and fibroblasts[84-87]. HSCs are defined by their capability of hematopoietic reconstitution *in vivo* and have also been shown to give rise to other tissue cell types including mast cells and osteoclasts. Our laboratory has developed a method for transplantation of a clonal population from a single sorted HSC defined as an $EGFP^+Lin^-Sca\text{-}1^+c\text{-}Kit^{hi}CD34^-$ cell. Using this single cell transplantation model, we have demonstrated that HSCs give rise to a variety of mesenchymal cell types including adipocytes[88], osteocytes and chondrocytes[89], cardiac valve interstitial cells[90]; circulating fibroblast precursors[91], and fibroblasts and myofibroblasts in multiple tissues[92-94] (reviewed in[95]). Further use of our unique clonal cell transplantation model revealed the generation of adipocytes *in vivo* from clonally derived bone marrow HSCs[88]. Similar to findings from Crossno *et al*[81], we found that rosiglitazone stimulated adipogenesis from the HSC[88]. *In vitro*, clones giving rise to monocytes/macrophages under hematopoietic conditions were also able to generate adipocytes under adipogenic conditions, suggesting a differentiation pathway from HSCs-myeloid precursors-adipocytes[88]. Similar results were obtained from the Klemm group who confirmed the *de novo* generation of a subset of adipocytes from bone marrow myeloid progenitor cells using a non-transplant transgenic mouse model in which LacZ expression was restricted to the myeloid lineage[96]. Moreover, Sterieter and colleagues reported that circulating fibrocytes were capable of adipogenic differentiation both *in vitro* and *in vivo*[97]. Due to the dual hematopoietic/mesenchymal nature of fibrocytes, they may be considered as an intermediate for myeloid-derived adipocyte population. These studies demonstrate the ability of the HSC to give rise to adipocytes through the myeloid lineage. While studies have not yet directly examined the role of HSC-derived CAAs in tumor progression, findings from our laboratory suggest that they can enhance tumor growth and tumor cell motility in breast cancer and melanoma models (unpublished data).

Origins of CAFs

Traditionally, CAFs are thought to arise from resident tissue fibroblasts[98]. However, recent studies have suggested alternative sources including other resident stromal cells, epithelial cells, epithelial-mesenchymal transition or endothelial-mesenchymal transdifferentiation (EndoMT), and adipose tissue. Several studies have also suggested a bone marrow origin for myofibroblasts and CAFs[99] (and reviewed in[100-102]). As described above, the bone marrow provides a rich source for both MSCs and HSCs. Using our model for transplantation of a clonal population from a single sorted HSC in conjunction with a variety of solid tumor models, we have demonstrated the presence of HSC-derived fibroblasts in tumor sections from mice transplanted with a clonal population of cells derived from a single, sorted HSC[91,103]. Analysis of sections from Lewis lung carcinoma (LLC) and melanoma (K1735-M2) tumors harvested from clonally engrafted animals showed the presence of HSC-derived CAFs[91,103]. These EGFP-expressing cells had a fibroblastic morphology and constituted 8%-28% of the tumor stromal cells[103]. Characterization of these HSC-derived cells indicated that they were activated fibroblasts, based on expression of αSMA and mRNA expression of collagen I [103]. Also prevalent in the specimens were $EGFP^+$ pericyte-like perivascular cells, suggesting that HSCs contribute to tumor vasculature[103].

Work from our laboratory has also identified a population of circulating fibroblast precursors (CFPs) that express markers of both hematopoietic cells (CD34, CD45) and fibroblasts [collagen I (Col I), discoidin domain receptor-2 (DDR2; a collagen 1 recpetor)](91] and unpublished data). The $CD45^+DDR2^+$ population was shown to differentiate along the monocyte/macrophage lineage, contain the $CD34^+Col\ I^+$ fibrocyte and rapidly differentiate to collagen 1^+, αSMA^+ cells with fibroblastic morphology. Using our clonal hematopoietic stem cell transplantation model, we conducted an *in vitro* examination of CFPs/fibrocytes derived from peripheral blood cells of clonally engrafted mice[92]. In these studies, nucleated blood cells were cultured and the appearance of $EGFP^+$ (HSC-derived), spindle-shaped or polygonal cells was detected by the seventh day. Flow cytometric time course analysis of the cultured cells demonstrated decreasing CD45 expression and increasing DDR2 expression. Our studies have demonstrated that CFPs may be stimulated to express markers of activated fibroblasts including collagen, vimentin, and αSMA by exposure to tumor conditioned media. This demonstrates a possible differentiation pathway from the HSCs-myeloid precursors-CFP and with exposure to tumor, HSCs-myeloid precursors-CFP-CAF[91]. These findings are supported by our *in vivo* data demonstrating the activated fibroblast phenotype of HSC-derived cells recruited from the bone marrow to the tumor stroma[91].

