HHS Public Access

Author manuscript

Compr Physiol. Author manuscript; available in PMC 2018 February 09.

Published in final edited form as:

Compr Physiol. ; 8(1): 237–282. doi:10.1002/cphy.c170008.

Contribution of Adipose Tissue to Development of Cancer

Alyssa J. Cozzo[1], **Ashley M. Fuller**[2], and **Liza Makowski**[*,1,3,4]

[1]Department of Nutrition, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA

[2]Department of Pathology and Laboratory Medicine, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA

[3]Department of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA

[4]University of Tennessee Health Science Center, Memphis, TN, USA

Abstract

Solid tumor growth and metastasis require the interaction of tumor cells with the surrounding tissue, leading to a view of tumors as tissue-level phenomena rather than exclusively cell-intrinsic anomalies. Due to the ubiquitous nature of adipose tissue, many types of solid tumors grow in proximate or direct contact with adipocytes and adipose-associated stromal and vascular components, such as fibroblasts and other connective tissue cells, stem and progenitor cells, endothelial cells, innate and adaptive immune cells, and extracellular signaling and matrix components. Excess adiposity in obesity both increases risk of cancer development and negatively influences prognosis in several cancer types, in part due to interaction with adipose tissue cell populations. Herein, we review the cellular and noncellular constituents of the adipose "organ," and discuss the mechanisms by which these varied microenvironmental components contribute to tumor development, with special emphasis on obesity. Due to the prevalence of breast and prostate cancers in the United States, their close anatomical proximity to adipose tissue depots, and their complex epidemiologic associations with obesity, we particularly highlight research addressing the contribution of adipose tissue to the initiation and progression of these cancer types. Obesity dramatically modifies the adipose tissue microenvironment in numerous ways, including induction of fibrosis and angiogenesis, increased stem cell abundance, and expansion of proinflammatory immune cells. As many of these changes also resemble shifts observed within the tumor microenvironment, proximity to adipose tissue may present a hospitable environment to developing tumors, providing a critical link between adiposity and tumorigenesis.

Introduction

Cancer is characterized by fundamental aberrations in cellular behavior, including the ability to multiply indefinitely in the absence of growth-promoting factors and a resistance to signals that normally result in programmed cell death (apoptosis) (160). In the case of solid tumors, carcinogenic transformation and cell proliferation are followed by establishment of a

*Correspondence to liza.makowski@uthsc.edu.

vascular supply, or tumor angiogenesis, which facilitates the delivery of oxygen and nutrients to the growing tumor (160). Subsequent invasion into and migration through surrounding tissues allows for the establishment of nearby satellite tumors or entry into the lymphatic or vascular systems for dissemination and secondary tumor formation (metastases) (160). Solid tumor growth and tissue invasion require the interaction of tumor cells with the surrounding tissue. It is well established that communication between cancer cells and the tissue-level context in which they reside, collectively referred to as the tumor "microenvironment," is pivotal in determining whether a given tumor will exist in dormancy or progress to malignancy (410). The tumor microenvironment includes, but is not limited to, the tumor cells themselves, blood vessels (endothelial cells and pericytes), lymphatic vessels (lymphendothelial cells), adipocytes, fibroblasts, and various stem and progenitor cells (6) (Fig. 1). Also present is a wide variety of innate and adaptive immune cells, which can act as critical antitumor defenses or, alternatively, play central roles in tumor promotion. The tumor "stroma" is the connective, functionally supportive framework of the tumor, and by definition refers to a complex mixture of signaling molecules and extracellular matrix (ECM; for a list of abbreviations see Table 1) components, as well as the stromal cells (e.g., fibroblasts and pericytes) that produce and are embedded within them (44). However, the term "stroma" may also be used to collectively refer to all of the aforementioned cell types and secreted factors, as all are present within the cancer cell-adjacent tissue. Thus, considerable heterogeneity, both within the cancer cells themselves and among the interacting stromal cells, leads to a view of tumors as communities, and the process of tumorigenesis as a tissue-level phenomenon occurring in conjunction with intrinsic genetic deviations within individual cancer cells (380).

Due to the ubiquitous nature of adipose tissue, many types of solid tumors grow in proximate or direct contact with adipocytes and other adipose-associated cell populations. Although the specific nature of the reciprocal communication occurring between a developing tumor and adjacent adipose tissue is an area of active study, a growing body of literature indicates that these interactions with the local adipose milieu are important drivers of malignancy. Many of these studies have focused on dysregulated adipose and associated systemic metabolic dysfunction in the context of obesity, as there is now adequate evidence establishing a link between obesity/adiposity and elevated risk for, or accelerated progression of, several cancers. Following an overview of the adipose organ, we will briefly address epidemiologic links between obesity and cancer. Subsequently, we aim to provide the reader with an understanding of the recently described mechanistic links between cancer development or progression and adipose tissue *per se*, as opposed to obesity-associated systemic alterations such as metabolic dysfunction. Thus, although adipose dysfunction in obesity will be addressed frequently, we have chosen to emphasize the local physical and paracrine roles of adipose tissue in solid tumor development and malignancy by focusing on individual components of the adipose tissue microenvironment.

The Adipose Organ

Adipose tissue is a type of loose connective tissue that was long considered to be largely physiologically inert, primarily storing energy in the form of lipids while cushioning and insulating the body. However, work over the past several decades has established that

adipose tissue is also a substantial contributor to whole body endocrine signaling, modulating feeding behavior and total body energy expenditure, as well as hematopoiesis and lymphopoeisis, overall immune function, and reproduction (400, 402). Additionally, adipose tissue is now understood to contribute to the pathogenesis of a variety of regional and systemic diseases. The adipose tissue "organ" is in fact comprised of a variety of distinct adipose depots (Fig. 2), each of which differentially exerts systemic and regional control on overall energy metabolism and signaling based on location and adipose tissue subtype. Specifically, adipose depots can be divided according to anatomic location into subcutaneous, intramuscular, and visceral subtypes. Whole adipose depots, or specific regions within depots, may be further subclassified as white, brown, or beige depending on, among other factors, cellular mitochondrial content, with a higher relative number of mitochondria corresponding to a darker adipocyte hue. In humans, subcutaneous adipose tissue comprises ~80% of total body fat, and is contained primarily in the abdominal, gluteal, and femoral depots (216) (Fig. 2A). The breast fat pad is also a nontrivial contributor to total subcutaneous fat content in women. On the other hand, visceral depots represent approximately 5% to 20% of total body fat in normal weight (i.e., not overweight or obese) individuals (216). Visceral adipose tissue surrounds vital organs, and includes omental, mesenteric, and epiploic adipose, as well as the gonadal, epicardial, and retroperitoneal fat pads. Finally, numerous smaller depots, such as intramuscular, intraorbital, and bone marrow adipose, nourish and protect tissues throughout the body. While the majority of these depots are comprised of white adipose tissue—discussed further in the *Adipocytes* section—smaller brown and beige adipose tissue caches are also found in adults (147, 162). Importantly, due to similarities in the location and composition of adipose depots and endocrine function relative to humans, the laboratory mouse (*Mus musculus*) is a commonly used model for investigation of adipose tissue anatomy and physiology (Fig. 2B).

Although adipocytes constitute approximately 90% of adipose tissue *volume*, the adipose tissue microenvironment is a rich ecosystem of additional stromal and vascular components (often referred to collectively as stromal-vascular fraction). The stromal-vascular compartment of human white adipose tissue includes endothelial cells (10–20% of cells), pericytes (3–5%), fibroblasts and other connective tissue cells (15–30%), and stem and progenitor cells (0.1%), which reside within a complex milieu of signaling molecules and ECM components (50) (Fig. 3). Adipose tissue also contains a rich and varied collection of innate and adaptive immune cells (macrophages, dendritic cells, mast cells, eosinophils, neutrophils, and lymphocytes; 25–45%) (50). However, the exact cellular proportions, degree of vascularity, ECM composition, metabolic characteristics, and secretory products of adipose tissue vary according to numerous factors, including depot location, sex, age, health status, and extent of adipose accumulation (216).

Obesity and Cancer

Adipose tissue exhibits an almost unlimited capacity to expand, a unique property that has received increased attention in recent years as obesity has moved to the forefront of global public health concerns. Overweight and obesity, defined by the World Health Organization (WHO) as abnormal or excessive adiposity that presents a risk to health, are frequently measured at the population level using the body mass index (BMI), an individual's weight in

kilograms divided by the square of his or her height in meters. However, it must be acknowledged that, at an individual level, the BMI formula can vary considerably by sex and race and says little about body composition, often underestimating adiposity (302,347). For this reason, additional measures specifically of adiposity, such as waist circumference or the Body Adiposity Index (BAI; [hip circumference (cm)/height (m)$^{1.5}$−18]) developed by Bergman et al. (41), are sometimes used to correlate adiposity with disease risk.

Current status of the obesity epidemic, globally and in the United States

Since the recognition of obesity as a global epidemic in 1997 (54), increasing resources have been allocated to more completely understanding the prevalence, risk factors, and longterm consequences of this health hazard. For example, a recent quantitative meta-analysis analyzed 1698 population-based data sources, encompassing 186 countries and more than 19.2 million adult participants (9.9 million men and 9.3 million women), to evaluate trends in mean BMI over the last four decades (270). The authors reported a global increase in overall age-adjusted prevalence of obesity in men from 3.2% to 10.8%, and in women from 6.4% to 14.9%, between 1975 and 2014 (270) (Fig. 4A). An additional cross-sectional analysis of the United States National Health and Nutrition Examination Survey (NHANES) for the years 2013–2014 reports that the overall age-adjusted prevalence of obesity (again by BMI) among US adults (age 20+ years) has reached 37.7% (120). Moreover, among men and women in the US, obesity prevalence has now reached a staggering 35% and 40.4%, respectively (120). Furthermore, extreme obesity (or class 3 obesity, defined as BMI >40) in the United States is currently 9.9% for women and 5.5% for men (120), considerably higher than the global prevalence of 1.6% and 0.64%, respectively (270) (Fig. 4B). Importantly, a disproportionate burden of obesity and overweight is observed among women who self-identify as Hispanic or non-Hispanic black minorities; NHANES data indicate that the overall age-adjusted prevalence of obesity in non-Hispanic black and Hispanic women measures 57.2% and 46.9%, respectively, compared to 38.2% in non-Hispanic white women (120) (Fig. 4C). Finally, it should be noted that rising obesity rates are not restricted to adults. The prevalence of obesity in US children and adolescents ages 2 to 19 years old rose from approximately 10% during the 1988 to 1994 NHANES period to 17.0% in the 2011 to 2014 period, with extreme obesity more than doubling from approximately 2.5% to 5.8% (287).

The obesity-cancer link

Cancer is currently the second leading cause of death in the United States, and is expected to surpass heart disease as the leading cause of death within the next few years (357). Approximately 40% to 60% of cancer patients are classified as overweight or obese (145, 320), and in 2004 it was estimated that overweight and obesity accounted for one in seven cancer deaths in men and one in five in women (56). Importantly, obesity is differentially associated with both increased risk of cancer *development* and increased risk of poorer cancer *prognosis*. Indeed, an association between obesity and increased risk of onset remains ambiguous for several cancer types for which there is strong support for an influence on outcome. With this caveat acknowledged, there is adequate evidence to support an association between obesity and increased risk of developing colorectal, post-menopausal breast, endometrial, kidney, esophageal, liver, gallbladder, pancreatic, and thyroid cancers,

as well as non-Hodgkin's lymphoma and myeloma (33, 55, 208, 210, 409). The American Society of Clinical Oncology (ASCO) has also acknowledged that obesity contributes to poorer cancer prognosis following diagnosis in a number of ways, including by impairing the delivery of systemic cancer therapies and by elevating risk of both tumor recurrence and development of additional primary malignancies (224). Interestingly, there is also a body of literature that supports a protective effect of obesity in overall survival for some cancer types, a finding known as the "obesity paradox." Potential explanations for the obesity paradox emphasize methodological issues, such as unmeasured confounders and/or a reliance on BMI as a metric for obesity (219, 368). As mentioned previously, BMI is a rather crude mathematical estimate that does not capture important considerations such as percent adiposity, regional distribution of adiposity (e.g., android vs. gynoid obesity), or differences in lean mass. Gonzalez et al. reported that the use of body composition indices resulted in a disappearance of the obesity paradox in 175 cancer patients in which BMI was previously associated with a protective effect, emphasizing the importance of considering body composition in epidemiologic analyses of cancer outcomes (149). In fact, when body composition was included, loss of lean mass (sarcopenia) was a more important prognostic indicator than BMI for patients exhibiting cancer-associated cachexia, a systemic wasting syndrome frequently observed in end-stage cancer patients that is characterized by a rapid loss of both skeletal muscle and adipose tissue (149, 240). Thus, additional evidence is needed to determine whether isolated reports of the obesity paradox are simply artifactual or in fact clinically relevant.

Nevertheless, leading hypotheses seeking to explain observed connections between obesity and increased cancer morbidity and mortality emphasize factors such as metabolic disruption-induced growth factor dysregulation; higher levels of circulating adipokines and cytokines secreted by inflamed obese adipose tissue; and elevated production of estrogens by adipose tissue (90, 297). These hypotheses emphasize the role of adipose as an endocrine organ and obesity as a potential state of adipose endocrine dysfunction. However, growth and invasion of some solid tumors into adjacent adipose may promote tumor aggression even in the absence of obesity. For example, adipose tissue invasion at the tumor margin is associated with an increase in lymph node metastasis in patients with invasive breast carcinoma, irrespective of BMI (454). Thus, whether select adipose-mediated mechanisms of tumor promotion are merely exacerbated by obesity or are unique to a dysregulated obese adipose microenvironment in many cases remains to be determined. Moreover, the mechanisms whereby adipose accumulation increases risk of tumor onset and/or mediates tumor progression in adipose-adjacent cancers are multifactorial, complex, and likely tissue/organspecific, in part due to unique paracrine and physical interactions occurring between cancer cells and adjacent adipose tissue. In this review, we have especially highlighted the role of obesity in the development and progression of breast and prostate cancers due to the prevalence of these cancer types in the US population and their significant contributions to cancer-related mortality.

Breast and prostate cancers are the most frequently diagnosed cancers and the second leading causes of cancer-related death among US men and women, respectively (357). Due to their now recognized genetic and molecular heterogeneity, these cancer types have been shown to exhibit complex associations with obesity. For example, although the association

between obesity and risk of postmenopausal breast cancer is now well established, the relationship between obesity and premenopausal breast cancer risk was controversial until studies began to consider molecular breast cancer subtypes. Specifically, recent work has clarified an association between obesity and premenopausal onset of triple-negative breast cancers (TNBCs), with differential risk according to race (12, 16, 67, 307, 405). Studies from our lab and others have also demonstrated that diet-induced obesity is associated with accelerated TNBC latency (time to development of a palpable tumor) in ovary-intact preclinical mouse models (18, 73, 375, 376). Additionally, in patients with confirmed breast cancers, obesity is associated with increased risk of breast cancer invasion (143, 272), development of distant metastases (111, 247, 294), tumor recurrence (42, 346), and mortality (2, 24, 55, 64, 84, 229, 420, 436) irrespective of molecular subtype. On the other hand, the role of obesity in risk of prostate cancer development remains equivocal (22, 32, 48, 283), in part because, similar to breast cancer, prostate cancer risk in obese individuals also appears to vary by race (32, 127). However, in confirmed prostate cancers, obesity is consistently associated with an elevated risk of cancer aggression (high Gleason scoring, a grading system used to inform the prognosis of men with prostate cancer) and prostate cancer-associated mortality (206, 463). Thus, rising obesity rates present an oncological crisis, both globally and within the United States.

Following a brief consideration of the anatomy of breast and prostate in humans and laboratory mice—a frequently used model in basic science and translational/pre-clinical cancer studies—potential mechanistic links between adipose tissue and breast and prostate cancer development or progression will be discussed in detail through a comprehensive examination of the available literature regarding adipose-cancer interactions in each organ.

Anatomy of the Breast and Prostate

The laboratory mouse remains the most widely used animal model for the study of cancer pathophysiology. Consequently, integration of experimental findings with studies of human disease requires an understanding of human and veterinary pathology and anatomy, as well as developmental, molecular, and cellular biology. While this level of detail is beyond the scope of this review, this section will provide a brief comparative biology overview of the breast and prostate in humans and mice as a backdrop for the studies reviewed in subsequent sections.

Mammary gland anatomy and adipose-cancer interaction in humans vs. mice

In both mice and humans, the mammary gland is a unique, dynamic organ that continuously undergoes anatomic and functional changes over the life course (180). In mice, the nascent mammary gland (“mammary tree”) consists of a network of epithelial ducts, each of which terminates in a stem cell-enriched structure called a terminal end bud (TEB; Fig. 5A). During sexual maturation, inductive hormonal and growth factor-derived signals stimulate the proliferation of ectodermal cells within these TEBs, driving ductal elongation and branching (168, 263, 361). The mature mammary epithelium continues to undergo further differentiation during later life stages such as pregnancy, lactation, and post-partum involution, or epithelial regression (98, 361). Development of the mammary tree and

pregnancy/lactation-associated expansion and involution require remodeling of the surrounding stroma. In mice, mammary ductal-adjacent stroma is primarily comprised of adipose tissue, without a significant collagenous matrix layer (Fig. 6).

In comparison to mouse, the human mammary gland is a more extensively branching structure. Beginning at the nipple, the lactiferous sinus branches into segmental, or interlobular, ducts (Fig. 5B). Segmental ducts branch further into terminal ducts and lobules, which together comprise the functional unit of the human mammary gland, the terminal ductal lobular unit (TDLU). Immediately surrounding the TDLU is a loose intralobular stroma, referred to as "specialized stroma," which contains abundant fibroblasts (Fig. 6) (98). Fibroblasts within the intra-lobular stroma exhibit phenotypic and functional differences from those found within inter-lobular stroma, including expression of select collagen isoforms (21) and ectoenzymes (20). Dense, collagenous inter-lobular stroma surrounds the entire human TDLU structure, forming a thick layer between the TDLU and adjacent adipose tissue. Surrounding the interlobular stroma is a large depot of subcutaneous adipose, comprising 7% to 56% of the volume of the adult breast (416).

The most extreme example of tumor infiltration into adipose tissue is seen in breast cancer. Breast cancer most frequently begins in ductal epithelial cells, which proliferate to fill the ductal lumen and generate a precancerous lesion called *ductal carcinoma in situ* (DCIS). Subsequently, *invasive ductal carcinoma* (IDC) cells invade the mammary stromal compartment, encountering an area rich in adipose tissue. On the other hand, approximately 1 in 10 invasive breast cancers originate in the lobules, beginning as *lobular carcinoma in situ* and progressing to *invasive lobular carcinoma*. The lack of intra-lobular stroma in mice (98) and relatively thinner collagenous matrix means that tumor cell invasion in mouse models of breast cancer results in immediate encounter of adipocytes and other adipose cell populations (Fig. 7A), whereas human invasive breast carcinoma must invade through both intra- and interlobular stroma before directly encountering adipose tissue (Fig. 7B).

Prostate gland anatomy and adipose-cancer interaction in humans vs. mice

Before progressing to a comparison of mouse and human prostate anatomy, it should be acknowledged that rat and canine models have generated important mechanistic knowledge in prostate cancer research, particularly in the context of the spontaneous development of prostate lesions (184). However, genetically engineered or xenografted mice remain the most commonly used model in prostate cancer research. For an overview and critique of currently available mouse models of human prostate cancer, the reader is directed to (151, 184).

Like the mammary gland, the prostate exhibits important inter-species differences. In mice, the prostate is comprised of four lobes lying anterior and lateral to the urethra. These lobes are named after their spatial orientation (anterior, dorsal, ventral, and lateral lobes, see diagram in Fig. 8) and exhibit distinctive histology (184, 291). The glandular acini of the prostatic lobes are surrounded by a thin fibromuscular tunica, and are embedded in a loose connective tissue stroma with minimal smooth muscle cells and sparse collagen fibers (291). Individual mouse prostate lobes are surrounded by a delicate mesothelium-lined capsule, and are separated from each other by fibrous and adipose connective tissue (291).

In contrast to mice, the human male prostate does not have exterior lobation, but instead contains distinct glandular regions (a peripheral zone, a central zone, and a transition zone; see diagram in Fig. 8) (291), again with characteristic histology. Similar to the breast, a conspicuous histological difference between mouse and human prostate lies in the stromal component. In humans, the prostate gland bears an anterior, well-developed, nonglandular fibromuscular stromal region. Abundant adipose tissue is present surrounding most of the posterolateral aspects of the prostate (424), and is used as a marker of extraprostatic tissue in biopsy samples (49). This region of adipose is referred to in subsequent sections as *periprostatic adipose*. Intraprostatic adipose, when present, consists of a small focus of a few adipocytes, and is rarely observed histologically (49).

The most common type of prostate cancer is acinar adenocarcinoma, which originates from the glandular epithelium. Pre-neoplastic *prostatic intraepithelial neoplasia* (PIN) progresses to *invasive adenocarcinoma*, in which extension of prostatic carcinoma through the prostatic capsule (extraprostatic extension) and resulting interaction with the surrounding adipose is an indicator of malignant progression and advanced histopathological stage (378). The periprostatic adipose depot unambiguously contributes to prostate cancer malignancy (326, 386, 396). In fact, interaction with periprostatic adipose tissue has been suggested to be amore important determinant of cancer recurrence than an invasive phenotype (192). Analogous to breast cancer, recent advances in molecular phenotyping by The Cancer Genome Atlas Research Network have identified several genomically distinct molecular subtypes of prostate cancers (31). Whether these subtypes interact differentially with adjacent adipose remains to be determined.

Microenvironmental Links between Adipose Tissue and Cancer

Context matters: Extracellular matrix in adipose tissue and cancer

Adipocytes and other stromal cells are embedded in a loose, three-dimensional ECM, the noncellular tissue component that provides both structural and biochemical support to surrounding cells, such as cell adhesion, paracrine communication, and differentiation signals. Maintenance of the adipose tissue ECM—primarily comprised of fibronectin and collagens (373)—involves a variety of cell types, including fibroblasts, macrophages, adipocytes, and preadipocytes. Importantly, adipocyte function and survival is tightly regulated by both the molecular composition and mechanical properties of the surrounding ECM (239).

