Concise Review: the Obesity Cancer Paradigm: Exploration of the Interactions and Cross-Talk with Adipose Stem Cells

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ABSTRACT

With the recognition of obesity as a global health crisis, researchers have devoted greater effort to defining and understanding the pathophysiologic molecular pathways regulating the biology of adipose tissue and obesity. Obesity, the excessive accumulation of adipose tissue due to hyperplasia and hypertrophy, has been linked to an increased incidence and aggressiveness of colon, hematological, prostate, and postmenopausal breast cancer cancers. The increased morbidity and mortality of obesity-associated cancers has been attributed to higher levels of hormones, adipokines, and cytokines secreted by the adipose tissue. The increased amount of adipose tissue also results in higher numbers of adipose stromal/stem cells (ASCs). These ASCs have been shown to impact cancer progression directly through several mechanisms, including the increased recruitment of ASCs to the tumor site and increased production of cytokines and growth factors by ASCs and other cells within the tumor stroma. Emerging evidence indicates that obesity induces alterations in the biologic properties of ASCs, subsequently leading to enhanced tumorigenesis and metastasis of cancer cells. This review will discuss the links between obesity and cancer tumor progression, including obesity-associated changes in adipose tissue, inflammation, adipokines and chemokines. Novel topics will include a discussion of the contribution of ASCs to this complex system with an emphasis on their role in the tumor stroma. The reciprocal and circular feedback loop between obesity and ASCs as well as the mechanisms by which ASCs from obese patients alter the biology of cancer cells and enhance tumorigenesis will be discussed. Stem Cells 2014; 00:000–000

INTRODUCTION

More than one third of adults in the United States are obese, which is a number that has increased significantly in the last 10 years [1]. According to the World Health Organization statistics, obesity rates across the globe have almost doubled since 1980. The distinction between being overweight and obese is determined by the body mass index (BMI), calculated based on the height and weight of an individual. An individual with a BMI of 24.9 to 29.9 is considered overweight, while a person with a BMI greater than 30.0 is defined as obese. On a global scale, 1.4 billion adults meet the requirements for being overweight and nearly 500 million adults meet the requirements for being obese worldwide [2].

In 2007, the World Cancer Research Fund employed meta-analytic procedures to study the effects of obesity on cancer incidence and mortality. They found that higher levels of adiposity were associated with increased rates of colorectal, postmenopausal breast, and renal carcinomas [3]. Furthermore, additional meta-analysis confirmed an association between obesity and several other cancers in both men and women, includ-
Types of Adipose Tissue and their Role in Obesity

Historically, endocrinologists have divided adipose tissue into two categories, white adipose tissue (WAT) or brown adipose tissue (BAT). WAT is further subdivided into unique depots based on the location and its function: visceral (around the organs) and subcutaneous (between the muscle and the dermal fascia). The visceral WAT stores excess energy but also provides physical protection to the organs. For instance, perirenal fat is superficial to the renal capsule and protects the kidney from trauma. In contrast, the primary function of subcutaneous WAT is to store excess triglycerides and release free fatty acids during extended periods of fasting, starvation, or exercise. It has also been suggested that subcutaneous WAT functions as a buffer during intake of dietary lipids to protect the organs against the lipotoxicity of free fatty acid oxidation [14].

In contrast, BAT oxidizes chemical energy to produce heat, through the actions of mitochondrial uncoupling protein-1 (UCP1), as a defense against hypothermia [15]. Human babies, who lack body hair or a protective coat, have significant brown fat depots, presumably to provide heat in the cold environment encountered following birth. As humans age, BAT levels decrease. However, recent studies have identified an additional type of adipose tissue that is a hybrid between white adipose tissue and brown adipose tissue, termed beige or brite (brown/white) adipose tissue. Adults who have been exposed to chronic cold conditions form brown-fat-like depots characterized by enhanced thermogenesis located in the supraclavicular and neck region [16-21]. These brown-fat-like depots maintain high levels of expression of UCP1 and appear morphologically similar to brown fat. These brown-fat-like depots have been located in regions where white adipose depots are generally found [22, 23]. Unlike classical BAT, which is derived from a myogenic factor 5 (Myf5) muscle-like cellular lineage, the beige/brite adipocytes lack Myf5 expression [24].