CAA and CAF common origins and plasticity

As summarized in Figure 2, multiple origins for CAAs and CAFs have been proposed. Evidence also suggests that CAAs and CAFs may share a common origin. Data from our laboratory using clonal cell lineage tracing demonstrated a monocyte lineage origin for adipocytes, specifically the $Mac1^{lo}$ fraction of bone marrow[88]. Similarly, lineage and gene expression analyses demonstrated that adipocytes and adipocyte progenitors arise from the hematopoietic stem cell *via* the myeloid lineage[96]. Our studies of CAFs

and their circulating precursors demonstrated that these cells originate in the Mac1^{hi} population of peripheral blood and that their participation in tumor may be regulated by MCP-1[91]. Additional evidence suggests plasticity between preadipocytes and macrophages, with preadipocytes being a source for macrophages[104] and tissue macrophages being a source for preadipocytes[105]. Histological evidence of a high ratio of adipocytes to fibroblasts at the tumor invasive front and an extremely high fibroblast-like cell to adipocyte ratio observed at the tumor center, suggests that CAAs may transition and/or give rise to CAFs as tumor progresses[14]. Breast cancer cells were also shown to induce de-differentiation of adipocytes to a more fibroblastic phenotype[21]. Human adipose tissue derived stem cells (hASCs) were found to give rise to CAF-like cells when cultured with conditioned media from MDA-MB-231 or MCF-7 breast cancer cell lines[106]. Under tumor conditions, the hASC-derived CAF-like cells were shown to have a myofibroblastic phenotype, with increased expression of aSMA and tenascin C. This change in phenotype was found to be dependent upon TGFβ signaling in the hASCs. Studies have yet to directly demonstrate a CAF to CAA conversion, however, we have observed *in vitro* that non-adherent bone marrow cells, enriched for hematopoietic progenitors, cultured in the presence of M-CSF and mouse serum give rise to lipid laden cells with a fibroblast-like morphology (unpublished observation). Together, these studies support an HSC origin for both CAAs and CAFs, suggesting plasticity exists between adipocytes, CAAs, and CAFs. This plasticity may be one mechanism by which heterogeneity of the TME is generated.

CONCLUSION

Evidence suggests that CAAs and CAFs play a critical role in tumor progression as well as patient prognosis and survival. It is thought that the metabolic changes associated with obesity underlie the increased risk of cancer and cancer-related mortalities. It has been estimated that excess weight and obesity were responsible for 20% of all cancer deaths in women in the United States[107], consistent with poor outcome of cancer in overweight/obese patients (reviewed in[108]). While no direct comparisons of CAAs derived from distinct sources have been conducted, it is clear that HSC-derived adipocytes represent a subpopulation distinct from conventional white and brown adipocytes based on their low expression level of leptin, low mitochondrial/peroxisomal content and oxidative capacity, and elevated inflammatory cytokine production[96]. HSC-derived adipocytes also share numerous features with CAAs including low expression of terminal adipocyte markers and high expression levels of inflammatory cytokines, indicating that HSC-derived adipocytes may be considered "activated" contributors to the TME. Like CAAs, HSC-derived adipocytes were found to be smaller in size than "resident" adipocytes ([81] and our unpublished observation), but whether, as with CAAs, this is related to a higher rate of lipolysis in these cells requires further exploration. It has been noted that HSC-derived adipocytes preferentially accumulate in visceral adipose tissue (VAT) rather than subcutaneous adipose tissue (SAT)[96]. Excess adiposity in VAT is specifically linked to type 2 diabetes and certain forms of cancer[76]. As compared to adipocytes from SAT, VAT adipocytes exhibited higher rates of fatty acid turnover and lipolysis[109] and produced more IL-6 and less adiponectin and leptin[110]. These data could indicate that VAT and SAT adipocytes are generated from different progenitors, or functional changes in different depots are due to differential accumulation of adipocytes arising from distinct progenitors. Furthermore, the accumulation of HSC-derived adipocytes was increased in female mice over males, which may have important inference in human biology[96], as women generally possess a higher percentage of body fat and tend to disproportionally gain fat in VAT following menopause. Coupled with preferential accumulation of HSC-derived adipocytes in VAT, this pattern of adiposity represents a higher risk of adipose-related gynecological cancers for postmenopausal women and suggests HSC-derived CAAs may represent a novel target these patients.

Several studies suggest that CAFs and their unique phenotypes are associated with increased malignant potential. In the case of breast cancer, women with denser breast tissue have an increased tendency to develop cancer[15]. The presence of a fibrous stroma was found to be associated with poor prognosis in squamous cell carcinoma[18]. In non-small cell lung carcinoma, molecular analysis revealed a gene signature for CAFs that was associated with patient prognosis[16]. Interestingly, recent pre-clinical studies in pancreatic ductal adenocarcinoma have demonstrated a protective role for CAFs[111,112], suggesting that the role of these cells is tumor-type dependent. CAFs are a heterogeneous population of cells that can differ based on both location within the tumor and between tumor types and demonstrate different phenotypes, activation states, and/or functions throughout tumor progression. This diversity may, in part, be due to the multiple proposed origins of CAFs, which have led to CAFs being referred to as a "cell state" rather than a specific cell type[113]. A more in depth understanding of the origins of CAFs may shed light on the array of markers expressed by these cells, help to better define the "CAF", and elucidate their roles based on origin and tumor type.