The structural flexibility of adipose tissue ECM facilitates transient volume changes in response to normal fluctuations in lipid stores throughout the feed-fast cycle. However, rapid adipocyte hypertrophy (increased adipocyte volume) during the development of obesity can result in intracellular or regional hypoxia. Reduced tissue oxygenation induces transcriptional programs in adipocytes and other stromal cells that ultimately lead to excess deposition of fibrillar ECM components such as collagens I, III, and VI and development of tissue fibrosis (373, 398). Indeed, adipose depots of obese subjects often exhibit greater total fibrosis, and particularly pericellular fibrosis around adipocytes, than lean individuals (95,363). Importantly, hypoxia-induced adipose tissue fibrosis is associated with onset of metabolic perturbations in adipocytes (199, 373), while dysregulation in visceral adipose

function is linked to the pathogenesis of insulin resistance and type II diabetes mellitus (95, 158, 199). Furthermore, as adipocytes become encapsulated in a shell of rigid ECM, impaired cellular function also results in apoptosis and necrosis (277). Release of damage-associated molecular patterns (DAMPs) from dead and dying adipocytes and adjacent live adipocytes promotes recruitment of macrophages and other inflammatory cells; histologically, these macrophages can be observed within crown-like structures (CLS), foci of macrophages and other inflammatory cells surrounding dead and dying adipocytes (265). Macrophages are fully integrated into all stages of the fibrotic process through secretion of soluble mediators and cytokines such as transforming growth factor β1 (TGF-β1), platelet-derived growth factor (PDGF), and chemokines that attract and activate fibroblasts and collagen-producing myofibroblasts (373, 446).

Interestingly, while adipose tissue fibrosis in the context of obesity is well described, increased adipose ECM deposition, fibrosis, and immune cell infiltration are also observed in cancer-associated cachexia (35). Abdominal subcutaneous adipose depots of lean cachectic subjects bearing gastrointestinal cancers displayed extensive adipose ECM remodeling, including a dramatic increase in deposition of collagens I, III, and VI as well as elastin and fibronectin (11). These changes were associated with increased myofibroblast content and elevated activation of TGF-β/SMAD signaling pathways (11). As described later in the *Adipocytes and adipocyte-cancer interactions section*, cancer-associated cachexia is also associated with metabolic dysfunction in adipocytes, which may be mediated in part by ECM modifications.

Importantly, epithelial tissue homeostasis and tissue organization is also heavily dependent upon a dynamic dialogue with the surrounding ECM. Enhanced ECM stiffness triggers the process known as epithelial-to-mesenchymal transition (EMT), which is characterized by the loss of epithelial polarity, de-differentiation, and local invasion (271,313,340,442). Furthermore, disruption of ECM structure or misinterpretation of ECM-derived signals due to alterations in signaling receptor profiles is associated with development of a malignant phenotype in transformed epithelial cells (43, 141, 230). Hence, modifications in the adipose tissue ECM that provide a hospitable environment to developing tumors, such as enhanced stiffness in obese breast tissue, may provide a link between adipose tissue and tumorigenesis.

As discussed in later sections, chronic low-grade inflammation, macrophage infiltration, hypoxia, and aberrant wound healing responses, including an increase in myofibroblast and activated fibroblast content, are features of both the tumor and adipose tissue microenvironments (44, 101, 230). In tumors, chronic activation of the wound repair response leads to excess deposition of ECM components and accumulation of scar-like fibrotic tissue in a process known as *desmoplasia*, or the *desmoplastic reaction* (Fig. 9A). Desmoplasia is associated with poor outcomes in both breast and prostate cancers (23, 258), and can facilitate cancer progression by interfering with drug delivery. Thus, ECM remodeling and the resultant disturbances in cytoskeletal tension and mechanotransduction have emerged as important factors that promote neoplastic transformation, cancer malignancy, and cancer metastasis (44, 220, 230), and may provide another connection between adipose dysregulation and cancer.

Adipose extracellular matrix composition and viscoelasticity: Influence on the normal breast and breast cancer—Mammographic density denotes the radiologic appearance of the breast, and is a metric of the fibroglandular (epithelial and nonfatty stromal) content in that tissue (322). A number of qualitative and quantitative methods have been developed to estimate mammographic density, including Breast Imaging Reporting and Data System (BI-RADS) categories, Wolfe's parenchymal patterns, Tabar's classification scheme, and numerous two- and three-dimensional image analysis techniques (452). Within heterogeneous breast tissue, tumors most frequently arise within the most mammographically dense regions of the breast, suggesting that denser fibroglandular tissue directly influences carcinogenesis (408). Indeed, regardless of the reporting method (322), high mammographic density is consistently and strongly associated with both elevated risk of breast cancer (51) and more aggressive tumor characteristics (453), even after adjustment for other risk factors such as age and BMI (178).

At the molecular level, high mammographic density reflects desmoplasia, a series of histological alterations including, but not limited to, the development of a dense, collagenous stroma rich in type I and/or type III collagen (88,126). Similar stromal changes are also observed in breast cancers (348), and are orchestrated by a heterogeneous, reactive population of so-called "cancer-associated fibroblasts" (CAFs). CAFs display remarkable plasticity, and frequently differentiate into myofibroblasts, a cell type exhibiting properties of both fibroblasts and smooth muscle cells (87,193,353). In nonmalignant tissue, myofibroblasts play an important role in wound healing responses, secreting a fibronectin- and collagen type I-rich ECM characterized by fibrillary architecture and increased cross-linking and density (344). They are also a predominant source of fibrogenic and/or inflammatory cytokines in fibrotic lesions (171). Despite the utility of this cell type to normal wound healing programs, however, the presence of myofibroblasts in tumors contributes to pathological desmoplasia (193), and may thereby promote cancer progression (198).

In addition to fibroblasts, local (adipose-derived) mesenchymal stem cells, bone marrow-derived mesenchymal stem cells, myeloid precursors, and cells derived from the epithelial-mesenchymal transition may also represent alternative sources of myofibroblasts in tumor stroma (93,251,304). Furthermore, in tumors growing in an adipose tissue-rich microenvironment, cancer cell-induced reprogramming of local adipocyte morphology, gene expression, and function has been observed to promote to adipocyte delipidation and atrophy/regression (46). This process occurs concurrently with the accumulation of fibroblast-like cells and a desmoplastic stroma; this synchronicity raises the possibility that some CAFs might be derived from dedifferentiated adipocytes (46) (Fig. 9B). However, as CAFs are a heterogeneous cell type, the extent to which their specific lineages determine their contribution to tumor progression remains inconclusive.

Although obesity is associated with reduced mammographic density, in part because fat is radiolucent, several studies have unveiled close links between chronically inflamed obese mammary adipose tissue and the development of fibrosis and associated ECM rigidity (301,344,372). Myofibroblasts are typically absent from normal, uninflamed breast tissue (401). However, Seo et al. showed that obesity elevated matrix rigidity in noncancerous

breast tissue by enhancing myofibroblast content in mammary adipose (344). Distinct from tumors (65), these obesity-associated increases in myofibroblast content and matrix rigidity occurred in a transforming growth factor beta (TGFβ)-independent manner (344), suggesting that ECM composition and stiffness may be differentially regulated in benign obese and malignant breast tissue. The same study showed that adipose stromal cells (ASCs, also called adipose-derived stem cells) isolated from obese mice exhibited increased expression of α-smooth muscle actin (α-SMA, a myofibroblast marker), as well as increased fibronectin and a more fibrillar, partially unfolded, and stiffer ECM (344), implicating ASCs as a source of myofibroblasts in obesity. Furthermore, obese ASCs also exhibited enhanced proliferative capacity and secreted increased quantities of matrix components (344), thereby mimicking characteristics of tumor-associated stromal cells (65, 193). Consistent with these results, histologically normal breast tissue from obese patient mastectomies exhibited increased α-SMA staining and collagen fiber length and thickness relative to tissue from lean individuals (344). Obesity-associated increases in α-SMA levels also correlated with formation of CLS, further implicating macrophages in the development of mammary adipose tissue fibrosis (344).

Increased matrix rigidity in breast adipose tissue may be an important mediator of cancer initiation and progression in obese individuals. To test the effects of obesity and ECM on tumor cell behavior, Seo et al. cultured preinvasive human MCF10AT cells upon decellularized matrices produced by ASCs isolated from lean or obese mice. The authors reported that, relative to ECMs deposited by lean ASCs, obesity-associated ECMs increased MCF10AT cell motility and promoted the formation of disorganized three-dimensional acini, indicative of greater tumorigenic potential (344). Additionally, ECM generated by obese mammary ASCs significantly enhanced the proliferation of the highly invasive MDA-MB-231 cancer cell line by altering mechanotransduction through enhanced RhoA/ROCK-mediated cell contractility and YAP/TAZ transcription factor activity (344). Collectively, these results are suggestive of a relationship between obesity-associated mammary adipose tissue fibrosis and accelerated tumor initiation and/or proliferative capacity.

In addition to fibroblasts/myofibroblasts, adipocytes play a vital role in defining the ECM environment through secretion and processing of factors such as collagen VI, an ECM component with both structural and signaling roles that is highly enriched in adipose tissue (199, 300, 419). Excess adipocyte collagen VI expression in obesity is associated with adipose tissue fibrosis and metabolic dysregulation, while the absence of collagen VI in mouse models of obesity allowed for uninhibited adipocyte expansion and an improved metabolic phenotype (199). Increased adipocyte collagen VI expression is also associated with elevated local concentrations of the collagen VI α3 chain cleavage product, endotrophin, which has been identified as a driving factor in adipose tissue fibrosis, macrophage chemotaxis, and inflammation, and appears to mediate adipose metabolic dysregulation in obesity (Fig. 10) (300, 372). Unsurprisingly, increased collagen VI production also coincides with increased adipose tissue macrophage content (300, 301). To further illustrate parallels in the obese adipose and tumor microenvironments, collagen VI and its cleavage product have also been implicated in the initiation and progression of breast cancers. Collagen VI is abundantly expressed by breast cancer-associated adipocytes (discussed at greater length in the *Adipocytes* section), and its increased deposition in the

ECM promotes tumorigenesis and malignant progression both *in vitro* and *in vivo* by inducing alterations in cancer cell signaling programs, gene expression patterns, and post-translational modifications (185,186). For example, treatment of MCF-7 human invasive breast cancer cells with collagen VI significantly elevated the activity of the oncogenic Akt-GSK3β–β-catenin–Tcf/Lef pathway, ultimately resulting in cyclin D1 protein stabilization and enhanced cell proliferation (185, 186). Accordingly, expression of the proto-oncogenes GSK3β and cyclin D1 in mammary tumors exhibited a steep immunohistochemical gradient, with increased staining intensities observed proximate to adipocytes. A similar gradient in collagen VI expression was also observed, further implicating adipocyte-derived collagen VI in the induction of mitogenic signaling pathways (186). In addition, adipocyte-derived endotrophin induces markers of EMT and acts as a potent adipokine that exerts growth-stimulatory and prosurvival effects on developing tumors (300). Furthermore, endotrophin overexpression in the breast tumor microenvironment is associated with increased rate of metastasis (300) and resistance to the platinum-based chemotherapeutic cisplatin (298). Thus, increased collagen VI deposition and endotrophin concentration in the extracellular milieu of obese adipose may influence both early tumor development and treatment outcomes.

Adipose extracellular matrix-derived factors: Direct effects on epithelial cells —In addition to modulating composition and viscoelasticity of the breast ECM, stromal cells within the obese breast microenvironment secrete numerous soluble signaling mediators that have direct effects on epithelial cells. In particular, hepatocyte growth factor (HGF) is an excellent candidate for stromal-mediated breast cancer promotion in the context of obesity. Serum HGF is elevated in obese individuals and is reduced with weight loss (39, 172, 379), and HGF has been detected in both normal and malignant breast tissue (404). Although HGF is classified as an adipokine (421), it is produced by a number of breast cell types including stromal fibroblasts. HGF is the only known ligand for its receptor, cMET, and HGF signaling impacts the phenotypes of both early- and late-stage breast cancers. With respect to early-stage lesions, we have reported that treatment of premalignant basal-like breast cells with HGF-blocking antibodies inhibited 3D morphogenesis, reflecting a reduction in epithelial malignant potential (63). Importantly, basal-like breast cancer is a clinically intractable TNBC subtype that is more prevalent in obese individuals (12, 16, 67, 307, 405), and an HGF gene expression signature generated via treatment of pre-malignant breast cells with recombinant HGF was found to correlate with both basal-like subtype and poor survival in >700 breast cancer samples from three publically available datasets (63).

In advanced tumors, HGF signaling initiates an invasive growth program that promotes cell migration, invasion, proliferation, and angiogenesis (Fig. 11) (255). HGF is also elevated in the serum of breast cancer patients and correlates with advanced disease (63, 173, 174, 351). In support of this observation, our laboratory previously demonstrated that high fat diet-induced obesity increased HGF concentration and enhanced expression and activation of cMET in the mammary fat pad of C3(1)-T-antigen (TAg) mice, a unique genetically engineered mouse model (GEMM) of spontaneous basal-like breast cancer (152, 170, 376). We also reported that obesity increased HGF production by primary murine fibroblasts isolated from both normal mammary glands and tumors, and that CAFs isolated from obese

animals induced epithelial cell migration in an HGF-dependent manner (376). Obesity-mediated regulation of HGF secretion from other stromal cell types such as adipocytes is currently under investigation.

Adipose extracellular matrix in prostate cancer—Despite being a common feature of mouse models of prostate cancer, histologically conspicuous reactive stroma is much less prevalent in human prostate tumors (184). However, like the breast, induction of a myofibroblastic phenotype and degree of reactive stroma carry important prognostic value for prostate cancer malignancy (23, 365, 406). Notably, as the literature regarding the contribution of adipose tissue to breast cancer onset and progression has greatly outpaced that of prostate cancer, obesity-associated ECM modifications are currently better characterized in the mammary, relative to the periprostatic, fat pad. Additionally, conflicting data exist regarding the association between periprostatic fat density (measured by magnetic resonance imaging or computed tomography) and tumor aggressiveness in prostate cancer patients (413,414,441). Our literature search also revealed no publications reporting that periprostatic adipose tissue fibrosis occurs in obesity, but whether this is due to a lack of occurrence or a lack of examination is unknown. Furthermore, no studies investigating links between adipocyte-derived endotrophin and prostate cancer were available at the time of writing this review. Therefore, future obesity-prostate cancer studies may be informed by the sundry findings linking breast cancer and adipocyte-associated fibrosis, modifications in ECM dynamics, and endotrophin release.

Adipocytes and adipocyte-cancer interactions

Adipocytes are specialized connective tissue cells that constitute a major cell type in both the normal-weight and obese breast. The majority of adipocytes in adult humans are white adipocytes, which contain a large, unilocular lipid droplet and are specialized for storage of neutral lipids. However, brown and/or beige adipocytes (also called “brite” or “inducible” adipocytes (147)) have also been reported in adults, and likely play important roles in thermogenesis (445). More recently, “pink” adipocytes have been described in murine mammary gland, arising exclusively during pregnancy and lactation due to a process wherein white adipocytes progressively transdifferentiate to acquire secretory, epithelial-like features (147). Adipocytes secrete a broad range of signaling molecules that exert local and/or systemic effects with the potential to influence tumor growth. Among the better studied adipocyte-derived factors are metabolic factors such as leptin, adiponectin, resistin, visfatin, and plasminogen activator inhibitor-1 (PAI-1); hematopoietic factors such as GM-CSF; growth factors such as angiopoietins, HGF, vascular endothelial growth factor (VEGF), insulin-like growth factor-1 (IGF-1), and TGF-β; and a variety of cytokines, including interleukin-6 (IL-6) and TNF-α and the chemokine monocyte chemoattractant protein (MCP-1) [also referred to as chemokine (C-C motif) ligand 2 (CCL2)] (Fig. 12) (60, 391). Several of the aforementioned adipocyte-derived growth factors influence development of a tumor vascular supply (*tumor angiogenesis*), as discussed in the *Endothelial Cells/ Lymphendothelial Cells* section below. Whereas leptin and adiponectin are considered true adipokines, many of the other signaling molecules, including resistin, visfatin, TNF-α, IL-6, MCP-1, and PAI-1, are not, as they are expressed by both adipocytes and immune cells populations such as macrophages, and play a variety of well-known roles in immunity (391).

Thus, select functions for several of these signaling molecules will be discussed within the section titled *Adipose*

Tissue Immune Populations in Cancer Development and Progression—Finally, although there are clear and important roles for leptin and adiponectin in tumorigenesis and malignancy, these roles have been reviewed extensively by others (137, 196, 284, 299, 421) and will be addressed only briefly within this review.

Adipocytes exhibit both short- and long-range interactions with cancer cells, and may be found in close proximity to tumors, along tumor margins, and within the tumor body. These *cancer-associated adipocytes* (CAAs; also referred to as peritumoral, intratumoral, or tumor-infiltrating adipocytes) influence tumor biology in a number of ways, including by promoting angiogenesis and inflammation (reviewed in 274, 423, 427). Although it is reasonable to hypothesize that proliferation and invasion of tumor cells into cancer-adjacent adipose may account for the presence of CAAs within the tumor body, the origin of CAAs in fact remains unclear. As explained in further detail in the section on *Adipose-derived Stromal Cells* below, several cell types may give rise to intratumoral CAAs.

In addition to indirect mechanisms of tumor growth promotion (e.g., stimulation of angiogenesis, production of proinflammatory cytokines), the proximity of CAA to growing tumors may also provide direct metabolic benefits to cancer cells. In the phenomenon known as *metabolic symbiosis*, cancer cells within hypoxic regions of a tumor undergo metabolic shifts that facilitate increased utilization of fuel sources such as lactate, glutamine, and fatty acids released by surrounding cells, including other cancer cells (8, 268) and adipocytes (241, 250). Lipid droplet size within mature white adipocytes is the net result of several processes, including fatty acid uptake or *de novo* fatty acid synthesis, esterification, and lipolysis. As mentioned previously, CAAs have been frequently observed to undergo delipidation. Interestingly, Nieman et al. showed that co-culture of primary omental adipocytes with ovarian cancer cells, which frequently metastasize to the omentum, induced lipolysis in adipocytes, upregulation of β-oxidation in cancer cells, and direct transfer of lipids between the two cell types (273). Notably, the transfer of lipids from adipocytes to cancer cells has also been observed in prostate cancer (139) and breast cancer (426). These findings indicate that active heterotypic cellular interactions between cancer cells and adipocytes induce metabolic symbiosis.

CAAs may also influence cancer cell phenotypes through the shedding of exosomes, small vesicular bodies released from cells as a form of short- or long-range communication. Lazar et al. (215) reported that exosome shedding by mature human adipocytes induced increased migratory and invasive behavior in melanoma cells, which grow in proximity to the hypodermal adipose layer. Proteomic analysis of adipocyte-derived exosome composition revealed enrichment for proteins involved in mitochondrial lipid metabolism, particularly fatty acid oxidation. Remarkably, their results suggested that these enzymes were incorporated and utilized by melanoma cells. Melanoma cells pretreated with exosomes exhibited increased ability to form lung metastases in mice and an increase in fatty acid oxidation without a concomitant change in glycolysis, indicating that augmentation of lipid oxidation pathways occurred in the absence of complete metabolic reprogramming. In

further support of these findings, administration of the mitochondrial fatty acid oxidation inhibitors etomoxir or trimetazidine reversed exosome-induced enhancement of migration without affecting basal migration levels. Importantly, increasing adiposity in obese individuals enhanced both the number of exosomes released from adipocytes as well as the potency of their effect on melanoma cell migration. Collectively, these studies reveal important roles for adipocytes in regulating cancer cell migration and metastatic potential.

Adipocytes in the normal breast and breast cancer—Mouse models have revealed that adipocytes act as local regulators of normal mammary epithelial cell growth and function. Thus, mammary epithelial cells possess an inherent requirement to reside among adipocytes during embryonic and postnatal development, as well as throughout later life stages such as pregnancy, lactation, and involution (176). Indeed, using the novel FAT-ATTAC mouse, a model of inducible and reversible adipocyte loss developed by Scherer and colleagues, Landskroner-Eiger et al. showed that adipocytes play crucial roles in normal growth and development of mammary ductal epithelium (71, 209), contributing both to ductal branching morphogenesis during puberty and to maintenance of normal alveolar structures in adulthood (209).

Due to the proximity of the adipose pad to the mammary glandular organ, ductal tumor invasion results in interaction of breast cancer cells with adipocytes and other adipose stromal constituents (Fig. 6 and Fig. 7), with dramatic implications for tumor cell biology. Carter and Church reported that mature breast adipocytes, but not preadipocytes, increased motility of both normal and malignant breast epithelial cell lines through secretion of PAI-1 (62). Similarly, higher levels of CAA-specific IL-6 expression in human breast tumors were associated with larger tumor size and more extensive lymph node involvement (92). Moreover, coculture with adipocytes induced mesenchymal features in human breast cancer cells, including repolarization of vimentin and downregulation of E-cadherin, thereby promoting tumor cell invasion and metastasis (92). Furthermore, adipocytes cocultured with malignant breast epithelial cells exhibited the profound phenotypic changes associated with CAA, including delipidation and decreased expression of adipocyte markers (92). Hence, bidirectional communication between adipocytes and breast tumor cells also alters adipocyte biology.

For example, reminiscent of findings in melanoma (215), prostate (139), and ovarian cancers (273) (discussed in the *Adipocytes and adipocyte-cancer interactions* intro section above), following coculture of breast cancer cells with adipocytes Wang et al. reported increased lipolysis by adipocytes and concomitantly increased fatty acid oxidation by breast cancer cells (426). Importantly, the signal released by tumor cells to induce adipocyte delipidation was not identified, although IL-6 and β-adrenergic stimulation—factors previously implicated in lipolytic induction in cancer-associated cachexia (393)—were eliminated as potential candidates (426). Similar to Lazar et al. (215), Wang et al. reported that coculture with adipocytes increased both *in vitro* invasion toward a stimulus and formation of breast cancer lung metastases *in vivo*, each of which were restored to basal levels by administration of the fatty acid oxidation inhibitor etomoxir (426). *In vitro* etomoxir administration also reduced the morphological hallmarks of EMT. Remarkably, the increase in fatty acid oxidation by breast cancer cells appeared to be dependent on an upregulation of both

adipocyte triglyceride lipase (ATGL) and the carnitine palmitoyltransferase 1 (CPT1) isoform CPT1A, enzymes not expressed at appreciable levels in noncancerous human breast epithelial cells. Short-hairpin (sh)RNA-mediated knockdown of CPT1A and ATGL reduced hallmarks of EMT and invasive potential, respectively.