While all adipose depot sites can increase in volume, only an accumulation of WAT increases the risk of developing various diseases, including heart disease, cancer, metabolic syndrome, and stroke [25-28]. Extensive reviews have focused on the association of obesity with heart disease, metabolic syndrome, and stroke [29-35]. The focus of this review will be on the relationship between increased adiposity, the biology of adipose stromal/stem cells (ASCs), and tumorigenesis.

Adipose Tissue and Adipose Stromal/Stem Cells (ASCs)

Once considered solely as an energy reservoir or thermal insulator, adipose tissue is now being recognized as a complex endocrine organ involved in energy homeostasis, feeding, reproduction, and inflammation. Adipose tissue is heterogeneous, containing adipocytes and cells from the stromal vascular fraction, namely ASCs (15-30%), endothelial cells (10-20%), pericytes (3-5%), granulocytes (10-15%), monocytes (5-15%), and lymphocytes (10-15%) [36].

Among the cell types within the stromal vascular fraction, ASCs have recently been the focus of research because they have the potential to differentiate into mesenchymal tissue such as osteocytes, chondrocytes, and adipocytes, are immune privileged and have immunomodulatory properties. Because they do not express MHC class II molecules or costimulatory molecules [37, 38], ASCs are immune privileged. ASCs have a complex biology in regards to their anti-inflammatory properties; these cells inhibit natural killer cell activation, resulting in impaired cytotoxicity processes [37]. ASCs reduce the proliferation of B cells, reduce immunoglobulin production, and suppress B cell functions [39]. These features make ASCs ideal for tissue engineering and regenerative medicine, since these cells have the potential to differentiate into many cell types and immunomodulate the immune system without causing rejection by the host or the grafted cells [40-45].

Obesity Related Alterations to Adipose Tissue and the Impact on Cancer

Obesity alters the physiological function of adipose tissue, resulting in chronic inflammation, skewed secretion of adipokines, and changes to the biology of ASCs. Adipose tissue expansion in obesity increases the distance between the enlarging adipocytes and their vasculature, leading to localized hypoxia. Adipocytes can grow up to 100-200 μm in diameter and subsequently exceed the typical diffusion distances of oxygen into tissue [46, 47]. The oxygen content in expanded adipose tissue is close to zero at 100 μm distances from the vasculature, implying that increased adipocyte size and adipocyte number results in significant hypoxia [47]. Furthermore, other studies have shown that despite the substantial increase in adipose tissue associated with obesity, neither cardiac output nor total blood flow to the adipose tissue is increased [48, 49]. In obese mice, the reduced blood perfusion and hypoxia appear to be specific to WAT [50]. The lack of oxygen to the adipose tissue results in the activation of hypoxia-induced factor 1-alpha (HIF-1α) and increased angiogenesis; however, the response is insufficient to compensate for the growing adipocytes, which leads to chronic low-grade inflammation [51, 52]. It is postulated that this chronic low-grade inflammation induces the excess secretion of pro-inflammatory cytokines, chemokines, protease, and protease inhibitors, such as tumor necrosis factor-alpha.
(TNF-α), interleukin 6 (IL-6), monocyte chemotactic protein 1 (MCP-1), leptin, and plasminogen activator inhibitor type 1 (PAI-1), which lead to adipose tissue dysfunction [53, 54]. The role that each of these factors plays in obesity and cancer will be presented in more detail.

**TNF-α.** TNF-α has an important role in the adaptive response of the immune system and other organ systems. TNF-α is an endogenous pyrogen that can induce fever, apoptotic cell death, inflammation as well as inhibiting tumorogenesis. However, dysregulation of TNF-α has been implicated in a variety of human diseases, including cancer, because it activates the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) pathway, leading to the expression of a variety of inflammation-related genes [55, 56]. TNF-α appears to contribute to the development of the tissue architecture necessary for tumor growth and metastasis [57]. It has also been shown to produce the induction of other cytokines, angiogenic factors and matrix metalloproteinases (MMPs), which may drive the survival and metastasis of tumor cells [58]. Furthermore, long-term exposure of hormone receptor positive breast cancer cells to TNF-α induces an epithelial-to-mesenchymal transition (EMT), a process by which tumor cells lose their cell-to-cell adhesion and gain migratory properties that facilitate metastasis [59].