Given the essential roles of the TME in tumor development, progression and metastasis, it is clear that successful anti-tumor therapeutics should include those directed at the support cells of the TME. A key step towards this goal is the gaining knowledge of the role(s) of the different TME cell types (*e.g.,* CAAs

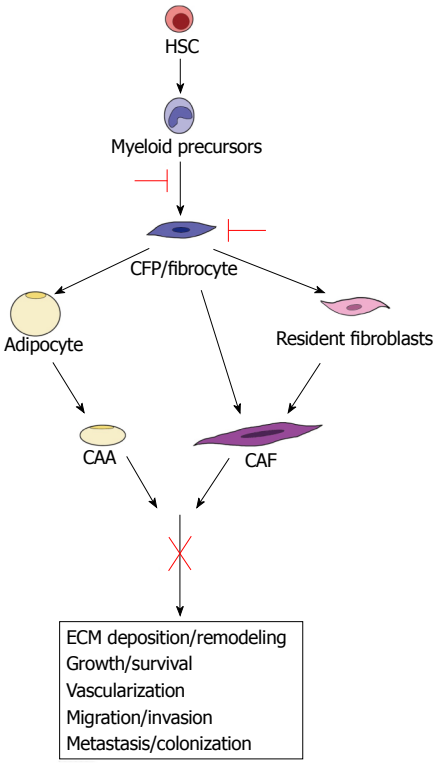

Figure 3 Therapeutic implications. We hypothesize that the identification of pathways from the hematopoietic stem cell (HSC) to the cancer-associated adipocyte (CAA) and cancer-associated fibroblast (CAF) provides a potential opportunity to target these pro-tumorigenic cells both early in their differentiation and at multiple points in their maturation, which may lead to a more encompassing downstream inhibition of their contributions to tumor progression and metastasis.

and CAFs), their origins, their temporal participation and mechanisms by which they influence tumor. However, the complexity of the crosstalk between the cells of the TME, the broad impact of CAAs/CAFs on the reactive stroma and their contribution to the evolving TME has made therapeutically targeting individual stromal cell derived factors difficult. For example, targeting fibroblast activation protein alpha (FAPα) produced by activated CAFs, while showing promise in preclinical studies[58,114,115], was demonstrated to have no beneficial response in Phase Ⅱ clinical trials for metastatic colorectal cancer and soft-tissue sarcoma patients[116] (and reviewed in[117]). However, we propose that targeting CAAs, CAFs and their precursors based on their origin may lead to significant advances in treatment by directly targeting the cells before their incorporation into tumor rather than targeting their varied products and multiple effects (Figure 3). We and others have shown that HSCs give rise to adipocytes *via* the myeloid lineage[88,96]. Likewise, our studies demonstrate an HSC origin for CAFs *via* the same myeloid lineage[91]. Studies have also demonstrated a myeloid lineage origin for the fibrocyte[118] that also gives rise to adipocytes[97] and fibroblasts[92,119]. These HSC-derived CAAs (unpublished observation) and CAFs[91,103] (and unpublished observation) contribute to the TME and have a significant impact on tumor progression in mouse models. Identification of pathways from the HSC to the CAA or CAF provides a potential opportunity to target CAAs and CAFs both early in their differentiation and at multiple points in their maturation. For example, early inhibition of CFP/fibrocyte differentiation from the myeloid lineage would lead to fewer CAA and CAF precursors available for incorporation in the TME. Likewise, directly targeting CFPs/fibrocytes in circulation may prevent their incorporation into the local and metastatic TME as both CAAs and CAFs, essentially hitting two arms of pro-tumorigenic stromal cells. Given their ability to invade, circulate and extravasate, therapeutically targeting HSC-derived CFPs/fibrocytes may also directly affect the population of CAFs demonstrated to chaperone cancer cells to metastatic sites. Finally, the ability to isolate HSC-derived CAA/CAF progenitors in circulation, combined with their intrinsic ability to home to tumor[91], may provide a novel modality for drug delivery vehicles for chemotherapy. Thus, targeting the precursors of CAAs and CAFs may lead to a more inclusive and encompassing downstream inhibition of their multiple contributions to tumor progression and metastasis. Taken together, these studies highlight the necessity of developing an understanding of the differences and similarities between TME cell types of multiple origins as well as research directed at elucidating the differentiation pathway of these populations for the ultimate goal of TME-based anti-tumor therapy.

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