In addition to oxidizing transferred fatty acids, breast cancer cells also esterified free fatty acid from adipocyte lipolysis (426), incorporating the newly synthesized triglyceride into lipid droplets within the cancer cells themselves. Breast cancer cell lipid droplet accumulation was supported by both *in vitro* coculture experiments employing radiolabeled palmitate and the observation of lipid droplet accumulation in breast cancer cells along the tumor margin in histological sections (i.e., in close proximity to adipocytes). Interestingly, despite increased fatty acid oxidation, breast cancer cells showed reduced ATP content and activation of AMP-activated protein kinase (AMPK). AMPK activation following coculture with adipocytes was associated with increased mitochondrial biogenesis and function, indicated by increased levels of PGC-1α and its associated transcription factor PPARα as well as an increase in the ratio of mitochondrial to genomic DNA. AMPK also inhibited acetyl-CoA carboxylase, the rate-limiting enzyme in fatty acid synthesis, ensuring uninterrupted flux of fatty acids into mitochondria. Furthermore, breast cancer cell fatty acid oxidation was determined to be uncoupled from ATP production and, unlike in melanoma (215), occurred with a concurrent increase in anaerobic glycolysis, consistent with activation of AMPK (426). Collectively, these findings provide new insight into mechanisms of metabolic symbiosis between adipocytes and cancer cells in breast tumors.

Interactions between cancer cells and adjacent adipose may also increase breast cancer stem cell abundance and facilitate metastatic progression. Picon-Ruiz et al. isolated human adipocyte stem cells and used adipogenic differentiation media to generate “immature” adipocytes. Coculture of these “immature” adipocytes with both primary breast cancer cells and established cancer lines conferred stem-like features to the epithelial cells, including elevated expression of the pluripotency markers Sox2, c-Myc, and Nanog (306). Coculture with adipocytes also increased mammosphere-forming capacity, indicating a more stem-like phenotype due to a greater ability to grow under nonadherent conditions. Furthermore, when co-cultured breast cancer lines were orthotopically injected into mouse models, the resulting tumors exhibited reduced latency, increased abundance of tumor-initiating cells, and an enhanced capacity to form distant metastases. Taken together, this study demonstrates that interactions between immature adipocytes and breast cancer cells drive initiation of highly metastatic cancers by enhancing epithelial cell tumor-initiating potential.

Due to the practice of autologous fat grafting as a method of breast reconstruction (oncoplastic surgery) following breast-conserving tumor excision, the impact of adipocytes on tumor malignancy may be a consideration for recurrence following treatment. Indeed, using a model of autologous fat grafting, Massa et al. reported increased proliferation of several breast cancer lines co-cultured with either induced adipocytes (i.e., differentiated from fibroblasts) or intact adipose tissue samples obtained from liposuction patients (245). However, a recently published prospective matched case-control analysis found no significant differences in locoregional recurrence in patients who received autologous fat grafting versus those who did not (249). Although cases and controls were matched for

hormone receptor status in this study, no analysis was conducted to evaluate potential differences in recurrence by molecular tumor subtype, potentially due to the limited sample size and low locoregional event rate. Therefore, based on the aforementioned complex relationships between obesity status and risk of specific breast cancer subtypes, as well as the reported roles for adipocytes in regulating breast epithelial tumorigenicity and metastatic potential, additional studies are needed to address concerns regarding the potential risks associated with fat grafting in breast reconstructive surgery. Stratification by BMI and/or molecular tumor subtype may be necessary to fully assess the influence of fat grafting on breast cancer recurrence rates.

Adipocytes and prostate cancer—Bidirectional communication between adipocytes and prostate epithelial cells also influences prostate tumor biology, particularly with regard to chemokine activity. Chemokines, or chemotactic cytokines, are small secreted signaling proteins that induce directed, gradient-driven migration (chemotaxis) in nearby cells that express the appropriate chemokine receptor. The functions of chemokines in malignancy depend on both tumor characteristics and the specific chemokine in question, but are frequently associated with leukocyte infiltration as well as metastatic potential and site-specific spread of tumor cells (26). Adipose tissue-specific expression of many CC subfamily chemokines and their receptors is upregulated in human obesity (177). For example, Laurent et al. (211) identified a CCR3/CCL7 axis regulated by obesity, through which secretion of CCL7 by mature periprostatic adipocytes supported the directed migration of prostate cancer cells, thereby promoting cell migration toward the periprostatic fat pad and the spread of cancer cells outside of the prostate gland. This process appeared to be augmented in obesity by both enhanced secretion of CCL7 by hypertrophic adipocytes and increased expression of the CCL7 receptor, CCR3, by prostate cancer cells (211).

Adipocyte-derived CCL2 is also implicated in prostate cancer progression. Ito et al. reported that adipocyte-derived CCL2 directly stimulated prostate cancer cell proliferation, promoting invasion and migration through induction of MMP-2 activity and ultimately leading to enhanced tumorigenesis and metastasis (183). Importantly, increased production of CCL2 by bone marrow adipocytes and other stromal cells is also strongly implicated in the propensity of prostate cancer cells to metastasize preferentially to bone (161, 222). Adipocytes are an important component of the bone marrow microenvironment. Bone marrow adipocyte content increases with age, obesity, and obesity-associated metabolic pathologies (169, 197), suggesting a potential link between obesity and elevated rates of prostate cancer metastasis (161, 222).

Interestingly, prostate cancer-adipocyte crosstalk also appears to induce tumor-promoting changes in periprostatic adipocytes. Treatment of periprostatic adipose tissue organotypic explants with PC3 prostate carcinoma cell-conditioned medium activated a cancer-promoting secretory profile, including increased secretion of osteopontin, TNFα, and IL-6, and reduced production of adiponectin (328). These changes were not observed upon treatment of cells comprising the periprostatic adipose stromal vascular fraction (i.e., all stromal populations except adipocytes) with PC3 cell-conditioned medium, suggesting that the observed increase in protumorigenic factor production by explanted tissue was due specifically to tumor-mediated education of adipocytes (328). Indeed, adipocytes appear to

be a major source of microenvironmental IL-6 in prostate cancer. Periprostatic adipose tissue harvested from patients undergoing radical prostatectomy secreted IL-6 at concentrations 375 times greater than that in patient-matched serum and correlated with histological grade (117). Additionally, Tang et al. (386) recently showed that co-culture of prostate cancer cells increased production of the cysteine protease cathepsin B by adipocytes. Further probing revealed that adipocyte co-culture induced secretion of the peptide hormone cholecystokinin (CCK) by prostate cancer cells, resulting in establishment of an autocrine/paracrine amplification loop in which CCK, acting through the CCK receptor CCKBR, induced expression of cancer stem cell markers such as CD49f and Sca-1 in prostate cancer cells and further production of cathepsin B by adipocytes. Importantly, cathepsin B has been shown to facilitate prostate cancer invasion and metastasis via degradation of ECM and basement membrane components (37, 252). Collectively, these studies demonstrate that prostate cancer cell-induced alterations in adipocyte function are important mediators of tumor progression. Figure 13 briefly summarizes adipocyte-cancer cell crosstalk findings.

Adipocytes and adipose wasting in cancer-associated cachexia—An example of long-range adipocyte-tumor interactions can be observed in cancer-associated cachexia (referred to hereafter as *cancer cachexia* or simply *cachexia*). Cancer cachexia is a fatal energy-wasting syndrome that is estimated to be the immediate cause of death in approximately 20% to 40% of end-stage cancer patients (392). A key feature of cancer cachexia is white adipocyte “browning,” characterized by greatly increased levels of brown fat-mediated thermogenesis in white adipose depots (201, 303). Accordingly, cachectic patients exhibit irreversible, pathologically elevated basal energy expenditure levels, adipocyte lipolysis and adipose tissue wasting, rapid weight loss, and eventually, death (4, 78, 201, 303). Although prolonged systemic inflammation plays a well-established role in cachexia-associated adipose tissue wasting (4, 78), tumor-derived factors have also been shown to contribute to the pathophysiology of this syndrome. For example, in a murine model of Lewis lung carcinoma, Kir et al. (201) demonstrated that tumor-derived parathyroid hormone-related protein (PTHrP) induced the expression of thermogenesis-associated genes in adipose tissue, implying a crucial role for this hormone in energy expenditure and tissue wasting. Accordingly, administration of a PTHrP neutralizing antibody prevented cachexia-associated weight loss and ablated thermogenic gene expression in white and brown adipose tissue. Furthermore, compared to cancer patients lacking detectable levels of blood PTHrP, patients with detectable blood PTHrP levels exhibited significantly higher resting energy expenditure levels per kilogram of lean body mass, implying a clinically relevant association between this hormone and wasting.

On the other hand, Rohm et al. (332) reported that browning and associated thermogenesis in major white adipose depots was not the primary mechanism of adipose tissue wasting in mouse models of colon cancer-induced cachexia. Although the brown adipose-associated protein cell death activator (CIDEA) was upregulated in both brown and white adipose depots of cachectic mice relative to healthy controls, this upregulation occurred in the absence of changes in other proteins implicated in adipocyte browning and thermogenesis, such as uncoupling protein 1 (UCP-1). Furthermore, while increased free fatty acid release was observed in primary mouse adipocytes exposed to serum from cachectic mice, this

increase in lipolysis was not associated with well-characterized lipolytic inducers such as increased expression of lipases (e.g., hormone-sensitive lipase and ATGL), or increased β-adrenergic receptor activation. Instead, CIDEA-mediated degradation of AMPK, evidenced by a reduction in AMPK protein and enzymatic activity, contributed to adipocyte metabolic dysfunction. For example, although increased lipolysis was observed, decreased AMPK activity also resulted in reduced inhibitory phosphorylation of acetyl-CoA carboxylase, suggesting the establishment of a futile cycle in adipocytes characterized by simultaneous increases in both lipolysis and lipogenesis. Microinjection of white adipose depots with a peptide designed to interfere with the AMPK-CIDEA interaction (termed AMPK–CIDEA-interfering peptide, or ACIP), followed by implantation of the cachexia-inducing colon cancer cell line C26, resulted in approximately 30% greater retention of adipose depot mass and greater adipocyte lipid droplet size compared to the contralateral control-injected depot. No significant effect was observed from ACIP injection into adipose depots of control, noncachectic mice, suggesting that the augmented AMPK-CIDEA interaction and downstream influences on lipid metabolism in adipocytes may be a cachexia-specific phenomenon.

These findings by Rohm et al. are particularly interesting in light of the reportedly opposite regulation of AMPK in breast cancer cells co-cultured with adipocytes that was highlighted in the previous section (426). Also interesting to note is the lack of a role for β-adrenergic signaling in either of these two studies (332, 426), as catecholamines are well-established regulators of lipolysis, while lipid mobilizing factor—a tumor-derived factor frequently implicated in cachexia (393, 394)—also signals through beta receptors. Thus, although the causes of cachexia are multifactorial and systemic, it is clear that adipocyte-cancer cell interactions are key players in the pathophysiology of this syndrome. Future work should seek to identify additional tumor-derived paracrine and hormonal signals that contribute to cachexia pathogenesis and progression.

Adipose-derived stem cells

Human adipose tissue stroma is a rich source of multipotent mesenchymal stem cells, termed adipose stromal cells or adipose-derived stem cells (ASCs), that can differentiate toward the osteogenic, adipogenic, myogenic, and chondrogenic lineages (467). Interestingly, several recent studies suggest that ASC recruitment substantially contributes to stromal populations in both breast and prostate cancers. Due to the abundance of adipose tissue, as well as the minimally invasive procedures required to collect it, ASCs are a celebrated approach for tissue engineering and regenerative medicine. For example, lipoaspirate preparations may be “enriched” by the addition of ASCs to improve graft volume retention (204, 403). However, the findings described below suggest that caution may be advised in use of ASCs in patients with a history of cancer. Notably, factors such as age and menopausal status have been found to influence the proliferation and differentiation capacities of ASCs (47). Future studies on the impact of age on ASC recruitment to tumors will yield interesting findings.

Adipose-derived stem cells in breast cancer—The varied stromal components of the tumor microenvironment must be recruited from either adjacent tissue or from distant

precursor sources such as bone marrow. Kidd et al. (200) investigated the relative contribution of ASCs *versus* bone marrow-derived stem cells to stromal populations in mouse models of ovarian and breast cancers, and found that the majority (greater than 70%) of intratumoral myofibroblasts, pericytes, and endothelial cells were recruited from neighboring adipose tissue. However, CAF subpopulations were recruited from multiple distinct sources, with fibroblasts positive for fibroblast specific protein and fibroblast activation protein originating from bone marrow-derived mesenchymal stem cells, while α-smooth muscle actin^{+}/chondroitin sulfate proteoglycan 4^{+} (α-SMA^{+}/NG2^{+}) CAFs were recruited from adjacent adipose. While the factors contributing to ASC recruitment to tumors are still ambiguous, Gehmert et al. have demonstrated that the PDGF-BB/PDGFR-β signaling pathway may be involved in ASC recruitment to breast cancers (140). Together these results imply that the diversity of the tumor microenvironment can be attributed, at least in part, to the heterogeneous origin of stromal constituents.

Although ASCs are primarily localized to fat depots, circulating ASCs have also been detected in obese individuals and cancer patients, with greater levels observed in obese patients bearing colon, prostate, or breast cancers (relative to lean) (142, 327, 367, 462). Additionally, relative to ASCs from lean adipose, ASCs isolated from obese adipose show enhanced potential to traffic to breast tumors in both humans and mice (366, 464). Zhang et al. (464) recently reported hematogenous seeding of breast and ovarian tumors by ASCs in obese mice, resulting in infiltration and subsequent differentiation to pericytes and intratumoral adipocytes/CAA. This process occurred in an obesity-dependent manner, with a sixfold increase in “shedding” of precursors from adipose depots in obesity contributing to tumor cell survival and angiogenesis. It will be interesting to note in future studies whether specific adipose depots shed ASCs to the circulation at different rates. Ultimately, these findings reinforce the need to more comprehensively evaluate the risk of breast cancer recurrence after autologous fat grafting, particularly in obese individuals.

Adipose-derived stem cells in prostate cancer—Similar to breast cancer, local and circulating ASCs have been reported in prostate cancer patients. Ribiero et al. observed higher levels of circulating ASCs in the blood of overweight or obese compared to lean prostate cancer patients (327). The authors also reported that periprostatic adipose tissue of prostate cancer patients bore significantly higher numbers of ASCs than nearby visceral adipose tissue, independent of BMI. Interestingly, increased recruitment of ASCs into prostate tumors in obesity has been reported, and was recently attributed to secretion of the chemokines CXCL1 and CXCL8 by cancer cells (Fig. 14) (462, 464). CXCL8 expression was restricted to malignant cells and was obesity-independent; on the other hand, secretion of CXCL1 by nonmalignant epithelium was exclusively observed in histological sections from obese individuals, while CXCL1 expression in tumor cells was found in a significantly higher percentage of tumor sections from obese as compared to lean patients (462). The extent to which periprostatic ASCs, as opposed to circulating ASCs released from other adipose depots, contribute to the cellular composition of prostate tumor stroma was not quantified in the highlighted studies and requires further investigation.

Adipose and endothelial/lymphendothelial cells

Vascularization mechanisms in adipose tissue and tumors—Expansion of adipose tissue during progression to obesity requires concomitant expansion of the adipose vascular bed through the process known as angiogenesis, the formation of new blood vessels from preexisting vessels. In fact, administration of antiangiogenic agents in models of both genetic and diet-induced obesity either prevented weight gain (385) or induced dose-dependent, reversible weight reduction and adipose tissue loss (52, 333). When expansion of the vasculature does not occur in proportion to the expansion of adipocyte volume (hypertrophy), cellular and/or regional hypoxia develops, resulting in activation of the transcriptional complex hypoxia-inducible factor 1 (HIF-1) through stabilization of the HIF-1α subunit. HIF-1-mediated upregulation of inflammatory and proangiogenic signaling pathways in adipocytes, endothelial cells, and immune cells induces vascular growth, facilitating further tissue expansion (216, 381, 434). In this way, the microenvironment during accumulation of adipose tissue resembles the tumor microenvironment during tumor vascularization (Fig. 15). The extensive list of signaling factors contributing to angiogenesis in both adipose tissue and tumors includes VEGF isoforms, angiopoietins 1 and 2, leptin, adiponectin, TNFα, fibroblast growth factor (FGF) isoforms, TGFβ, HGF, and cytokines such as IL-6 and IL-8 (60, 225, 266). Among these, the VEGF/VEGFR system—one of the best characterized and most potent of the known proangiogenic signaling pathways—is the main mediator of angiogenic activity in adipose tissue (115, 166, 225). The VEGF-A ligand in particular is abundantly expressed by adipocytes and other adipose stromal populations (166, 225). An additional shared factor of particular importance is angiopoietin-2, which signals through the receptor tyrosine kinase TIE2 to induce ECM degradation and disruption of endothelial-pericyte interactions during sprouting angiogenesis (157, 203). Importantly, several of the pro-angiogenic factors listed above, including multiple VEGF isoforms, leptin, HGF, and angiopoietin-2, are also elevated in the serum of obese subjects and are implicated in systemic effects of obesity on cancer progression (39, 253, 358).

Similar to adipose tissue, growth of solid tumors is also heavily dependent upon synchronous expansion of their vascular beds. In early stage solid tumors, rapid proliferation leads to *diffusion-limited hypoxia*, wherein cells within the tumor mass end up at a distance from the surrounding vasculature that is beyond the diffusion limit of oxygen. Resulting hypoxia-induced apoptosis and necrosis limit further tumor growth unless an intratumoral vascular system is established. The shift in developing primary or metastatic tumors from avascular to vascularized is termed the “angiogenic switch,” and is a discrete and requisite step for exponential tumor growth and progression to malignancy (Fig. 15) (40,159,324). Accordingly, tumor microvessel density is a powerful and independent prognostic indicator for several human cancers, including breast, prostate, melanoma, ovarian, gastric, and colon cancers (324). However, in light of the myriad options for tumor vascularization described below, it is interesting to note that themicrovessel density in solid tumors is often lower than in their normal tissue counterparts (103).

New tumor vessel formation can occur through a number of nonmutually exclusive mechanisms, including sprouting and migration of endothelial cells (“classical” sprouting angiogenesis) or intussusceptive (nonsprouting) microvascular growth, a process in which

tumor cells induce splitting and rapid remodeling of existing endothelial vessels (324). Remarkably, along with endothelial cells, tumor cells themselves may integrate into newly forming blood vessels, resulting in mosaicism (324). Tumor cells may also engage in a process known as *vasculogenic mimicry*, the arrangement of tumor cells into vascular channels, which anastomose with adjacent blood vessels (100, 234, 324). An additional mechanism for perfusion of tumors is vessel co-option, wherein tumor cells simply track alongside existing vessels for their own oxygen and nutrient gain, thereby exploiting nearby mature vessels in the host organ (324). Given that adipose tissue is one of the most vascularized tissues in the body (225, 423), it is unsurprising that co-option of adipose tissue vascular beds was recently shown to promote accelerated tumor growth and intratumoral vascularization (226).

Among other abnormal features, tumor vasculature is characterized by enhanced permeability, including transcellular holes and fenestrae, which drives further angiogenesis and increases nutrient and oxygen delivery, immune cell infiltration, and tumor cell extravasation during metastasis (25, 99). Similar to adipose tissue, the VEGF/VEGFR system—and particularly VEGF-A—is highly expressed in tumors and is a potent inducer of tumor vascular permeability (102). Given the extensive similarities of the pro-angiogenic signaling networks in adipose and tumors, it is unsurprising that the vasculature in these two tissue types is structurally similar. For example, adipose tissue capillaries also contain fenestrations, the presence of which depends upon a poorly understood synergistic relationship between VEGF, leptin, and FGF-2 signaling (59). It is tempting to speculate that the fenestrations within adipose vasculature may provide a convenient means of escape for tumor cells invading into adipose tissue.

In addition to hematogenous metastasis, a tumor cell can also escape from its primary location through lymphatic dissemination. In a number of cancer types, including breast cancer, melanoma, and prostate cancer, metastasis to the tumor draining lymph node(s), also referred to as the “sentinel” lymph node(s), is a common initial route for metastatic dissemination from solid tumors (7). For this reason, sentinel lymph node biopsy in newly detected and early-stage cancers is a frequent and evidence-based clinical practice required for staging of disease, determination of prognosis, and development of the treatment approach. In a process similar in principle to classical sprouting angiogenesis, secreted factors in some solid tumor types and other inflamed tissues can also initiate lymphangiogenesis, the formation of new lymphatic vessels from preexisting vessels. These newly formed lymphatic vessels exhibit morphological differences from those in their healthy tissue counterparts, including structural disorganization (7). Interestingly, tumor-associated lymphangiogenesis appears to involve both incorporation of bone marrow-derived endothelial progenitors and endothelial mimicry by CD11b+ tumor-associated macrophages, although there are conflicting reports regarding the extent to which the latter occurs (167, 323, 341, 468).

Although *peritumoral* lymphatic vessel density can act as a prognostic indicator in several cancer types, including cervical, colorectal, breast, and prostate cancers (79, 105, 135, 256, 334), several studies have suggested that *intratumoral* lymphatic vessels in solid tumors may be either collapsed due to intratumoral pressure, occluded by infiltrating tumor cells and

therefore nonfunctional, or simply absent altogether (295, 399, 418, 439). Thus, the high frequency of cancer cell detection in regional lymph nodes implicates peripheral, peritumoral lymphatic vessels in mediating tumor metastasis in these tumor types (439, 440). However, results showing nonfunctional intratumoral lymphatic vessels have not been uniformly supported (360). Consequently, the role of tumor lymphangiogenesis and the relative contribution of intratumoral *versus* peritumoral lymphatics to lymph node metastasis remains controversial.