**IL-6.** Similarly, IL-6 is an important regulator of immune cell growth and differentiation. Recent studies demonstrate that IL-6 regulates chronic inflammation, which can create a cellular microenvironment conducive to cancer growth [60]. High concentrations of circulating IL-6 in obese patients correlate with an increased risk of developing tumors. The production of the IL-6 receptor/ligand complex activates both Janus kinase (JAK) and the signal transducer and activator of transcription 3 (STAT3) pathways, which are key regulators of cell proliferation and apoptosis.

**MCP-1.** MCP-1 has been shown to recruit macrophages in both obesity and cancer [61, 62]. MCP-1 levels in adipose tissue and plasma are increased in genetically obese diabetic (db/db) mice and in wild-type mice fed a high fat diet [63]. With respect to cancer, stromal MCP-1 is involved in both tumor progression and metastasis [64]. Treatment of immunodeficient mice bearing human breast cancer cells with a neutralizing antibody to MCP-1 resulted in a significant reduction in macrophage infiltration, angiogenic activity, and overall tumor volume [64].

**Leptin.** In an obese state, leptin resistance causes hyperphagia, increased adipose tissue volume and hyperleptinemia, as the body attempts to compensate for the resistance [65-67]; however, increasing leptin secretion is ineffective. In fact, it has been shown that the plasma concentration and mRNA expression of leptin in adipose tissue are directly related to the severity of obesity [68, 69]. Hyperleptinemia is also partially responsible for the chronic low-grade inflammation associated with obesity. Excess leptin results in enhanced T-cell and macrophage activation as immune cells respond to the leptin in the microenvironment. Leptin also increases the expression of TNF-α, reactive oxygen-species (ROS) production, MCP-1 expression, and endothelial cell proliferation and migration. These factors all increase cancer cell growth and mobility.

**PAI-1.** PAI-1 is a serine protease inhibitor (serpin) produced by many different cell types, including endothelial cells, stromal cells, and adipocytes. PAI-1 affects adipocyte differentiation and the expression of PAI-1 increases with higher levels of adiposity [70]. PAI-1 principally inhibits urokinase plasminogen activator (uPA), which acts as an inducer of fibrinolysis and extracellular matrix degradation [71]. PAI-1 expression is also associated with increased tumor cell invasion and metastasis [72], and some studies have shown that PAI-1 is a poor prognostic indicator for a number of cancers, including breast cancer and colon cancer [72, 73].

While most of the studies to date have focused on adipose tissue as a whole, few studies have investigated the impact of obesity on the ASCs. Due to the chronic low-grade inflammation within microenvironment of the adipose tissue, the biology of the ASCs within these depots may be altered. Studies have shown that obesity diminishes ASC differentiation potential along adipogenic and osteogenic lineages, indicating a possible reduction in stem cell properties in cells conditioned by obese environments [74, 75]. Other studies have indicated that ASCs from obese individuals promote luminal breast cancer cell proliferation, angiogenesis, and metastasis [76-78].

**ASCs in the Tumor Stroma**

The tumor stroma is composed of numerous cell types (immune system cells, fibroblasts, myofibroblasts, and vascular cells). One of the key cell types is the cancer-associated fibroblast (CAF). The number of CAFs increases with the aggressiveness of the cancer [79-82]. CAFs demonstrate similar characteristics as myofibroblasts and express alpha-smooth muscle actin (α-SMA), tenascin-C, nestin, neural/glial antigen 2 (NG2), and PDGFR-α [83, 84]. It has been shown that ASCs are recruited to the tumor, transition into CAFs, and then integrate into the stroma [85-87]. Recent data indicates that ASCs that have been exposed to cancer cells or tumor cell conditioned media express tenascin-C and α-SMA, which are characteristic of CAFs, and may provide some insights into their role in the tumor stroma [87]. The recruited ASCs can also stimulate tumor growth, promote angiogenesis, and increase cancer cell invasion [88-90]. When ASCs are exposed to exosomes from breast cancer cells, they increase the expression of tumor-promoting factors, such as stromal cell-derived factor 1 (SDF-1), vascular endothelial growth factor (VEGF), chemokine ligand 5 (CCL5), platelet-derived growth factor D (PDGF-D), and transforming growth factor beta (TGF-β) [85-87, 91-93]. This phenomenon correlated with the increased expression of TGF-β receptor and phosphorylation of key factors in the TGF-β receptor-mediated SMAD pathway in ASCs [85, 86].
Consequently, these ASCs promote cancer cell growth and stimulate metastasis [94]. In vivo studies have confirmed that simultaneous co-injection of primary breast cancer and ASCs into nude mice results in integration of ASCs into the tumor stroma, thereby increasing tumor volume and increasing the vascularity of the tumor [95-97].