Adipose and breast cancer angiogenesis—*In vivo* tumor models have demonstrated the ability of breast tumors to obtain a blood supply through all of the aforementioned processes: vessel co-option, intussusceptive growth, vasculogenic mimicry, and classical sprouting angiogenesis (124, 343). Additional mechanisms have also been described for breast cancers, such as vasculogenesis and glomeruloid angiogenesis, albeit to a lesser extent (124). Nevertheless, remodeling of existing vessels appears to be the dominant mechanism for establishing new vasculature in human breast cancers (97, 123). In support of this assertion, Lim et al. (226) demonstrated that implantation of the E0771 murine mammary tumor line into either brown or white adipose tissue resulted in accelerated tumor growth rates and increased intratumoral vessel densities as compared to tumors grown subcutaneously. These results were attributed to co-option of preexisting adipose vascular beds, as tumor growth and vascularity reflected the differential degree of vascularity within the respective adipose types. Furthermore, adjacent adipose tissue fostered both reduced pericyte coverage and enhanced permeability, features associated with worse prognosis.

In obesity, both the increased abundance of white adipose and the resulting chronic inflammatory conditions of the microenvironment may promote tumor vascularization. Indeed, enhanced tumor angiogenesis in the context of obesity is observed in both mice and humans (18, 153, 218, 422, 464). In one compelling study, Arendt et al. (18) developed a novel humanized mouse model wherein human adipose stromal populations overexpressing CCL2 were injected into cleared mammary fat pads (cleared of endogenous mammary epithelium) to generate an obese-like microenvironment. *Prior* to tumor formation, the authors reported enhanced angiogenesis in CCL2-overexpressing mammary fat pads, which was shown to be mediated by elevated levels of macrophage recruitment and activation. Upon transplantation of transformed human breast epithelial cells, the obese-like microenvironment augmented macrophage-associated angiogenesis in early premalignant lesions as well as tumor-adjacent adipose following tumor formation, which induced the formation of larger and higher-grade tumors. Whether the observed tumor-promoting effects were due to specific macrophage phenotypes in “obese” versus lean mammary adipose or simply to an increase in macrophage numbers was not explored. Moreover, this study did not differentiate whether increased tumor-associated macrophage content in obesity was due to accelerated recruitment of bone marrow-derived macrophages or to co-option of nearby mammary adipose tissue macrophages. Nevertheless, similar results were reported by Cowen et al., who demonstrated that high-fat diet-induced obesity in the MMTV-PyMT model of spontaneous breast cancer resulted in mammary adipose tissue inflammation, enhanced macrophage recruitment, and increased mammary tumor vascular density (73).

As described in the previous section, obesity is also associated with elevated levels of circulating and infiltrating ASCs (464) which produce a range of proangiogenic factors, including VEGF and HGF (217). Our lab has demonstrated that inhibition of the HGF receptor, cMET, *via* the small molecule kinase inhibitor crizotinib significantly reduced tumor burden and tumor vascularity in both lean and obese C3(1)-TAg mice (74). Reversal of high fat diet-induced elevation of HGF/cMET expression in both normal mammary gland and tumors was also observed with weight loss, which significantly blunted the effects of obesity on both pre-neoplastic lesion formation (316) and tumor progression (377) (Fig. 16). Importantly, endothelial cell upregulation of cMET is one mechanism attributed to inherent or acquired resistance to anti-angiogenic therapies targeting VEGF (91, 355). In fact, the HGF/cMET pathway has been reported to act synergistically with VEGF (355, 371), and clinical trials investigating crizotinib alone [ClinicalTrials.gov: NCT 02101385 (342)] or in combination with anti-VEGF therapy [ClinicalTrials.gov: NCT 02074878 (36)] for the treatment of advanced TNBC are currently underway at the time of preparation of this review.[1]

However, one response to anti-angiogenic therapies is vessel pruning and regression, leading to intratumoral hypoxia. Such hypoxic conditions induce an influx of tumor-associated macrophages and other myeloid cells, triggering tumor revascularization and tumor relapse (248, 321, 329, 431). In addition, peritumoral adipose tissue is characterized by a dense macrophage infiltrate and a high degree of vascularization. Indeed, Wagner et al. demonstrated that inflamed, tumor-associated adipose tissue acts as a source of both vascular endothelium and activated proangiogenic macrophages, thereby fueling the growth of malignant cells (15, 422). Importantly, the presence of macrophages within adipose tissue increases considerably in obesity (429). Thus, obesity-associated mammary adipose inflammation and resulting macrophage infiltration and angiogenesis may contribute to tumor relapse following antiangiogenic therapies.

Adipose tissue and lymphangiogenesis in breast and prostate cancers— Lymphatic vessels in the normal breast are dispersed throughout the interlobular stroma and adipose tissue (418), the latter of which acts a source of molecules that directly affect the lymphatic endothelium. For example, the lymphangiogenic factors VEGF-C and VEGF-D are chemotactic for macrophages in mice, and their blockade in a diet-induced obesity model attenuated macrophage infiltration, adipose tissue inflammation, and onset of insulin resistance (194). An increase in circulating levels of pro-lymphangiogenic factors such as HGF and VEGF-C in obesity may also alter lymphatic vessel density or function by enhancing capillary permeability and inducing lymphendothelial hyperplasia (58,254,358). Indeed, obesity is associated with dysfunction of the adipose lymphatic system, including decreased lymph node size and number (430), reduced drainage of macromolecules (19), increased perilymphatic inflammation (281), and altered lymph node immune cell composition (430). These changes were recently attributed to the condition of obesity *per* se —specifically injury to lymphatic endothelial cells caused by inflamed adipose tissue— rather than the high fat diet used to generate the obese phenotype (136). Interestingly, using

[1]During peer review and publication of the present review, clinical trial NCT 02074878 was terminated due to poor accrual.

a model of *Prox1* haploinsufficiency, Harvey et al. demonstrated that lymphatic vascular defects and resulting abnormal lymph leakage into surrounding tissues induced adult-onset obesity (163). A follow-up study by Escobedo, et al. further reported that the obese mutant phenotype of *Prox1*$^{+/-}$ mice could be rescued with tissue-specific restoration of *Prox1* in lymphatic endothelial cells (110). Whether lymphatic vessel density is altered in peritumoral adipose, either normal or obese, has not been reported. However, Yamaguchi et al. observed a more than threefold increase in lymph node metastasis with adipose tissue invasion at the tumor margin in patients with invasive breast carcinoma (454).

The role of adipose tissue in prostate carcinoma angiogenesis and lymphangiogenesis is not well understood. However, as mentioned previously, ASCs are abundant in periprostatic adipose tissue (327) and are a source of lymphangiogenic factors (383). Indeed, implantation of ASCs has been used successfully in mice to induce lymphangiogenesis in a model of lymphedema (352, 459). Importantly, obesity may influence the degree of proangiogenic/lymphangiogenic factors released from the periprostatic adipose depot. Venkatasubramanian et al. reported that conditioned media generated *via* explant culture of human obese periprostatic adipose stimulated prostate cancer cell proliferation and angiogenesis to a significantly greater degree than explants from lean patients, providing a potential link between obesity and worse prostate cancer prognosis (417). Paradoxically, elevated leptin concentration in obese mouse models is associated with attenuated tumor cell proliferation and reduced angiogenesis and lymphangiogenesis in prostate cancers *in vivo* (259,325). Furthermore, rate of lymph node metastasis in patients with clinically localized prostate cancer does not appear to be altered by obesity (53). Thus, there are lingering questions surrounding the role of periprostatic adipose tissue in prostate tumor progression in both lean and obese individuals, particularly with regard to its influence on tumor angiogenesis.

Adipose Tissue Immune Populations in Cancer Development and Progression

Acute inflammatory responses, such as those that occur in the context of pathogen infections, are usually self-limiting and are characterized by an “acute inflammatory infiltrate” consisting primarily of neutrophils and sometimes eosinophils (72). However, when triggering factors persist or inflammatory resolution mechanisms fail, a shift occurs in the immune profile to a “chronic inflammatory infiltrate,” predominantly comprised of lymphocytes and mononuclear cells such as macrophages and dendritic cells. Chronic inflammation is consistently associated with increased risk of carcinogenesis and is a well-known hallmark of cancer (28, 72), leading Dvorak to describe tumors as “wounds that do not heal” (101). Solid tumors frequently contain a dense infiltrate of immune cells, including lymphocytes, neutrophils, macrophages and mast cells, each of which directly or indirectly influence the course of tumor progression. In fact, many of the changes that occur in the tumor microenvironment are largely orchestrated by immune cells (107, 310, 435). Chronic inflammation is also highly prevalent in obesity, and as discussed in previous sections, plays pivotal roles in adipose tissue (lymph)angiogenesis and development of fibrosis. Thus, the final section of this review will focus on adipose tissue immune populations. We will emphasize the changing immune profile during adipose accumulation and progression to

obesity and the potential impact of these alterations on adipose-adjacent tumor progression. However, it should be noted that the immune profile of adipose tissue depends upon both the degree and the duration of adiposity, as well as a variety of other factors that are beyond the scope of this review, including physical activity, dietary intake, the microbiome, and certain therapeutics such as thiazolidinediones (188).

Healthy adipose tissue contains a wide variety of innate and adaptive immune cells, including macrophages, dendritic cells, mast cells, eosinophils, neutrophils, and lymphocytes, which collectively constitute ~25% to 45% of stromal cells in humans (50). In lean adipose, these “resident” immune cells maintain tissue homeostasis by clearing apoptotic cells, suppressing inflammation, and mediating basal ECM remodeling and angiogenesis in response to routine fluxes in caloric availability (51). However, during progression to obesity, rapid expansion of adipose tissue and associated adipocyte dysfunction trigger a dynamic infiltration of innate and adaptive immune populations (Fig. 17). These immune cells act as potent sources of inflammatory cytokines, chemokines, growth factors, and matrix-degrading enzymes such as matrix metalloproteases (MMPs), which rapidly remodel the tissue microenvironment and result in chronic low-grade, or “smoldering,” inflammation (373). A decrease in relative influence of select adipose resident populations known for their anti-inflammatory action (e.g., immunosuppressive macrophages, eosinophils, regulatory T cells, and innate lymphoid cells [ILC2s])may further exacerbate adipose inflammation in obesity and associated sequelae, thereby indirectly mediating differential immune responses during tumor-adipose interactions in lean versus obese individuals.

Despite a surge in research over the past 15 years on the roles of immune cells in adipose tissue biology, many fundamental lines of investigation remain incompletely understood. For example, a growing understanding of the complexity of innate lymphocyte subsets and their remarkable parallels with adaptive lymphocyte subsets (362) complicates interpretation of innate *vs.* adaptive influence. In addition, data regarding roles for select immune cell types, such as basophils, in adipose tissue remain in short supply. Notably, while comparing the immune response to tumor growth in lean and obese individuals many studies have failed to take into account co-morbidities associated with obesity, which may alter the immunometabolic milieu. For example, type II diabetes is a metabolic condition in which insulin resistance, often due to prolonged obesity and associated inflammation, results in hyperinsulinemia, hyperglycemia, and dyslipidemia. In addition to elevating risk of both cancer development and cancer mortality in several solid tumor types (146, 458), metabolic dysregulation in type II diabetics shifts availability of metabolic substrates such as glucose and fatty acids, which can alter immune cell number and behavior (66, 128, 189). Furthermore, medications prescribed for glucose control in type II diabetics, such as metformin, may have profound and confounding effects on antitumor immunity through suppression of inflammation in macrophages (165) or augmentation of the cytotoxic T cell response (104). With these caveats acknowledged, the increased presence of adipose inflammatory cells in obesity may provide a link between adipose tissue and the pathophysiology of adipose-associated cancers. Thus, when considering the effects of adipose tissue on cancer development, the potential for cross talk between adipose immune populations and the developing tumor is paramount. Due to a current dearth of literature

addressing immune populations in periprostatic adipose, the structure for this final section of our review will diverge from the format above, which emphasized breast and prostate adipose pads individually, and instead focus more generally on literature regarding immune populations in a variety of adipose depots.

T cells in adipose and cancer

T cell diversity in the tumor microenvironment—Tlymphocytes, or Tcells, are central to cell-mediated immune responses and mediate exquisitely specific adaptive immune defenses within a given disease context, including cancer. Broadly speaking, T cells can be classified into CD4+ helper T (Th) and CD8+ cytotoxic T (Tc) cell subsets. CD4+ Th cells can be further subdivided into pro-inflammatory effector Th1 cells or immunoregulatory Th2 cells, which influence both generation and activity of CD8+ Tc cells and antigen-presenting cells (APCs), such as macrophages and dendritic cells, within the tumor microenvironment. Other T cell subsets include Th17 cells, γδT cells, and certain types of natural killer (NK) cells, the latter of which exhibit cytotoxic activity and play a role in antitumor immune defense. While each of these T cell subsets, along with other, less well-characterized populations, influence both tumor progression and adipose immunity (275, 466), a comprehensive review of T cell function in these contexts is beyond the scope of this review. However, several of the most well characterized subsets will be addressed below, with particular emphasis on how adiposity-associated alterations in CD8+ T cells and a subset of CD4+ T cells termed “classical T regulatory cells,” or Tregs, may contribute to cancer development in obese individuals.

CD8+ T cells and CD4+ Tregs generally exhibit opposing immunologic functions in both the tumor microenvironment and normal tissues. CD8+ Tc cells are a critical component of antitumor immune defense, *directly* killing tumor cells through release of cytotoxic granules containing perforin and granzyme B, and *indirectly* promoting tumor rejection by stimulating APC activity. On the other hand, Tregs are a subset of CD4+ T cells identified by expression of the cell surface markers CD4 and CD25 and the transcription factor forkhead box P3 (FOXP3), which acts as the master regulator of the Treg phenotype (122, 175). Tregs directly regulate the activity of other T cells through suppression of CD8+ Tc cell proliferation following T cell receptor (TCR) stimulation and activation of immune checkpoint pathways, which provide a critical defense against T cell-mediated responses to self-antigens (autoimmunity). Specifically, in T cells, the amplitude and duration of TCR-mediated immune responses are determined by immune checkpoint proteins, which exert co-stimulatory and/or inhibitory signals to effectively “tune” the immune response and curtail collateral tissue damage. For example, FOXP3-mediated constitutive expression of the immune checkpoint protein CTLA4 by Tregs inhibits development of self-reactive CD8+ Tc cells in secondary lymphoid organs such as lymph nodes (382). In peripheral tissue, including tumors, expression of the inhibitory checkpoint protein Programmed Death-1 (PD-1) by “exhausted” or chronically activated T cells impairs cell-mediated responses. Binding of ligands to the PD-1 receptor triggers T cell senescence, apoptosis, or conversion to a Treg phenotype (14,425), thereby attenuating cell-mediated immune responses (190). Additionally, Tregs potently suppress the function of other immune cells such as APCs, NK cells, and CD8+ Tc cells through production of cytokines including IL-10 and TGF-β (190,

275, 466). While these immune-regulatory functions provide a critical defense against rampant immune responses, by suppressing immunosurveillance and promoting immune tolerance in the tumor microenvironment Tregs actively prevent robust elimination of developing cancers. Accordingly, the density of Tregs in solid tumors is correlated with adverse clinical outcomes in melanoma, as well as ovarian, gastric, pancreatic, hepatic, breast, and prostate cancers (34,119,437).

Differential T cell content and activation in lean and obese adipose tissue: Links to cancer—In addition to their well-established roles in the tumor microenvironment, Tregs have also recently been shown to contribute to the maintenance of adipose tissue metabolic homeostasis. Feuerer et al. (116) demonstrated that nearly half of the CD4+ T cells in lean visceral adipose of male mice expressed FOXP3. In fact, visceral adipose in 30-week-old mice contained a greater abundance of Tregs than lymphoid tissues such as spleen and lymph nodes. Interestingly, these adipose-resident Tregs were frequently detected in CLS, which are typically associated with inflammatory cells. Expression profiling of isolated adipose Tregs revealed a distinct gene signature from that of “conventional” T cells from spleen and lymph nodes. Divergent transcription patterns in adipose Tregs included a relative increase in chemokines involved in leukocyte migration and extravasation and greatly elevated IL-10 expression (>100-fold) as compared to lymph node Tregs. Adipose-resident Tregs also exhibited limited TCR diversity relative to spleen or lymph node Tregs (116). Similarly, Yang et al. reported that adipose T cells displayed a TCR profile distinct from that of splenic T cells, further demonstrating that depot-specific microenvironments modulate lymphocyte phenotypes (455).

Feuerer et al. (116) also noted that the presence of Tregs in visceral adipose declined with increasing adiposity in three mouse models of obesity, although the abundance of lymphoid tissue Tregs was unaffected. Subsequent mechanistic studies employing Treg stimulation and depletion suggested that IL-10 secretion by Tregs dampens inflammation in adipose tissue, thereby safeguarding insulin sensitivity. A second study published the same year by Nishimura et al. (276) also reported a decrease in Treg content in obese murine visceral adipose, with a simultaneous and substantial increase in the presence of CD8+ Tc cells displaying markers of activated effector T cells. Of note, in obese mice the accumulation of CD8+ Tc cells preceded macrophage infiltration by 3 to 4 weeks, indicating that T cells may effect microenvironmental changes enabling macrophage recruitment (Fig. 17). An increase in CD8+ Tc cells, particularly within CLS, was also observed in subcutaneous adipose. Genetic or antibody-mediated depletion of CD8+ Tc cells during the course of high-fat feeding attenuated the onset of insulin resistance, prevented macrophage infiltration, and blunted obesity-associated increases in TNFα and IL-6 expression in whole adipose tissue; these phenotypes were “rescued” upon reintroduction of CD8+ Tc cells *via* adoptive transfer. CD8+ T cell depletion in *established* obesity similarly reduced the presence of proinflammatory macrophages and CLS density in adipose tissue. These findings were confirmed *in vitro*, as coculture of CD8+ T cells from obese adipose with macrophages induced significantly greater macrophage-specific TNFα expression than did CD8+ T cells from lean adipose. In sum, these studies illustrate that reduced Treg content and increased CD8+ T cell presence promote macrophage-specific expression of pro-inflammatory

mediators, thereby contributing to adipose inflammation and metabolic dysfunction in obesity, both of which are drivers of tumor malignancy.

However, the nature of these reported shifts in T lymphocyte profiles of obese murine adipose has not been consistent in human studies. In fact, the opposite has been observed. In obese adults, the expression of Treg activation markers and Treg cytokines increased with increasing adiposity, particularly in subcutaneous as compared to visceral adipose (397, 461). One potential explanation for these observed increases in Treg activation relates to increased local estrogen concentration in adipose tissue of obese subjects. Indeed, Subbaramaiah et al. provided evidence that elevated cyclooxygenase-2 (COX-2)-induced prostaglandin E2 (PGE_2) production by CLS-associated inflammatory cells mediates increased risk of breast cancer in obesity by inducing activity of aromatase in mammary adipose tissue (260, 370). Increased aromatase activity in adipose tissue increases the conversion of circulating androgens to estrogens, and thus is of particular concern for development of estrogen receptorpositive breast cancers in postmenopausal women, a population in which obesity is strongly linked to elevated risk of cancer (70, 412). Estrogen also exerts a positive effect on both expansion of Tregs and augmentation of their immunosuppressive activities (309, 411). Elevated PGE_2 also induces FOXP3 expression and Treg function (29, 30, 349). Paradoxically, however, elevated aromatase and PGE_2 levels are also present in adipose of obese mice. Thus, the significance of interspecies differences in obesity-associated Treg abundance and/or activation is unclear.

Interspecies differences in T cell content are not exclusive to Tregs. For example, although increases in Tc and Th1 cell content are frequently reported in murine models of obesity, the prevalence of these cell types in obese human adipose is controversial. Indeed, while Yang et al. reported that the stromal-vascular fraction of abdominal subcutaneous adipose from obese human subjects displayed an increased percentage of both CD4+ and CD8+ T cells compared to lean individuals (455), two additional studies profiling T cells in obese human adipose did not reach the same conclusions (397,461). Accordingly, although CD8+ T cells appear to contribute to adipose inflammation in mice, their role in human obese adipose remains ambiguous. Furthermore, in addition to identifying potentially critical cross-species differences in adipose T cell function, these results also suggest that, in humans, an increase in pro-inflammatory cell abundance in adipose occurs with a parallel protective response driven by Tregs. Should this be the case, an elevated presence of Tregs in human obese adipose may contribute to immunosuppression of anti-tumor responses in adipose-adjacent cancers.

In addition to influencing Treg-mediated immunosuppression, obesity may also impair T cell-mediated antitumor responses through systemic mechanisms. For example, obesity reportedly accelerates age-associated declines in immune function, including thymic atrophy. The thymus is a specialized primary lymphoid organ located in the mediastinum that houses maturing T lymphocytes. Beginning at puberty, the thymus undergoes involution, or atrophy, exhibiting fibrotic and fatty changes that culminate in its replacement by adipose tissue (96). Following thymic involution, the peripheral T cell pool is primarily maintained independently of thymic lymphopoiesis, such as by expansion of existing T cell populations; however, it should be noted that some studies in humans have reported that the

aged thymus retains a limited capacity to produce naïve T cells (387). Eventually, the age-related decline in naïve T cell production, in combination with steady exposure to antigenic challenge and resulting expansion of effector-memory T cells, depletes the naïve T cell pool and reduces diversity of the TCR repertoire (432). Thus, these processes reduce the capability of the adaptive immune system to respond to new antigenic challenges, increasing susceptibility to infection, autoimmune responses, and cancer. Importantly, Yang et al. (456) reported that prolonged obesity in mice increased perithymic adipose tissue content, reduced thymocyte counts, and enhanced thymocyte apoptosis relative to lean animals, each of which are associated with thymic aging. Similarly, increased frequencies of CD4+ and CD8+ effector-memory cells in subcutaneous adipose of obese mice, concomitant with a notable decrease in TCR diversity and depletion of the CD4+ and CD8+ naïve T cell pools, further supported an acceleration of the immune aging process. Moreover, splenic T cells isolated from obese mice exhibited reduced expression of pro-inflammatory mediators important for antitumor immune defenses, including interferon-γ and TNFα. Finally, in humans, analysis of mature thymus-derived T cells demonstrated that increasing adiposity significantly correlated with a reduction in thymic output in overweight and obese middle-aged subjects. These obesity-related restrictions in TCR diversity and T cell function may account for reports of impaired adaptive immunity in obese patients (195, 296) and suggests a reduced capacity to mount an effective antitumor immune response.

Recent clinical successes with tumor immunotherapies targeting the PD-1 immune checkpoint pathway have increased interest in the regulation of this pathway in the context of obesity. As described above, PD-1 expression by T cells is an important driver of immunosuppression and reduced cytotoxic T cell response in the tumor microenvironment (68), prompting development of PD-1-targeting monoclonal antibodies (e.g., pembrolizumab and nivolumab) for clinical use. Recently, Shirakawa et al. reported B cell-dependent accumulation of CD4+ T cells constitutively expressing PD-1 within visceral adipose of obese mice and human omental adipose from obese patients (354), further suggesting that tumor-adjacent adipose in obese individuals may present an immunosuppressive environment. In light of the accelerated thymic aging and naïve T cell depletion reported in obese patients, it will be interesting to see whether adipose contributes to increased PD-1+ T-cell content in the solid tumor microenvironment.

Macrophages and myeloid-derived suppressor cells

Macrophage ontogeny and activation—Macrophages, or “big eaters,” are myeloid-lineage immune cells typically classified within the innate immune system, yet bridge innate and adaptive immunity through extensive interactions with adaptive immune cells such as T cells. Conventionally, macrophages have been classified according to the “M1/M2” dichotomy, wherein “M1” polarized, or “classically activated,” macrophages are proinflammatory, and “M2” polarized, or “alternatively activated,” macrophages are anti-inflammatory. M1 macrophages are generated *in vitro* upon exposure to Th1 cytokines (e.g., IFN-γ) or stimuli such as bacteria and lipids (191, 337, 338). In contrast, M2 macrophages are most commonly generated by culture in the presence of Th2 cytokines such as IL-4 and/or IL-13 (150). However, a variety of other compounds may also be used for M2 macrophage polarization, including TGF-β, IL-10, glucocorticoid hormones, M-CSF, and

PGE_2 (236). Importantly, a lack of standardized nomenclature and macrophage polarization strategy (267), coupled with the multifarious nature of tissue macrophages and their exquisite ability to respond to context-dependent cues (138), has resulted in a tremendous influx of literature about the respective roles of M1 vs. M2 macrophage subsets in disease that is often contradictory and difficult to reconcile (242). Furthermore, while much of our understanding of the M1 and M2 phenotypes have come from animal and *in vitro* studies, genomic profiling of human and mouse macrophages treated with M1 or M2 stimuli revealed that only approximately 50% of macrophage polarization markers are shared across both species (243). With these caveats acknowledged, despite their utility to *in vitro* research, truly polarized macrophages are rare *in vivo*. Instead, tissue macrophages display a diverse array of functional phenotypes and often express one or more markers of both M1 and M2 subtypes, resulting in a mixed phenotype with specific expression and function varying by tissue type and timing of residence, as discussed below (Fig. 18) (82, 212, 262, 451).

Over the past few decades, macrophage ontogeny studies have revealed multiple origins for what are now referred to as “tissue resident” macrophage populations (for two excellent reviews on macrophage ontogeny the reader is referred to (144, 212)). During primitive hematopoiesis in early embryonic development, macrophages arise in the blood islands of the yolk sac from an erythromyeloid precursor, differentiating to macrophages without passing through a monocyte stage (148,244). These early embryonic macrophages are followed by a second wave derived from fetal monocytes and originating in the fetal liver (148, 244). Collectively, macrophages within these waves of early hematopoiesis populate tissues throughout the body and develop specialized functions based on their tissue of residence (e.g., microglia in the brain, Kupffer cells of the liver, etc.) (144, 212). Tissue-resident macrophages persist through adulthood and, in most tissues, self-maintain through local proliferation without significant contribution from circulating monocytes (exceptions include the intestine and the dermis) (81, 164). Only in later stages of embryonic development and postnatally do macrophages develop from bone marrow-derived circulating monocytes, which are recruited to tissues as needed when insults arise (38, 52).

Although the embryonic origin of many specialized tissue macrophage populations has been identified, the precise origin of adipose tissue macrophages (ATMs), and the degree to which resident ATM populations are replaced by circulating monocytes, remains unclear (Fig. 19). In one recent study, Franklin et al. demonstrated that ablation of the CCL2 receptor, CCR2, significantly reduced mammary fat pad macrophage content in lean mice (125); CCL2 mediates egress of monocytes from bone marrow and thereby augments the abundance of circulating monocytes (345). This study by Franklin and colleagues therefore suggests that mammary-specific ATMs in lean mice are replenished throughout adulthood by circulating monocytes. Whether this replenishment also occurs in other lean adipose depots under physiologic conditions has not been reported.

Macrophage content and phenotypes in obesity—Macrophages are the most highly represented immune cells in adipose tissue, and their numbers increase considerably in both visceral and subcutaneous adipose in obesity. However, the increased presence of ATMs in obesity appears to arise from multiple tissue sources. For example, using bone marrow

transplant studies employing *CD45.2*-expressing recipient mice and syngeneic *CD45.1*-expressing donor mice, Weisberg et al. reported that adipose-infiltrating macrophages in obesity had differentiated from bone marrow-derived, circulating monocytes (429). However, Amano et al. demonstrated that elevated CCL2 in visceral adipose drove local proliferation of macrophages in obesity, which contributed to ATM accumulation (13). Local ATM proliferation was also observed by Hasse et al., with live imaging of adipose explants showing that macrophages expressing M2-identifying markers underwent mitosis within CLS, followed by migration to interstitial spaces between adipocytes (154). Moreover, *in vivo* proliferation in a subset of bone marrow-derived macrophages has also been described, a surprising finding as bone marrow-derived macrophages were long believed to be terminally differentiated and thus nonproliferative (80). Importantly, however, recruitment of bone marrow-derived macrophages and local ATM proliferation need not be mutually exclusive, and future studies should examine obese ATM ontogeny in a longitudinal fashion.

Regardless of their tissue of origin, the increased presence of macrophages in obese adipose tissue can be best observed histologically as an increase in CLS formation. Indeed, Weisberg et al. demonstrated that macrophage influx and CLS formation in both mice and humans were significantly correlated with both adipocyte diameter and BMI (429). Time course studies probing the changing immune profile in obesity report that this macrophage accumulation occurs subsequent to neutrophil and T cell infiltration (106,276). However, there is variability in both the reported timing of macrophage influx and the degree of infiltration across adipose depots. For example, Elgazar-Carmen et al. observed an increase in CLS formation in murine visceral adipose tissue as early as 3 weeks into high fat feeding, which increased in density over time until the study endpoint at 16 weeks of diet exposure (106). On the other hand, Nishimura et al. reported that the presence of macrophages in the stromal-vascular fraction of visceral adipose tissue did not increase until 10 to 12 weeks of high-fat feeding (276). These temporal differences may be due to variation in the age at which obesity was induced and the dietary composition used to generate adiposity (i.e., both the percent kilocalories obtained from lipids as well as the lipid profile), as each are important considerations in diet-induced obesity studies. Nevertheless, although the initial timing of macrophage infiltration varies across studies, macrophage accumulation continues with prolonged obesity, with ATMs eventually comprising up to 50% of adipose stromal-vascular cells (75, 292, 429, 449). Due to sexual dimorphism in mice with regard to degree of adiposity in response to high-fat feeding, as well as differential contribution of adipose depots to obesity-associated metabolic dysregulation, many obesity studies have preferentially quantified changes in macrophage content in abdominal adipose depots of male mice (i.e., inguinal and periepididymal). However, we and others have also demonstrated obesity-associated CLS formation in the mammary fat pad of female mice, as well as human breast adipose tissue (260, 369, 370, 374).

As mentioned in previous sections of this review, obese adipose tissue frequently exhibits elevated levels of proinflammatory cytokines such as TNFα and IL-6. Although obese adipocytes have been shown to contribute to the secretion of these factors (130), macrophages and other stromal-vascular cells are thought to be the primary source of proinflammatory mediators in both mice (429) and humans (76, 112). Following initial reports of adipose macrophage influx in 2003 (429, 449), early characterization of ATMs

reported the appearance of a CD11c-expressing population of ATMs in adipose tissue of obese, but not lean, mice (131,231), as well as a phenotypic switch in the collective ATM population from an anti-inflammatory (M2) polarized state in lean animals to a pro-inflammatory (M1) state in obese animals (231). Importantly, however, more recent research indicates that the nature of ATM phenotypes in obesity is more dynamic and complex than originally expected. For example, the pro-inflammatory phenotype of CD11c-expressing ATMs appears to be malleable, and may be modulated by degree of insulin sensitivity in obese animals (221). In addition, more extensive profiling of ATMs in obese adipose of mice and humans has revealed that these cells harbor a “mixed” pro-and anti-inflammatory phenotype (350, 460). For example, in human abdominal subcutaneous adipose, ATMs accumulating in CLS expressed both CD11c and the commonly used M2 marker mannose receptor C type 1 (CD206), as well as both pro- and anti-inflammatory interleukins (IL-1β, IL-6, IL-8, and IL-10) (433). These results are further supported by Nakajima et al., who reported accumulation of ATMs expressing both CD11c and CD163, the latter of which is commonly associated with M2-like macrophages, in abdominal visceral and subcutaneous adipose of obese subjects (269). Shaul et al. (350) also described a mixed M1/M2 phenotype in obese murine CD11c+ visceral ATMs, suggesting phenotypic and functional similarities between murine and human ATMs in obesity. Interestingly, in the latter study, these mixed phenotype ATMs exhibited a shift toward a more M2-like transcriptional profile as obesity progressed.

Due to the phenotypic overlap between ATMs and canonical M1- and M2-polarized macrophages, the precise stimuli that activate ATMs, as well as the specific surface marker profile of this cell population, have only recently been described. Using a membrane proteomics approach, Kratz et al. (205) described a unique, “metabolically activated” phenotype in visceral ATMs from obese mice, which displayed surface markers distinct from those of classically activated macrophages generated *in vitro*. When these metabolically activated ATMs were recapitulated *in vitro* by exposure to conditions characteristic of the metabolic syndrome (high glucose, insulin, and palmitate), they were further found to exhibit increased surface expression of M2-associated lipid metabolizing proteins, but not other M2-defining markers. Metabolically activated ATMs also exhibited increased PPARγ activation, as well as a strong and selective induction of protein sequestome-1/p62, a scaffold protein with a variety of signaling roles including activation of the transcription factor nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) (205, 261). Importantly, PPARγ is a transcription factor crucial in the generation of the M2-like macrophage phenotype, while the NF-κB transcription factor family mediates several aspects of the M1 inflammatory response. Ablation of PPARγ or p62 in metabolically activated macrophages increased expression of several proinflammatory mediators, indicating that PPARγ and/or p62 attenuate proinflammatory responses in ATMs in obesity (205). Moreover, Ferrante and colleagues (450) observed elevated lysosome biogenesis and lipid metabolism in visceral adipose ATMs from obese mice relative to lean, without concomitant activation of inflammatory pathways. In fact, the authors suggested that the driving force for the chronic low-grade inflammation observed in obesity may simply be the increased density of macrophages in obese adipose, rather than a shift in the

inflammatory potential of individual macrophages. Thus, questions remain regarding our understanding of ATM phenotype and degree of plasticity within adipose tissue.

Adipose tissue macrophages: Connections to cancer—Increased ATM content in obesity suggests a clear inflammatory link between obese adipose and initiation of adipose-adjacent cancers. For example, as mentioned previously, macrophage infiltration into obese breast adipose tissue and resulting inflammation are linked to increased risk of mammary carcinogenesis (260, 370). Additionally, in various sections of this review we have addressed roles for ATMs in development of adipose tissue fibrosis (373, 446), which may influence early stages of tumor initiation. Macrophages are also highly represented within the body and margins of many solid tumor types, and directly promote progression of both early and established tumors (317,438). Indeed, macrophages are implicated in every aspect of tumor progression, including induction of the angiogenic switch (227); generation of an immunosuppressive environment (236); ECM degradation to facilitate invasion and migration of tumor cells into surrounding tissue; and physical participation in tumor cell metastasis (315, 438). Macrophages have also been shown to negatively influence response to anticancer therapies in breast and prostate cancers (86,89,109,235,356). Accordingly, in human breast tumors, degree of macrophage infiltration is an independent prognostic indicator strongly associated with high vascular grade, reduced relapse-free survival, and decreased overall survival (57, 218, 438).

Differences in phenotype and trophic potential between embryonic-resident, locally proliferating, and bone marrow-derived ATM populations may influence tumor development and ATM participation in the tumor microenvironment. Collectively, macrophages found both along the solid tumor periphery and within the tumor mass are referred to as tumor-associated macrophages (TAMs). Studies investigating the origins of TAMs in mice have reported that circulating bone marrow-derived monocytes are the primary source of TAMs in syngeneically grafted (264) and spontaneously arising mammary tumors (125), as well as in breast cancer pulmonary metastases (314). Furthermore, Franklin et al. reported that monocyte-derived TAMs in the MMTV-PyMT mouse model of spontaneous breast cancer proliferate within the tumor site and are phenotypically and functionally distinct from the resident mammary tissue macrophages present before tumor development (125). Together these observations argue against recruitment of local tissue-resident macrophage populations. However, studies probing TAM ontogeny have investigated this question *exclusively in lean animals*. The term “tissue-resident macrophages” is often used to refer to embryonic macrophages, but may also refer to any macrophages residing in a given tissue before an insult induces recruitment of bone marrow-derived inflammatory monocytes. Both expansion of adipose tissue in obesity and the presence of a developing tumor act as inflammatory insults; thus, the marked increase in ATM content in obesity, as well as their variable tissues of origin and distinct phenotypic differences from macrophages in lean adipose, requires an evaluation of the ATM-TAM relationship in the context of obesity.

Similarities between adipose tissue macrophages and tumor-associated macrophages—In a similar vein to ATMs, discrepancies exist between reports of the defining “TAM phenotype.” Conventionally, TAMs have been described as resembling

alternatively activated M2 macrophages (108, 236, 237). However, large-scale transcriptome analyses of TAMs in breast cancer suggest that TAMs collectively exhibit a mixed phenotype, expressing both M1-like and M2-like markers (288). Interestingly, this same study also showed that the gene signature of breast TAMs resembled that of fetal macrophages, with increased abundance of transcripts for genes regulating angiogenesis, tissue remodeling, and immune response (288). On the other hand, Franklin et al. recently reported that TAMs in the MMTV-PyMT model of metastatic, luminal-B breast cancer did not resemble M2-like macrophages, nor were they dependent upon tumor-elicited Th2 immune response (125). Together these studies indicate that, at least in breast cancer, TAMs are highly heterogeneous, and their phenotypes depend on tumor type, subtype, and location within the tumor (i.e., margins vs. periphery and extent of hypoxia) (315). Alterations in TAM phenotypes may also occur over the course of tumor development and progression, as Qian and Pollard have described a shift in TAMs throughout tumorigenesis from an "inflammatory" type during tumor initiation to an anti-inflammatory, M2-like trophic type in later stages of tumor progression (315). As mentioned previously and discussed further in the following section on *Myeloid-derived suppressor cells*, a similar shift has been described in ATMs over the course of prolonged obesity (350).

Shared characteristics between the tumor and obese adipose microenvironments, such as fibrosis, elevated ECM stiffness, angiogenesis, and regional hypoxia, may foster similarities between ATMs and TAMs. In particular, transient hypoxia activates the NF-κB transcription factor family (388). While numerous molecules are involved in generating inflammation, NF-κB has long been considered to lie at the center of the inflammatory response. However, due to the plurality of NF-κB family members, as well as the sheer number of combinatorial interactions within canonical and noncanonical signaling pathways, NF-κB activation can have both pro- and anti-inflammatory effects. Inflammatory mediators controlled by canonical NF-κB signaling include the TNF superfamily, IL-1β, IL-6, several chemokines, COX-2, 5-lipooxygenase, MMPs, VEGF, and cell surface adhesion molecules (3). Some of these gene products also activate NF-κB, with TNFα being a particularly potent stimulus (3). On the other hand, noncanonical NF-κB activities, such as regulation of IL-10 and TGF-β, play a role in inflammation resolution (213, 214). As discussed throughout this review, many of these signaling mediators also contribute to tumor malignancy through a variety of mechanisms, including growth promotion, matrix degradation, and tumor angiogenesis. In fact, NF-κB signaling is a known mediator of the tumor promoting activities of both early-stage, proinflammatory TAMs, and late-stage immunosuppressive TAMs (45, 155, 156, 293). A study by Mayi et al. (246) provided direct evidence underscoring the similarities between ATMs and TAMs. Specifically, ATMs from obese individuals expressed several of the same cancer-promoting genes as TAMs, including angiogenic factors, chemokines, cytokines, proteases, and growth factors. In fact, many of these protumoral genes, including VEGF-C and CXCL12, were expressed to an equal or greater extent in obese ATMs compared with TAMs (246), and are known targets of noncanonical NF-κB signaling (232). Taken together, these findings indicate that chronically activated NF-κB signaling and dysregulated immune responses are likely unifying themes between ATMs and TAMs.

Myeloid-derived suppressor cells—For reasons that are not well understood, abnormalities in myelopoiesis under conditions of prolonged inflammation such as chronic infections and cancer generate a poorly differentiated group of myeloid-lineage cells collectively termed myeloid-derived suppressor cells (MDSCs) (132). MDSCs include immature monocytes, neutrophils, dendritic cells, and macrophages, and are defined by their expression of the myeloid lineage markers CD11b and Gr1 and their potently immunosuppressive properties (132,133,311). Although they are comprised of multiple myeloid cell types, MDSCs are frequently described as immature macrophages. However, MDSCs in mice are reported to lack markers of mature macrophages such as major histocompatibility complex II (MHCII) and/or F4/80 (311, 447).

Factors implicated in promoting the egress of MDSCs from bone marrow, as well as their arrest in an immature state and their immunosuppressive nature, include PGE_2, IL-6, TNFα, IL-1β, and VEGF (311). Of these factors, PGE_2 is a particularly potent inducer of MDSCs that triggers upregulation of arginase metabolism, thereby suppressing T cell function (285,330,359). Several of these signaling molecules are in turn produced by MDSCs, resulting in a positive feedback loop of MDSC recruitment. Notably, as discussed in various sections throughout this review, each of these factors is also elevated in obese adipose tissue, and increased MDSC content in adipose tissue of obese mice has recently been reported. Indeed, Xia et al. (447) demonstrated that increased MDSC content in peripheral tissues (e.g., adipose and liver) of obese mice acted as an important safeguard of insulin sensitivity in both genetic and diet-induced models of obesity. Depletion of Gr1-expressing cells exacerbated symptoms of glucose intolerance and increased the presence of CD8+ T cells in adipose tissue. On the other hand, adoptive transfer of MDSCs improved fasting glucose and insulin levels in obese mice and reduced levels of circulating proinflammatory cytokines. Interestingly, the onset of MDSC accumulation coincided with previously reported windows of CD8+ T cell and proinflammatory macrophage recruitment, supporting the putative role of MDSCs in suppression of a rampant inflammatory response. Accordingly, the percentage of CD11b+ Gr1+ MDSCs in adipose tissue increased with the duration of obesity (447). Factors contributing to the accumulation of adipose MDSCs in obesity are poorly understood, but may include development of insulin resistance or increased local concentrations of estrogen and IGF-1, each of which have been found to influence MDSC biology (289). Importantly, influx of MDSCs into adipose in prolonged obesity may provide a partial explanation for reports of a shift in overall ATM phenotype over the course of obesity from pro-inflammatory M1-like to that of more immunosuppressive M2-like macrophages (350). For example, isolated MDSCs cultured with media conditioned by explanted obese adipose tissue displayed a greater shift toward an M2-like macrophage profile than MDSCs exposed to lean adipose explant-conditioned media (447). Future studies should examine the extent to which MDSCs in obese adipose differentiate to M2-like macrophages *in vivo*.

While the presence of MDSCs in obese adipose tissue is a relatively recent finding, a large body of literature supports the immunosuppressive functions of MDSCs within the tumor microenvironment. However, similarities in marker expression and immunosuppressive activation states may complicate a clear distinction between TAMs and MDSCs. Moreover,

MDSCs can also differentiate into mature TAMs upon entry into the tumor microenvironment (207). Functional similarities between MDSCs and certain TAM subsets have also been documented. For example, MDSCS suppress the function of critical antitumor defense cells (e.g., CD8+ cytotoxic T cells and NK cells) through expression of cytokines such as IL-10 and TGF-β and through arginine metabolism via the enzymes arginase-1 or inducible nitric oxide synthase (iNOS) (311). Interestingly, simultaneous expression of arginase-1 and iNOS is a hallmark of MDSCs that is rarely observed in other immune cells (311).

As described in the *T lymphocytes* section above, activation of the PD-1 pathway in T cells is a critical checkpoint promoting immunosuppression in the tumor microenvironment (395). Prima et al. reported that coculture of bone marrow-derived myeloid cells with bladder tumor cells elevated production of PGE_2 by both MDSCs and TAMs, and induced expression of the PD-1 ligand, programmed death-1 ligand (PD-L1), in these populations in a PGE_2-dependent manner (312). PD-1 and its ligands PD-L1 and PD-L2 were also more highly expressed in prostate tumors of obese mice compared to those from lean animals (457). Importantly, hypoxia-induced HIF-1 activation in TAMs was also recently shown to control TAM-specific PD-L1 expression (279). Whether regional hypoxia in obese adipose and resulting HIF-1 activation increases PD-L1 expression in ATM remains to be seen. However, the presence of MDSCs in prolonged obesity, as well as their influence on ATM activation, further suggests that adipose-adjacent cancers in obese individuals may encounter an environment conducive to suppressed immunosurveillance.