Other studies have demonstrated that ASCs stimulate invasion and metastasis of cancer cells. Recent evidence demonstrated that ASCs enhanced the migration of several types of cancer: breast, colon, prostate, gastric, and head and neck tumors [95, 98-101]. Data from Mueller and colleagues indicated that implanting spheroids formed with breast cancer cells and ASCs into nude mice increased the number of lung metastases [102]. Together, these studies suggest that cancer cells can recruit ASCs to the tumor microenvironment, which in turn increases cancer cell proliferation and metastasis.

Mechanisms of ASC induced alterations in cancer cells and tumorigenesis

Breast cancer. While many studies have described the interaction between ASCs and breast cancer cells, only recently have studies extensively explored the mechanism by which this interaction occurs. ASCs stimulated by cancer cells secrete a wide range of cytokine, chemokines, and growth factors that, in turn, increase the proliferation of breast cancer cells in an ASC/cancer cell reciprocal feedback loop (Figure 1) [74]. More specifically, cancer cells activate ASCs to secrete SDF-1, which then binds to its receptor CXCR4 on breast cancer cells and induces cellular proliferation through protein kinase B (AKT), extracellular signal-regulated kinases 1/2 (ERK1/2), and Janus kinase- signal transducer and activator of transcription 3 (JAK2-STAT3) [102]. Potter and colleagues showed that ASCs induced the expression of chemokine (C-C motif) ligand 2 (CCL2), ETS domain-containing protein (ELK1), Ezrin (VIL2), and MMP-11 in primary epithelial cells and breast cancer cell lines, leading to increased tumor volume, neoangiogenesis, and epithelial cell migration [103].

A primary role for ASCs in the microenvironment is their ability to induce EMT and promote metastasis. Devarajan et al. found that ASC conditioned media induced expression of fibronectin, α-SMA, and vimentin in breast cancer cells, which are markers of EMT [91]. These results correlated with increased expansion of CD44^high/CD24^low cancer stem cells and anchorage-independent growth of cancer cells, leading to EMT of cancer cells [91]. Furthermore, Pinilla and colleagues described the association between CCL5 secretion by ASCs and elevated levels of MMP-9 activity within the tumor microenvironment, leading to increased tumor invasion. ASC-derived IL-6 and IL-8 have also been shown to increase migration, invasion, and anchorage-independent growth of breast cancer cell lines, including MDA-MB-231, T47D, and MCF7 cells [84, 100].

Colorectal cancer. While limited information on the effects of ASCs on colorectal cancer cells exists, studies have provided some insights on the interactions between ASCs and colorectal cancer cell proliferation, neoangiogenesis, and efficacy of chemotherapy agents. ASCs that underwent conversion to CAFs have been shown to release a variety of growth factors and cytokines, including SDF-1, IL-6 and VEGF that enhance the growth of colorectal cancer cells (Figure 1)[104-106]. Similar to breast cancer cells, SDF-1 elicits its effects through activation of CXCR4. This SDF-1/CXCR4 axis regulates phosphoinositide 3-kinase (PI3K/AKT), mitogen-activated protein kinase (MAPK), and mTOR cascades, which ultimately alter chemotaxis, angiogenesis, and tumor metastasis in colorectal cancer cells [104-106]. Additional cytokines and chemokines secreted by ASCs into the tumor microenvironment increase the survival of the cancer cells [107]. For example, studies have demonstrated that ASCs secrete sufficient VEGF and IL-6 to induce neoangiogenesis, which is necessary to provide sufficient nutrients to the growing tumor [108]. Inhibition of VEGF or IL-6 leads to reduced angiogenesis and inhibition of tumor growth [109].