Neutrophils

Neutrophils infiltrate adipose tissue early in progression to obesity—

Neutrophils are the most abundant white blood cells in human circulation and are typically the first immune cells recruited in response to infection or sterile tissue injury. Upon arrival, neutrophils secrete a variety of proinflammatory cytokines and participate in presentation of antigen to, and activation of, T cells, while helping to recruit additional inflammatory cells such as macrophages (443). In lean animals, neutrophils represent a small fraction of total adipose tissue immune cells (<1%) (114). However, Elgazar-Carmon and colleagues (106) demonstrated that transient neutrophil infiltration into visceral adipose depots occurs early during the course of adipose tissue expansion in diet-induced obesity models, suggesting induction of an acute inflammatory response. Indeed, neutrophils accumulated in visceral (peri-epididymal) adipose of male mice as early as 3 days after initiating high-fat feeding—well before weight gain—with a corresponding increase in the neutrophil enzyme myeloperoxidase. Maximal myeloperoxidase was detected within 3 to 7 days, followed by a slow decline and return to baseline levels within 2 to 3 weeks of high-fat feeding, and neutrophils were no longer detectable histologically at 16 weeks on diet. Talukdar et al. (384) also reported a rapid and dramatic increase in adipose tissue neutrophil content by 3 days of high fat feeding. This increase was maintained for up to 90 days by FACS analysis of immune cells within the epididymal adipose stromal-vascular fraction of obese male mice, with a corresponding increase in neutrophil elastase mRNA. However, the exact adipose tissue-derived chemoattractant(s) that mediate neutrophil recruitment so early during the course of adipose tissue expansion remain unclear, as adipocyte hypertrophy and

death do not typically occur until several weeks into diet-induced obesity studies. In either case, once inflammation is established, neutrophils in inflamed adipose engage in bidirectional interactions with macrophages, dendritic cells, natural killer cells, lymphocytes, and mesenchymal stem cells, with important implications for adipose metabolic homeostasis. For example, neutrophil elastase appears to be an important mediator in the development of obesity-associated insulin resistance in response to adipose inflammation, signaling through Toll-like receptor 4 and downstream NF-kB activation to influence both recruitment and inflammatory activation state of infiltrating immune cells in obesity, including neutrophils themselves (384).

Tumor-associated neutrophils—Within the tumor microenvironment neutrophils exhibit varied content and multiple phenotypes, and have been found to exert both pro- and antitumoral effects. Similar to the M1/M2 dichotomy long used for macrophages, tumor associated neutrophils (TANs) have been described as either “N1” (anti-tumoral) or “N2” (protumoral) (Fig. 20) (129). The N1 neutrophil profile is reported to be promoted by increased levels of interferon-β (305) and pro-inflammatory cytokines such as IL-1β and TNF-α (290,305), while transforming growth factor β (TGF-β) is an important determinant of the N2 phenotype (129). Relative to N2 neutrophils, N1 neutrophils display elevated oxygen radical-dependent cytotoxicity and increased expression of the chemokine CCL3 and the cell adhesion molecule ICAM (129), which recruit additional inflammatory cells and act to increase adherence and extravasation, respectively. These proinflammatory N1 neutrophils promote CD8+ cytotoxic T cell recruitment and activation by producing T-cell attracting chemokines and proinflammatory cytokines (339). The N2 subpopulation can be distinguished morphologically, with less pronounced segmentation of the nuclei than N1 neutrophils and elevated expression of proangiogenic mediators including chemokines (CXCR4, CCL2), growth factors (VEGF), and remodeling factors such as MMP9 (38, 290). Neutrophil-derived MMP9 was shown to contribute to the angiogenic switch in early-stage pancreatic adenocarcinoma (282). Additionally, tumors formed by highly disseminating variants of prostate carcinoma recruited elevated levels of MMP9-positive TAN, which correlated with tumor cell dissemination and increased levels of angiogenesis and intravasation (38). N2 neutrophils are also immunosuppressive; elevated expression of the enzyme arginase-1 by N2 neutrophils contributes to depletion of arginase within the tumor microenvironment, inhibiting T-cell receptor expression and antigen-specific T-cell responses (331).

Adipose tissue neutrophils and cancer—Potentially due to the minimal presence of neutrophils in lean adipose, very few studies have addressed the influence of adipose tissue on neutrophils specifically in tumors that are adipose-adjacent or adipose-invading. Wagner et al. reported that melanoma cell lines implanted within white adipose tissue of lean mice showed significantly greater infiltration of CD11b+ cells than tumors implanted at a site distant from adipose (422). Although these cells were initially described as monocytes and/or macrophages, CD11b is expressed by multiple myeloid lineage cells, including neutrophils (415). Furthermore, inflamed peritumoral adipose exhibited increased expression of proinflammatory cytokines and chemotactic factors implicated in both macrophage and neutrophil recruitment, including CXCL1, macrophage-inflammatory protein-2 (MIP-2),

and CCL2 (422). In obese adipose, neutrophils likely contribute to both tumor initiation and tumor progression. In addition to facilitating recruitment of additional inflammatory cells, neutrophils participate in establishment of the mutagenic pro-inflammatory microenvironment associated with cancer initiation. Indeed, neutrophil-derived reactive oxygen species and myeloperoxidase are genotoxic, and are recognized mutagens in certain tumor types, such as lung cancer (202). Furthermore, the skewed cytokine profile of inflamed obese adipose, such as elevated CCL2, may influence recruitment of neutrophils to developing tumors.

Alternatively, tumor-adjacent adipose may impinge upon the phenotype of TANs. Incio et al. (179) reported that pancreatic tumors from obese animals contained higher concentrations of adipocyte-derived IL-1β than those from lean animals, resulting in increased TAN recruitment, TAN-induced activation of pancreatic stellate cells, and enhanced deposition of fibrillary collagen (i.e., desmoplasia). Obesity was also associated with greater tumor weight, which was reverted to lean levels by TAN depletion. Importantly, tumor formation in this study was induced, via orthotopic cell injection or tumor fragment implant, following 10 weeks on a high fat diet—a period during which, as illustrated above, the presence of neutrophils in visceral adipose depots is elevated (106, 384). Reversion of tumor growth rate was only observed when TAN depletion was initiated on day 1 following tumor induction, as opposed to day 7 (179). Thus, it is unclear whether neutrophils recruited from the visceral adipose, as opposed to newly trafficked peripheral blood neutrophils, were the primary contributors to induction of the desmoplastic response.

Taken together, the balance of N1/N2 TAN subtypes is an important factor in tumor progression, and future studies should consider the functions of adipose tissue neutrophils in initiation and/or progression of adipose-adjacent or adipose-invading tumors in obese individuals. Notably, although the presence of neutrophils in visceral adipose is clearly enhanced in early stage obesity, it is important to acknowledge that the time course studies described earlier regarding neutrophil adipose infiltration used exclusively male mice, and therefore it is unknown to what extent, or when, neutrophils also infiltrate the obese mammary fat pad.

Mast cells

Mast cell content and activation states in adipose tissue—An understudied immune cell in both adipose and tumor biology is the mast cell. Historically described as mediators of allergic hypersensitivity reactions (77), mast cells are found in virtually all tissues and are frequently classified into one of two subtypes: those residing in connective tissues, which express both tryptase and chymase, and those residing in mucosal tissues, which express only tryptase (181). However, similar to other immune cells, mast cells exhibit plasticity based on microenvironmental conditions, and thus several phenotypic subtypes may exist (134).

Accumulation of mast cells in visceral white adipose in obesity has been reported in both mice (10, 228) and humans (94,228), with documented heterogeneity across specific adipose depots. Altintas et al. found that mast cell density in the epididymal fat pad of male mice increased up to 230-fold under conditions of prolonged obesity, with mast cells intermingled

with macrophages in the interstitial spaces between adipocytes (10). A similar study published the same year by the same group also found dramatically increased mast cell infiltration in mesenteric and perirenal adipose, but no significant obesity-induced changes in mast cell density in inguinal subcutaneous adipose (9). However, Liu et al. reported increased numbers of mast cells in abdominal subcutaneous adipose tissue from obese human subjects, as well as significantly elevated serum tryptase levels, relative to lean individuals (228). Many of these mast cells were found in association with microvessels (228), implicating mast cells in the regulation of endothelial cell biology and angiogenesis in adipose tissue. Interestingly, increased serum tryptase levels were not found in obese children and adolescents, suggesting an adult-specific window of susceptibility to adipose-mast cell interactions (428).

Degree of mast cell activation is also affected by obesity. Divoux et al. (94) reported that mast cells isolated from omental and subcutaneous adipose depots of obese subjects exhibited a more activated state than mast cells isolated from lean subjects, secreting increased levels of pro-inflammatory cytokines, chemokines, and growth factors. Histological sections also revealed that mast cells in obese subjects preferentially localized to fibrotic bundles or proximate to endothelial vessels, and showed increased degranulation relative to those in lean tissue (Fig. 21A). Collectively, these results suggested that mast cells in obesity harbor a pro-inflammatory profile, a phenotype that was recapitulated by culture of mast cells in a 3D matrix designed to mimic fibrotic conditions. Furthermore, a positive correlation was observed between mast cell density and both fasting glucose and glycated hemoglobin, suggesting a role for mast cells in altered glycemic status in obese subjects. Finally, Zhou et al. recently showed that mast cells in both white adipose and bone marrow of obese mice express elevated levels of leptin, potentially in response to increased regional concentrations of IL-6 or TNFα in obesity (465).

Similar to the other immune cell populations described above, mast cells have been ascribed both pro- and antitumoral roles. Tumor promotion by mast cells has been attributed to secretion of proangiogenic factors such as MMP9 and VEGF, immunosuppression through release of histamine, or growth promotion by mitogenic factors including PDGF (390). Mast cells also secrete IL-1, TNFα, IL-6, IL-10, and IL-4 (390), each of which plays complex—and sometimes controversial—roles in solid tumor biology (17,27,113,118,223,286). Thus, below we consider the potential relevance of adipose mast cells to cancer progression with regard to potential changes induced with increased adiposity and prolonged obesity.

Mast cells in breast cancer—In breast cancer, mast cell tryptase levels are linked to angiogenesis and lymphangiogenesis (238, 318), lymph node metastasis (448), and myofibroblast differentiation (233). Samoszuk et al. (336) reported elevated serum tryptase in the blood of breast cancer patients as compared to healthy controls, as well as mast cell infiltration and mast cell tryptase expression adjacent to or within the stroma of *every* breast cancer patient sample examined, including DCIS specimens. Interestingly, in patients with invasive breast cancers, tryptase was found more frequently as extracellular deposits, suggesting mast cell degranulation, whereas in patients with early stage breast cancer, tryptase was located intracellularly, within intact mast cells (336).

Remarkably, mast cell activation state and influence on the course of tumor development appear to also depend upon their localization within the tumor microenvironment (Fig. 21B). For example, correlation between mast cell density and lymphatic microvessel density varied based on breast cancer subtype and peritumoral *versus* intratumoral mast cell location (318). As discussed in an earlier section of this review, peritumoral lymphatic vessel density is a prognostic indicator in several cancer types, including cervical, colorectal, breast, and prostate cancers (79, 105, 135, 256, 334). Indeed, *peri*tumoral mast cell density was significantly positively correlated with lymphatic density in luminal A and basal-like breast carcinomas; on the other hand, *intra*tumoral mast cell density showed a low inverse correlation with lymphatic density in both luminal A and HER2+ breast cancer subtypes, yet a positive correlation with basal-like carcinomas (318). In addition, Rajput et al. investigated over 4,000 clinically annotated tissue microarrays from invasive breast cancer patients with long-term follow-up, and reported that intratumoral mast cell infiltration was a strong marker of favorable prognosis independent of age, tumor grade, tumor size, lymph node status, and ER or HER2 status (319). Future work should address the molecular significance of the differential prognostic implications based on mast cell localization observed across breast cancer subtypes.

Mast cells in prostate cancer—Mast cell location also appears to influence prognosis in prostate cancers. Nonomura et al. reported that increased peritumoral mast cell count was associated with reduced recurrence-free survival and higher Gleason scores in prostate cancer patients treated with radical prostatectomy, irradiation therapy, or androgen deprivation therapy (280). Androgen deprivation therapy, also called castration therapy, is the gold standard for treatment of patients with metastatic prostate cancer. However, despite high initial response rates, nearly all men eventually develop progressive disease, referred to as “castration-resistant” prostate cancer. Johansson et al. (187) found that androgen deprivation therapy increased mast cell recruitment to the peritumoral tissue compartment of locally relapsing human prostate tumors, but not to the tumor itself. Peritumoral mast cells promoted tumor growth and tumor angiogenesis, which were further exacerbated by mast cell degranulation. Moreover, patients with higher peritumoral mast cell density had higher Gleason scores and significantly shorter cancer-specific survival, while patients with low numbers of *intra*tumoral mast cells exhibited the same patterns. Low intratumoral mast cell count was also associated with high tumor stage, higher tumor cell proliferation index, and metastatic spread (187). Similar results have been reported by others, with poorest outcomes in prostate cancer patients lacking intratumoral mast cells (121). These studies raise several important questions: how different are peritumoral vs. intratumoral mast cells, and what are the factors determining which phenotype develops? Are these factors tumor-intrinsic or determined by the surrounding tissue, particularly adipose tissue?

Impact of obesity on peritumoral mast cells—Given consistent reports regarding the increased mast cell content and altered mast cell activation state in obese adipose, we were surprised to find not a single publication addressing the impact of obesity or adipose tissue on the density or phenotype of peritumoral mast cells. In fact, the only study found even peripherally linking mast cells in adipose tissue to cancer outcomes addressed the frequency of metastatic ovarian cancer colonization within “milky spots,” vascularized accumulations

of mononuclear cells in human omental adipose that include mast cells (69). It must also be noted that BMI was not included as a variable in any of the aforementioned studies addressing mast cell function in breast and prostate tumors.

Increased adipose tissue mast cell density in obesity suggests the potential for elevated peritumoral mast cell concentrations in adipose-infiltrating tumors of obese individuals. However, although increases in adipose mast cell density have been reported in visceral adipose tissue of obese mice (10) and abdominal subcutaneous adipose of obese patients (228), whether obesity influences mast cell density in breast subcutaneous or periprostatic adipose tissue has not been reported. Ishijima et al. demonstrated that mast cells influence preadipocyte-adipocyte transition under both physiological and pathological conditions (182), suggesting a possible role for mast cells in adipose expansion. Furthermore, adipose tissue hematopoietic progenitor cells contain a population committed to the mast cell lineage, allowing white adipose tissue to act as a reservoir for mast cells that traffic to other tissues such as skin and, potentially, developing tumors (308). Thus, considering the differential associations between peritumoral vs. intratumoral mast cells and cancer outcomes, future studies should investigate the positioning and granulation status of peritumoral mast cells in relation to adipose tissue in lean and obese patients.

Eosinophils

Eosinophils are granulocytes typically associated with allergy and asthma that play key immunoregulatory roles in antigen presentation, suppression of inflammation, and maintenance of metabolic homeostasis (5, 83). Under physiologic conditions, circulating eosinophils are rare. However, eosinophils comprise ~4% to 5% of cells in the stromal-vascular fraction of lean adipose (444). Indeed, Wu et al. (444) demonstrated that eosinophils are the primary source of IL-4 in adipose tissue, as ~ 90% of IL-4-expressing cells recovered from visceral adipose of lean mice were eosinophils. Interestingly, they also noted an inverse relationship between adiposity and adipose eosinophil content in both genetic and diet-induced models of obesity. Furthermore, mice engineered to be eosinophil-deficient developed significantly greater adiposity and impaired glucose tolerance in response to high-fat diet feeding. These results were attributed to impaired eosinophil-mediated maintenance of alternatively activated, anti-inflammatory macrophages, which are generated upon exposure to IL-4 and/or IL-13 and are generally considered to be protective against diet-induced obesity and associated metabolic dysregulation. Subsequent studies have revealed that visceral adipose eosinophil populations, and thus alternatively activated macrophages, are in turn dependent upon innate lymphoid type 2 cells (ILC2s) through their production of IL-13 and IL-5, an eosinophil colony stimulating factor (257). In light of their direct or indirect anti-inflammatory effects, it is tempting to speculate that the presence of eosinophils and ILC2s in lean adipose, and their relative absence in inflamed obese adipose, may be a contributing factor to the differential cancer risk profile in lean versus obese individuals.

In light of the role of eosinophils in the maintenance of alternatively activated macrophages in normal, uninflamed adipose, it may seem surprising that these cells appear to promote proinflammatory macrophage polarization in tumors. Accordingly, an E1/E2 classification

scheme analogous to the macrophage M1/M2 and T helper cell Th1/Th2 subsets has been proposed (335). Eosinophil peroxidase enhances TNF-α and hydrogen peroxide release by human monocyte-derived macrophages, suggesting that paracrine signaling between eosinophils and macrophages within the tumor microenvironment may be relevant in promoting activity of certain tumoricidal TAM populations (364). In agreement with this proposition, injection of exogenous eosinophils in a mouse melanoma model reportedly reprogrammed TAMs toward a pro-inflammatory, tumoricidal phenotype, a result attributed to increased production of eosinophil-derived IFN-γ (61). However, it should be noted that while eosinophils facilitate tumor rejection in numerous cancer models, increased levels of circulating eosinophils are associated with poor prognosis in some hematologic malignancies, such as non-Hodgkin's and T cell lymphomas (335). Therefore, future research should systematically address relationships between local and circulating eosinophil content, site-specific tumor promotion vs. rejection, and eosinophil-mediated modulation of macrophage polarization.

Although little research has addressed these functions in the context of obesity, it is clear that eosinophils also facilitate anti-tumor immune reactions independent of their effects on macrophage polarization. For example, Carretero et al. (61) recently reported that eosinophil-mediated production of the chemoattractants CCL5, CXCL9, and CXCL10 promoted cytotoxic T cell recruitment in developing melanomas. Antibody-mediated depletion of eosinophils reduced CD8+ T cell infiltration, impaired tumor rejection, and severely reduced animal survival. Moreover, injection of melanoma cells together with exogenous eosinophils resulted in tumor vessel normalization, as evidenced by reduced permeability, enhanced perfusion, and reduced tumor hypoxia, alterations sometimes associated with reduced tumor aggression and more efficient vascular delivery of chemotherapies. In addition to their effects on other immune cells within the tumor microenvironment, eosinophils may also exhibit direct cytotoxicity. Tepper et al. (389) reported that mouse melanoma and plasmacytoma cells engineered to express IL-4 exhibited reduced or absent tumorigenicity in transplant studies due to elicitation of an inflammatory infiltrate comprised predominantly of macrophages and cytotoxic eosinophils. Accordingly, administration of a monoclonal antibody with granulocyte-specific cytotoxicity depleted eosinophils and restored tumorigenicity of IL-4-producing cells. However, these results were called into question by a subsequent study in which eosinophil-deficient IL-5-knockout mice showed similar degrees of IL-4-expressing melanoma rejection wildtype animals, a phenotype attributed to a neutrophil-mediated response (278). Ultimately, the conflicting results of these two studies indicate that the putative cytotoxic functions of eosinophils in anti-tumor immunity warrant further study. Moreover, additional investigation into eosinophil content in lean vs. obese adipose and their potential influence on adipose-tumor interactions should yield interesting findings.

Conclusion

Although adipocytes comprise the bulk of adipose tissue volume, adipose also contains a rich variety of stromal and vascular cells, as well as matrix and signaling components, which together constitute the adipose tissue microenvironment. A growing body of literature indicates that reciprocal, heterotypic interactions between developing tumors and the local

adipose milieu influence the course of solid tumor progression. Herein, we have provided an overview of interactions between select adipose tissue components and developing adipose-adjacent cancers, emphasizing breast and prostate cancers and the known or potential impact of changes that occur in the adipose tissue microenvironment during progression to obesity. As described throughout this review, obesity-associated adipose modifications often resemble aberrations observed within the tumor microenvironment. For example, similar to tumors, dysregulated obese adipose tissue is characterized by chronic low-grade inflammation, macrophage infiltration, hypoxia, and aberrant wound healing responses, including an increase in myofibroblast and activated fibroblast content. Obese adipose tissue is also a harbor for soluble mediators of cancer development, including metabolites, exosomes, cytokines, growth factors, and extracellular matrix scaffolding proteins, which collectively provide a critical link between adiposity and tumorigenesis. Thus, we posit that adipose-adjacent epithelium in obese individuals encounters an environment particularly conducive to tumor initiation and progression.

Despite a recent increase in research regarding the contributions of adipose tissue in cancer development, many questions still remain. For example, the identities of many adipose-derived microenvironmental signaling mediators that modify tumor biology are largely unknown. Furthermore, while immune cells in both adipose tissue and cancer biology have been characterized individually, few studies have attempted to quantify recruitment of immune cells originating in adipose tissue adjacent to tumors. This potential for recruitment becomes especially important in the context of obesity, wherein adipose tissue immune cell content is greatly increased, yet the relative immune composition and phenotype shifts dramatically. Thus, the extent to which specific adipose-derived cell lineages contribute to tumor development and/or progression remains inconclusive. Ultimately, given the rising global prevalence of obesity, a better understanding of the molecular interactions between adipose tissue components and tumor cells is critical for the identification of novel targets for prevention and/or treatment of obesity-associated cancers.

Acknowledgments

The authors thank Dr. Melissa Troester, PhD, from the University of North Carolina, Chapel Hill for providing human breast histology through the UNC Normal Breast Study. We further show our gratitude to Drs. Laura Bowers, PhD, and Stephen Hursting, PhD, also from the University of North Carolina, Chapel Hill, for sharing mouse mammary histology. Finally, the authors would like to acknowledge Kathryn Hobbs and Ottavia Zattra for their help with formatting and editing during manuscript preparation.

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Didactic Synopsis

Major teaching points

1. Solid tumor growth requires the interaction of tumor cells with the surrounding tissue, leading to a view of tumors as communities rather than exclusively tumor cells.
2. Adipose tissue, or fat, plays important roles in cancer risk and outcome because many tumors grow close to or in direct contact with adipose.
3. The adipose community—or microenvironment—includes adipocytes and adipose-associated stromal and vascular components, such as fibroblasts and other connective tissue cells, stem cells, endothelial cells, innate and adaptive immune cells, and extracellular signaling and matrix components.
4. Herein, we review the cellular and noncellular parts of the adipose “organ” and the mechanisms by which varied microenvironmental components contribute to tumor development, with emphasis on obesity.
5. Obesity dramatically modifies the adipose tissue microenvironment in numerous ways, which intriguingly resemble shifts observed within the tumor microenvironment.
6. Understanding neighboring adipose is critical in tumorigenesis.