ASCs can also induce chemoresistance in colorectal cancer cells. These cells have been shown to become activated during treatment with platinum analogs and secrete factors that protect tumor cells against a variety of chemotherapeutic drugs [110, 111]. Distinct platinum-induced polyunsaturated fatty acids in minute quantities induced cancer cell resistance to a broad spectrum of chemotherapeutic agents [111]. Additional studies suggest that the secretion of interleukin 17 (IL-17) from ASCs, in response to chemotherapeutic agents, leads to chemoresistance and thus increases the number of colorectal cancer cells [112].

Prostate cancer. In prostate cancer, ASCs have been implicated in altering the gene expression profile of cancer cells, inducing a more aggressive phenotype, and increasing angiogenesis within the tumor (Figure 1) [92]. The number of ASCs was increased in cancer patients compared to prostatic nodular hyperplasia patients [99]. The ASCs are converted into CAFs and provide nutrients and support for the growing tumor. Ribeiro and colleagues found that adipose tissue and ASCs exposed to conditioned media from PC3 cells (prostate cancer cell line) had an altered adipokine expression profile, including increased osteopontin, TNF-α, and IL-6 [113]. These factors have been implicated in prostate cancer tumorigenicity and metastasis [114-117]. Prostate cancer cells co-injected with ASCs into nude mice caused increased tumor volume. The local delivery of oncostatin M exacerbated the effect of ASCs on prostate cancer cell proliferation and tumor volumes doubled in size [118]. Other studies have shown that ASCs mediate their effects via the SDF-1/CXCR4 axis. ASC-secreted SDF-1 increases the levels of CXCR4 that result in a more aggressive prostate cancer cell phenotype [101, 119]. ASCs have also been shown to increase capillary density as evidenced by increased expression

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of VEGF, basic fibroblast growth factor (FGF2) and CD31 [101, 120]. There is emerging evidence that suggests ASCs primed with prostate cancer conditioned media can undergo neoplastic transformation, and these ASCs form prostate-like neoplastic lesions in vivo and produce aggressive tumors upon serial transplantation [121]. Additional studies will be necessary to determine the precise mechanism by which these primed ASCs undergo neoplastic transformation.

**Obesity induced alterations to ASCs**

Studies have shown that ASCs isolated from obese women have an increased potential to traffic to the tumor compared to the ASCs isolated from lean women [77]. Furthermore, studies investigating the impact of obesity on ASC have observed increase recruitment of ASCs to the tumor in obese, resulting in an increase in the number of circulating ASCs [77, 122]. Zhang and colleagues revealed that a higher number of ASCs could be isolated from the WAT of obese mice compared to lean mice, possibly due to increased volume of WAT in obese mice [122]. These studies have shown that once localized to the tumor microenvironment, the mobilized ASCs enhanced the tumor vasculature by transdifferentiation into perivascular cells and incorporating into the tumor microenvironment [122]. With more ASCs recruited to the tumor site in obese mice, the perivascular cells are able to provide oxygen and nutrients to the tumor, enhancing survival and limiting apoptosis of cancer cells (Figure 2) [122]. Consistent with Zhang et al., Bellows and colleagues found increased frequency of ASCs in the circulation of obese patients, compared to lean patients [123, 124].

Additional studies have shown that ASCs from obese women (obese ASCs) enhanced the proliferation of breast cancer cells in vitro (Figure 2) [78]. Interestingly, this phenomenon was restricted to ER− breast cancer cells, suggesting that ASCs may act through an estrogen-mediated pathway [78]. These obese ASCs also express higher levels of leptin when they are stimulated with estrogen, suggesting an estrogen-mediated leptin-response [78]. Inhibiting leptin expression using a leptin neutralizing antibody reduced the impact of obese ASCs on breast cancer cell proliferation in vitro [78]. Furthermore, obese ASCs have been shown to alter the expression of several key regulatory genes involved in the cell cycle, apoptosis, angiogenesis, EMT, and metastasis [78]. The expressions of these molecular markers in breast cancer are associated with poorer prognosis due to increased invasion and metastasis of breast cancer cells to distant organs [125-129]. These studies suggest the source of leptin within the microenvironment is the ASCs, and robust secretion of leptin by ASCs can promote cancer cell growth and progression.