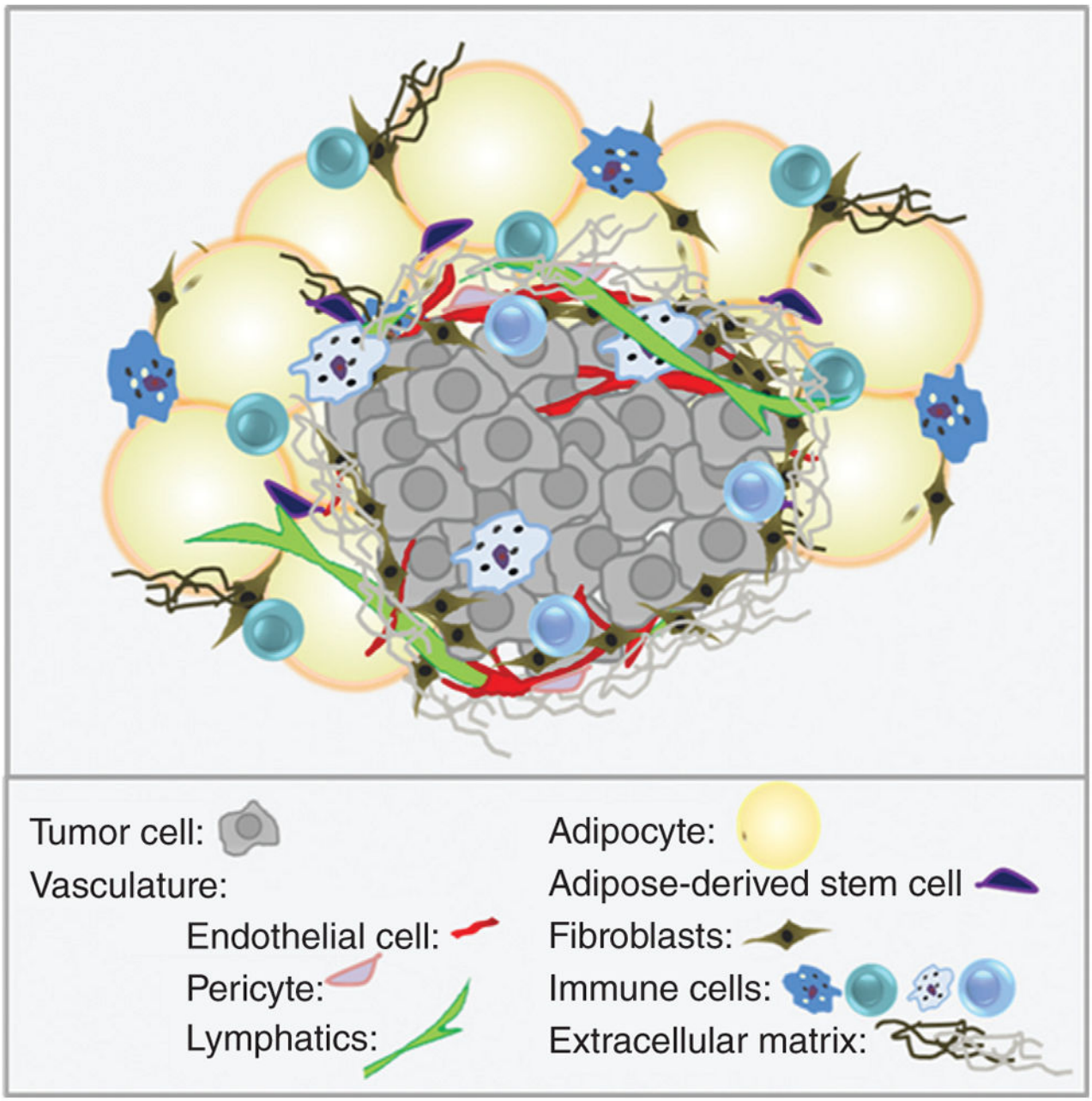

Figure 1. Tumors as communities

Tumor cells coexist with a variety of stromal and immune cells, and reside in a complex mixture of signaling molecules and extracellular matrix components. Adjacent adipose tissue may provide a hospitable environment to developing tumors.

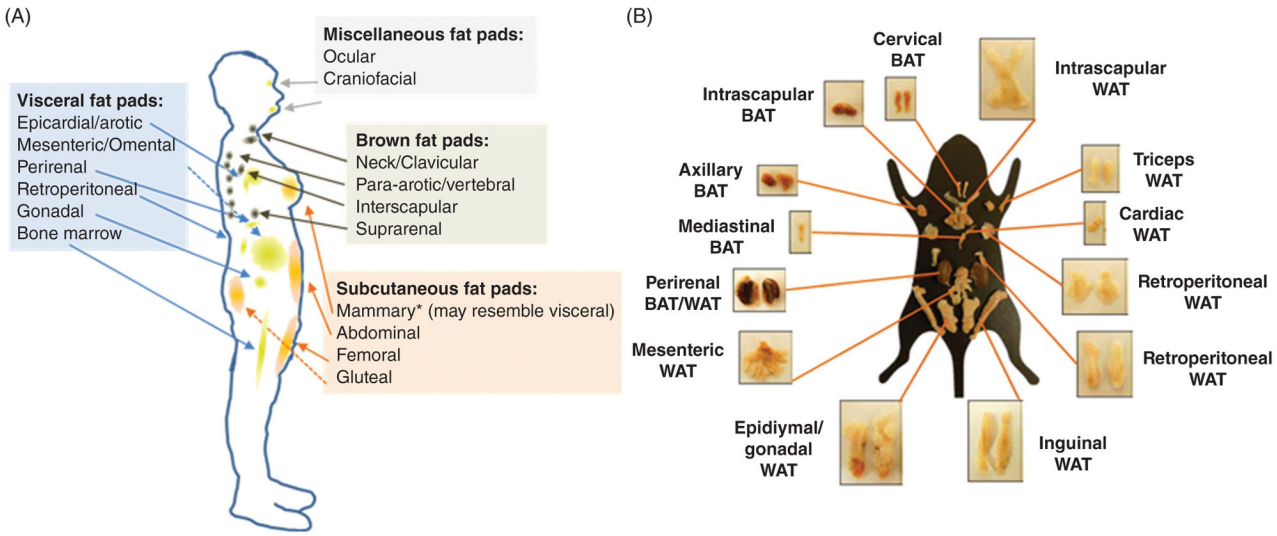

Figure 2. The adipose organ is comprised of several distinct adipose depots

Adipose depot locations and subtypes in (A) humans and (B) mice [panel B adapted from (85) with permission].

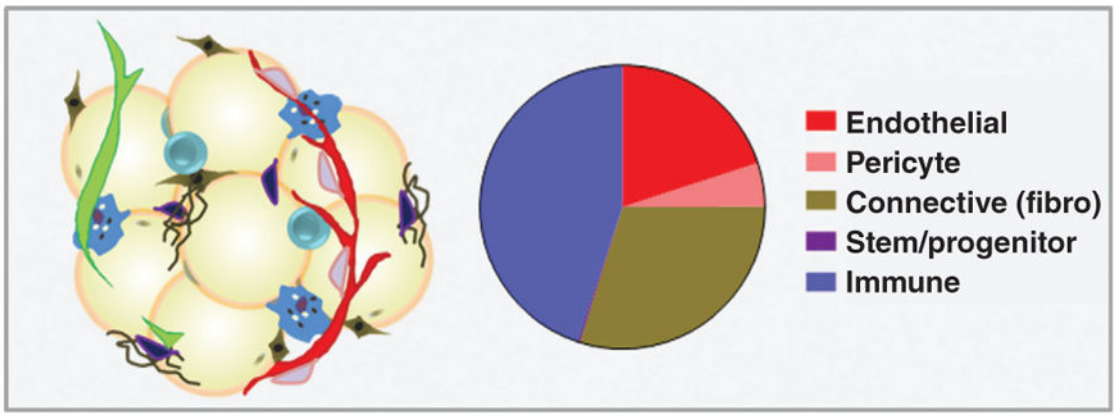

Figure 3.
Approximate composition of human white adipose tissue stromal-vascular fraction (percent cellularity).

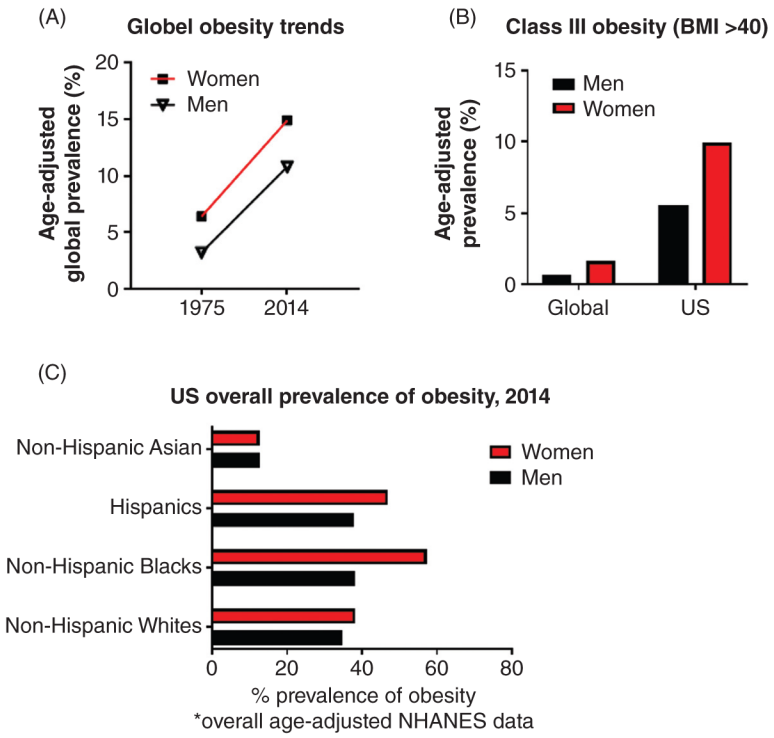

Figure 4. Rising global and US obesity rates

(A) Global age-adjusted prevalence of obesity in men and women, 1975 and 2014; (B) Class III obesity (BMI >40), globally and US; and (C) US obesity prevalence by race, ethnicity (270).

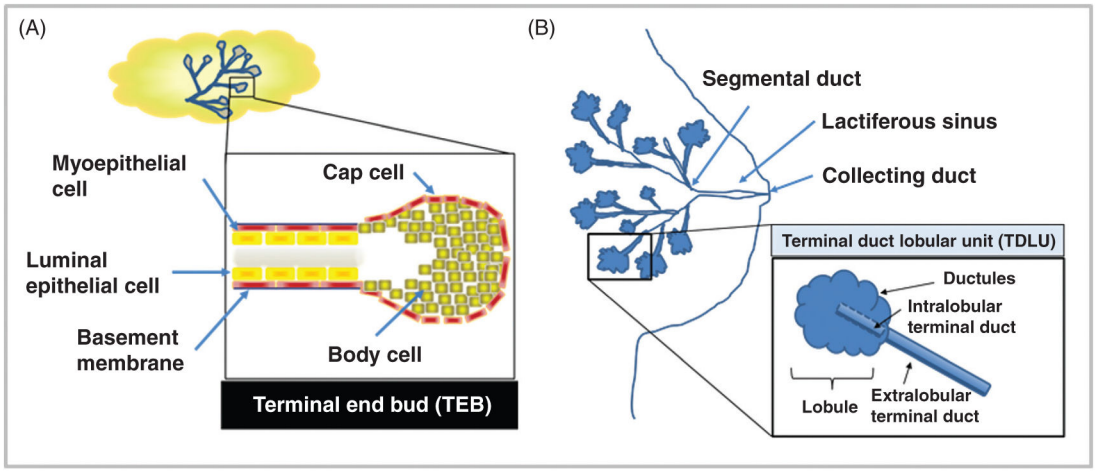

Figure 5. Comparison of mouse and human mammary gland anatomical structure

(A) Murine ductal elongation and branching occur at the Terminal End Buds (TEBs). (B) The human mammary gland is extensively branched, culminating in the functional terminal ductal lobular unit (TDLU).

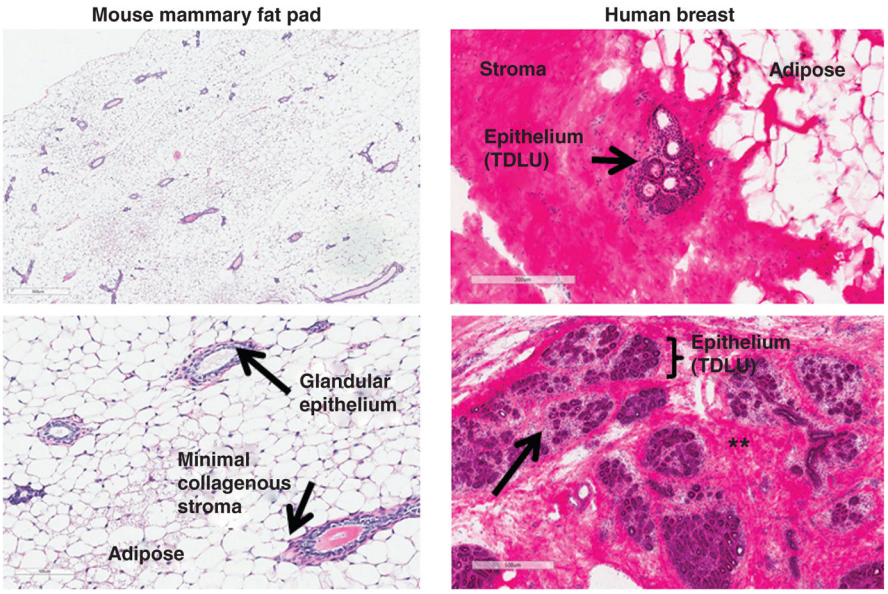

Figure 6. Comparison of mouse and human mammary gland histology

Left: Adult mouse mammary fat pad from nulliparous C57BL/6 mouse (4× and 10×, H&E staining). Right: H&E-stained normal human breast tissue. Arrowhead and asterisks in right panel refer to loose intra- and dense interlobular stroma, respectively. Human histology images courtesy of Melissa Troester and the UNC Normal Breast Study (unpublished).

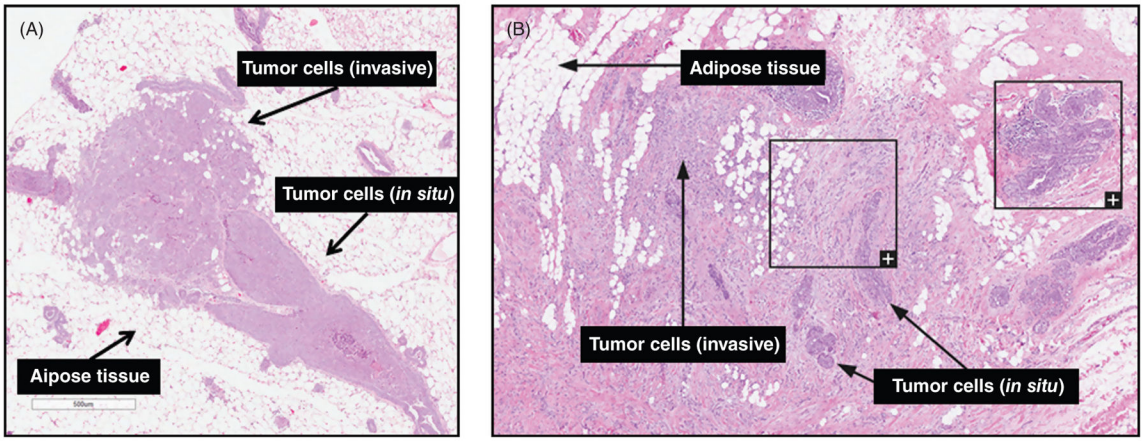

Figure 7. Adipose-breast cancer interactions in mice and humans

(A) Early invasive lesions in H&E-stained mammary gland tissue from the C3(1)-TAg genetically engineered mouse model of spontaneous basal-like breast cancer (unpublished images). (B) Human breast cancer—female, 50 years, lobular carcinoma, grade 1, Elston-Ellis score 5. Image credit: The Human Protein Atlas (1,407).

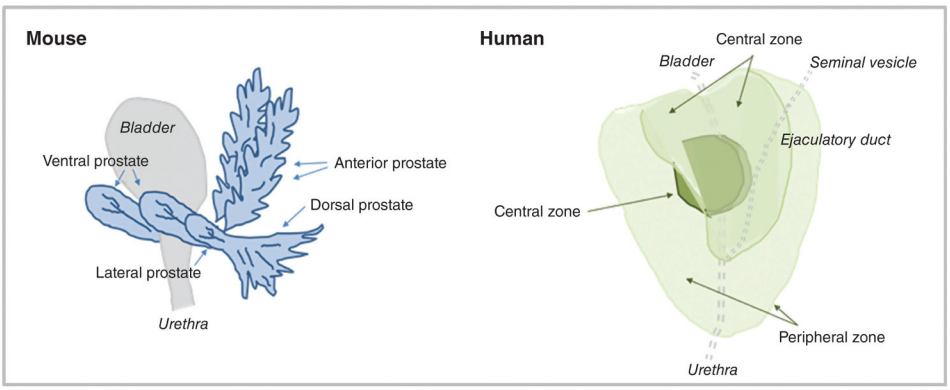

Figure 8.
Anatomical comparison of mouse (left) and human (right) prostate glands.

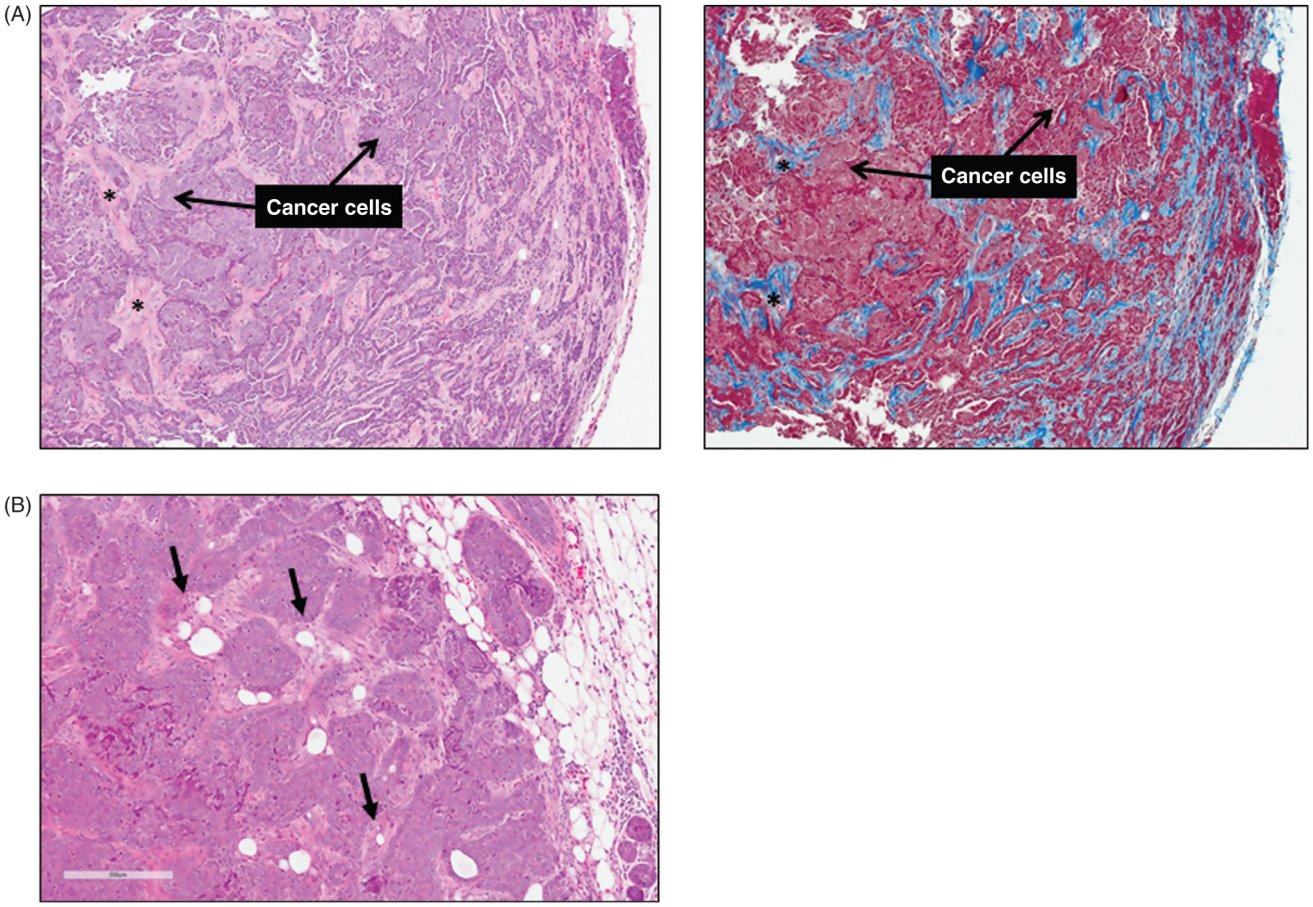

Figure 9. Desmoplasia and cancer-associated adipocytes

(A) Mammary tumors from C3(1)-TAg mice are stained with Hematoxylin/eosin (left) and Masson's trichrome (right) (unpublished). In tumors, chronic activation of the wound-repair response results in desmoplasia, or excess collagenous extracellular matrix production, within tumors. Asterisks (*) indicate desmoplastic stroma. (B) Cancer-associated adipocytes (black arrows) at or near the tumor invasive front become smaller and exhibit decreased expression of adipocyte markers, while the number of fibroblast-like cells increases.