Delivery of leptin to cancer cells either *in vitro* or *in vivo* has also demonstrated increased proliferation, migration, invasion, angiogenesis, and metastasis of the cells [130-132]. Pre-neoplastic colon epithelial cells exposed to leptin upregulated VEGF expression, resulting in VEGF-driven angiogenesis and vascular development [133]. In breast cancer cells, leptin functions through the JAK2-STAT3, PI3K-AKT, ERK1/2, and activator protein 1 (AP-1) pathways, increasing the expression of proteolytic enzymes that are required in tumor growth, metastasis and neoangiogenesis [134-136]. In estrogen receptor-positive human breast cancer cell lines, leptin has been shown to exert its influence through the activation of the MAPK pathway [136]. Thus, high levels of leptin resulting from obesity may result in increased breast cancer incidence. In addition, future research on this topic should provide clues to the therapeutic potential of anti-leptin strategies.

**CONCLUSIONS**

Obesity is a major public health concern because it increases the risk of several debilitating and deadly diseases, including cancer [137]. While intense discussions on the mechanism(s) by which obesity impacts cancer are ongoing, recent studies suggest that ASCs, altered by obesity, integrate into the tumor stroma and provide support for the growing tumor. Numerous genes are differentially expressed in ASCs isolated from obese patients compared to those from lean patients. The data suggests that ASCs isolated from obese patients have an increased potential to assist cancer cells. Furthermore, the number of circulating ASCs in obese patients was significantly higher than in lean patients, which in turn may increase the opportunity for ASCs to home to tumors. Once recruited to the growing tumor, ASCs isolated from obese women not only produce a novel chemokine and cytokine repertoire but also express higher levels of chemokines and cytokines that further drive cancer cell proliferation and migration, tumor migration and invasion, and metastasis to distant organs.

While the body of literature presented in this review provides insight into our current understanding of the ASCs in the tumor stroma and the effects of obesity within this intricate microenvironment, further investigations are required. Future studies focused around the effects of obesity on ASCs and understand how obesity primes the ASCs resulting in increased tumorigenesis and/or metastasis will provide valuable insight to reducing cancer morbidity and mortality. Studies have also investigated the use of ASCs as vehicles for gene therapy and have gained significant attention [138-140]. Therefore, it is essential to identify the mechanism(s) by which ASCs influence cancer cells, since novel therapeutic targets can be developed to target ASCs and inhibit the growth and metastasis of cancer cells.

**AUTHOR CONTRIBUTIONS**

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Figure 1. Model of the tumor-promoting effects of CAFs formed from ASCs. (A) Cancer cells secrete a wide range of cytokines, chemokines, and growth factors that play a role in the recruitment of several different cell types into the tumor. The tumor microenvironment is composed of cancer cells, endothelial cells, adipose stromal cells (ASCs), cancer associated fibroblasts (CAFs), and immune cells. (B) A reciprocal and circular feedback loop between cancer cells and ASCs is initiated by the secretion of cytokines from cancer cells. These cytokines activate ASCs, resulting in the conversion of ASCs into CAFs as noted by the increased expression in alpha-smooth muscle actin (α-SMA), tenascin-C, nestin, neuro-glial antigen 2, and platelet derived growth factor receptor-alpha (PDGFR-α). In turn, the CAFs secrete cytokines and chemokines that alter cancer cells, leading to an increase in the number of cancer cells, increased invasive potential of cancer cells, and potentially increased chemoresistance of cancer cells. (C) Cancer cells recruit ASCs into the microenvironment and induce their transformation into CAFs. This cellular conversion results in secretion of cytokines, chemokines, growth factors, and enzymes that enhance cancer cell proliferation, induce EMT and the metastasis of cancer cells to distant sites.
**Figure 2.** Model for the role of obesity in promoting tumorigenesis and cancer progression. The accumulation of adipose tissue in obese individuals, results in formation of an hypoxic environment surrounding adipocytes more distal to blood vessels. Consequently, the adipose tissue releases angiogenic factors that circulate through the vasculature to combat the hypoxia. The hypoxic environment also results in significant inflammation, which results in the secretion of pro-inflammatory cytokines. The secretion of pro-inflammatory cytokines within the adipose tissue microenvironment may, in turn, alter the tissue-resident stem cells (ASCs). The production of angiogenic factors, the secretion of inflammatory cytokines, and the perturbations to ASCs promote a microenvironment favorable for tumorigenesis and cancer progression.