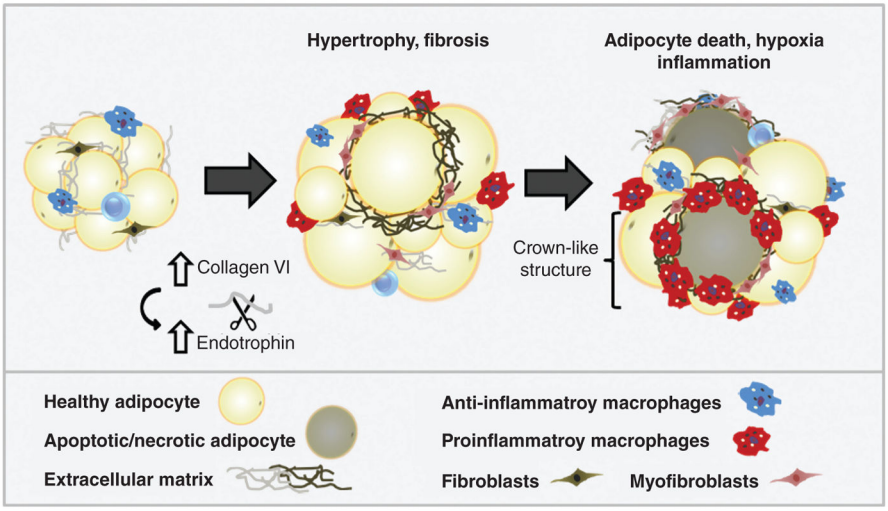

Figure 10. Obesity-associated modifications in the adipose tissue microenvironment

Adipose tissue expansion in obesity occurs in association with extracellular matrix changes such as fibrosis. Adipocyte hypertrophy and hypoxia trigger macrophage infiltration and crown-like structure formation, which further exacerbates development of fibrosis and inflammation.

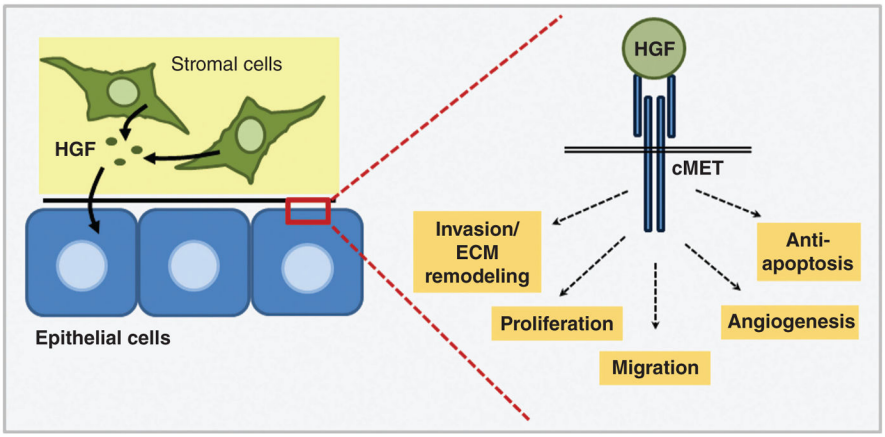

Figure 11. HGF/cMET: an oncogenic signaling cascade

HGF secretion by stromal cells such as fibroblasts, adipocytes, and macrophages initiates an invasive growth program in epithelial cells.

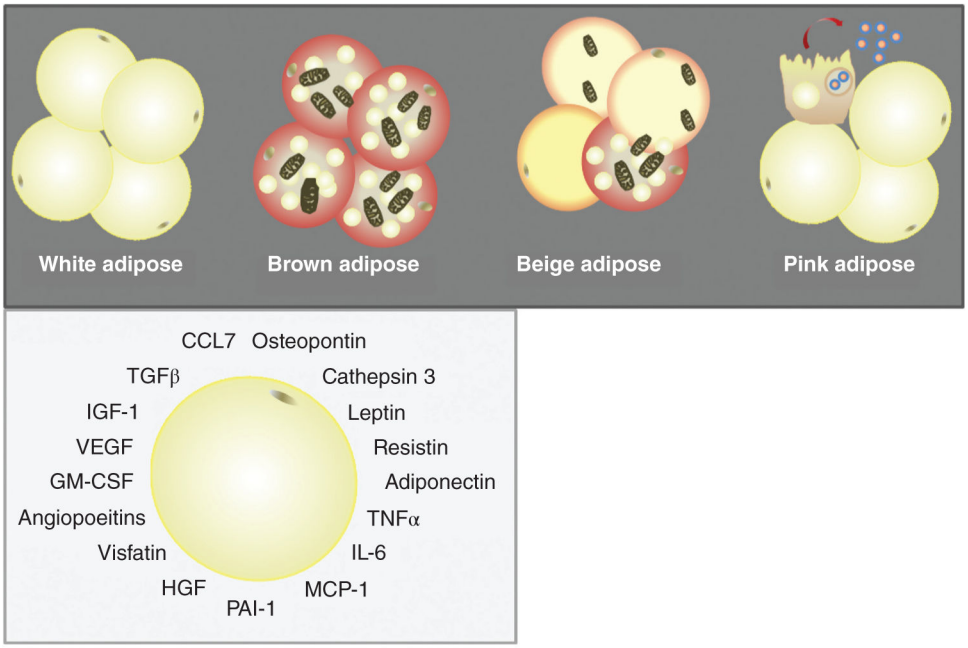

Figure 12. Adipocyte subtypes and secreted factors

White adipocytes contain a large, unilocular lipid droplet and are specialized for storage of neutral lipids. Brown and/or beige adipocytes have increased mitochondrial content relative to white adipocytes and play important roles in thermogenesis. “Pink” adipocytes have been described in murine mammary gland, arising exclusively during pregnancy and lactation. Collectively, adipocytes secrete a broad range of signaling molecules.

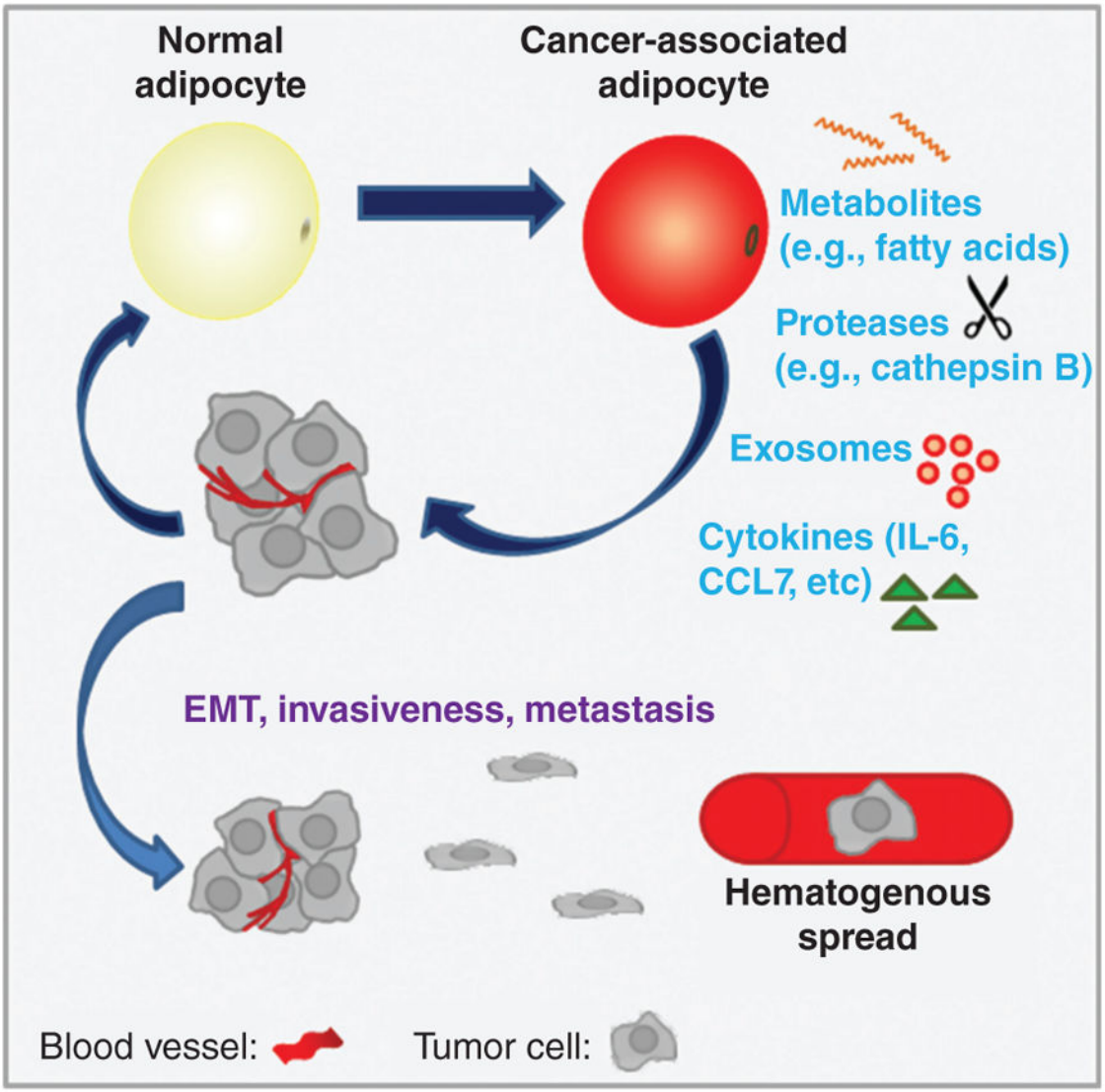

Figure 13. Adipocytes promote tumor progression and metastasis

Adipocytes may provide metabolic substrates directly to cancer cells, or may indirectly influence cancer metabolism through exosome secretion. Adipocytes also secrete a variety of factors that promote tumor growth, EMT (epithelial-mesenchymal transition), acquisition of stem-like features, invasive behavior, and metastasis.

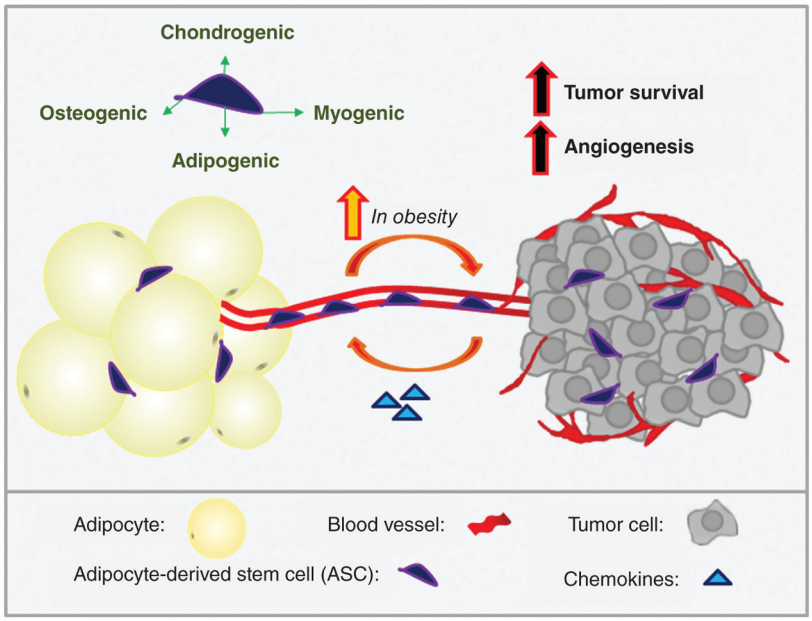

Figure 14. Obesity, cancer increase circulating ASCs

Human adipose tissue stroma is a rich source of multipotent ASCs, which enter the circulation and traffic to other tissues. This “shedding” process is increased in obese and/or tumor-bearing individuals. Tumor chemokine secretion (e.g., CXCL1, CXCL8) is influenced by obesity and is implicated in ASC recruitment to developing tumors and differentiation into stromal populations such as fibroblasts, pericytes, and adipocytes.

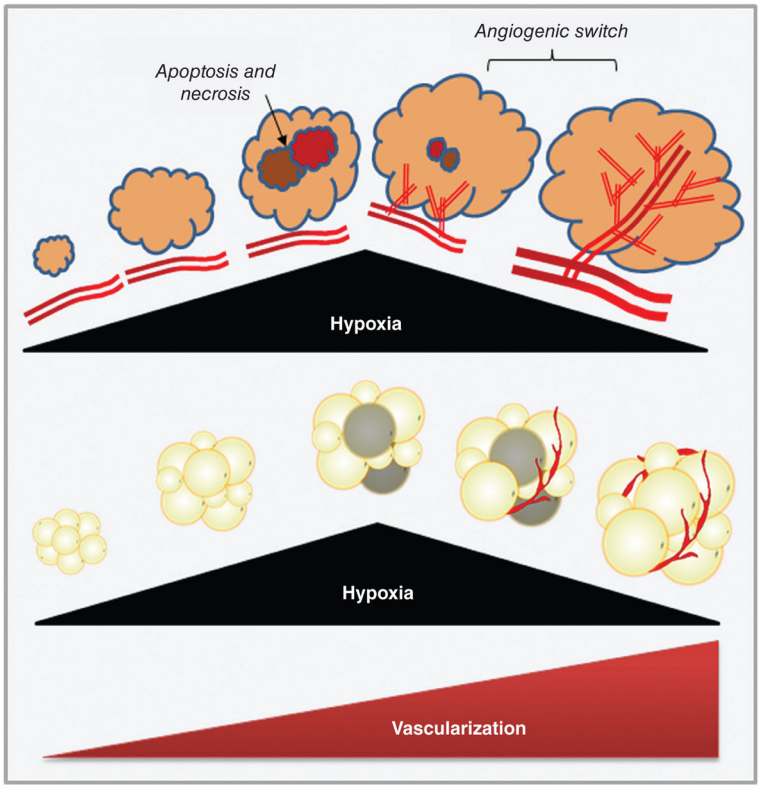

Figure 15. Hypoxia & the angiogenic switch

An extensive list of proangiogenic factors is involved in both induction of the angiogenic switch in developing solid tumors and expansion of adipose tissue during progression to obesity. As tumor cells proliferate or adipocytes hypertrophy, hypoxia develops and triggers stabilization of the HIF-1 complex, a transcription factor which promotes increased production of growth factors such as VEGF-A, FGF1, TGF-β, HGF, and angiopoietins 1 and 2. Additional proangiogenic factors include the adipokines leptin and adiponectin; cytokines such as TNFα, IL-6, and IL-8; and matrix metalloproteases, which degrade the extracellular matrix. Ultimately, increased vascularization alleviates regional hypoxia and facilitates further tissue expansion.

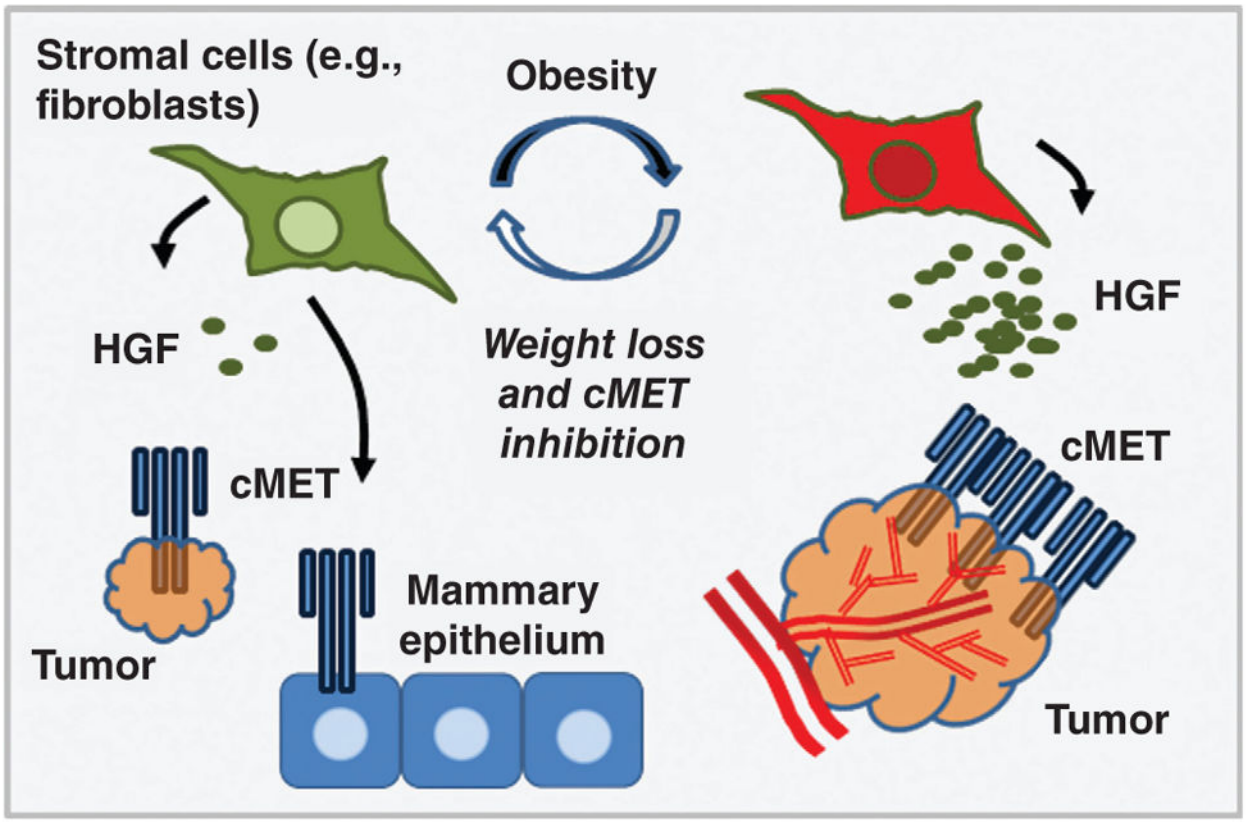

Figure 16. Mammary HGF/cMET signaling in the in C3(1)-Tag mouse model of basal-like breast cancer

Obesity increased HGF production by stromal cells, promoting tumor growth and angiogenesis. HGF/cMET-mediated tumor promotion was reversible by weight loss or cMET inhibition.

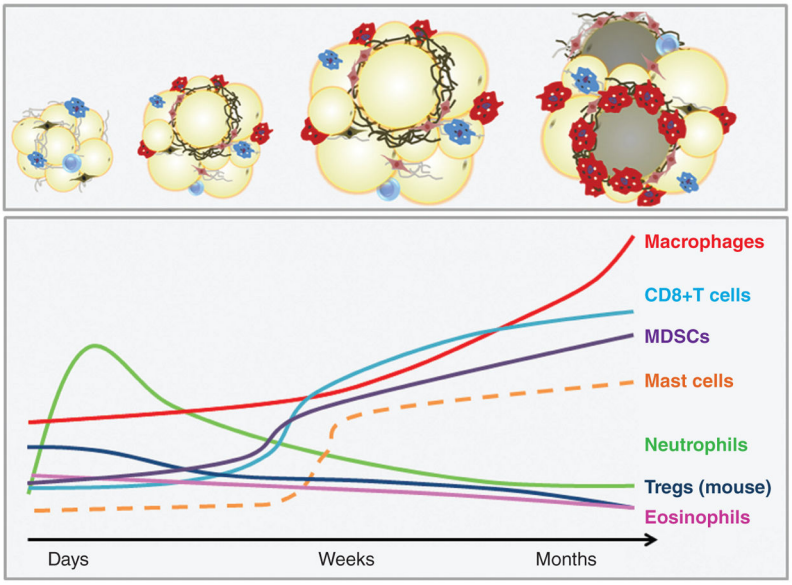

Figure 17. Summary of changes in immune cell profile during progression to obesity

In the lean state, adipose tissue contains a variety of immunoregulatory cells such as M2-like tissue-resident macrophages, regulatory T cells, and eosinophils. Within days of exposure to an obesogenic diet neutrophils infiltrate adipose. Over weeks to months, an increase in CD8+ T cells, macrophages, and myeloid-derived suppressor cells (MDSCs) results in a mix of pro- and anti-inflammatory cells. In prolonged obesity, adipose mast cell content may also increase.

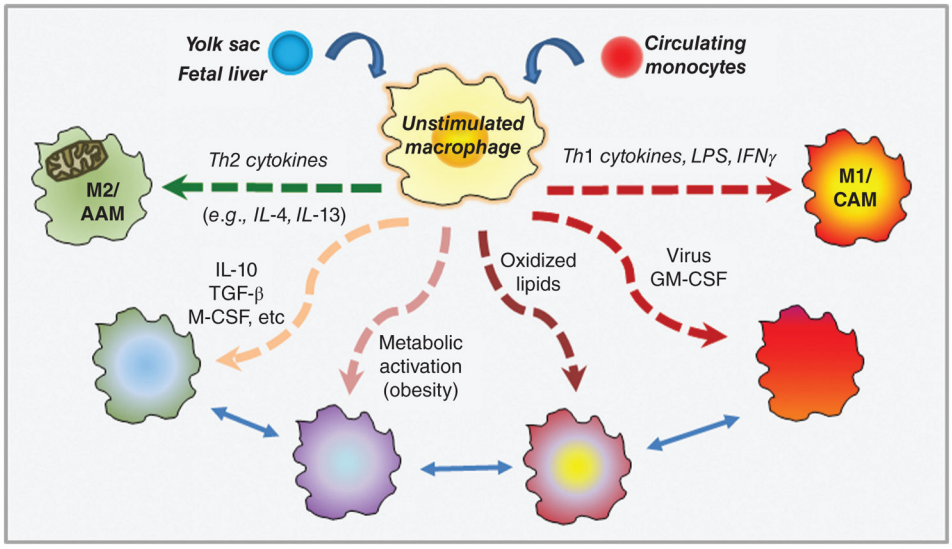

Figure 18. Macrophage activation as a spectrum

Unstimulated macrophages can be polarized *in vitro* to generate M1 (right) or M2 macrophages (left) using single cytokines or cytokine and other stimuli cocktails. However, tissue macrophages are exquisitely plastic, often expressing one or more markers of both M1 and M2 subtypes. Thus, tissue macrophage activation lies along a spectrum, resulting in mixed phenotype with specific expression and function varying by tissue type and timing of residence.

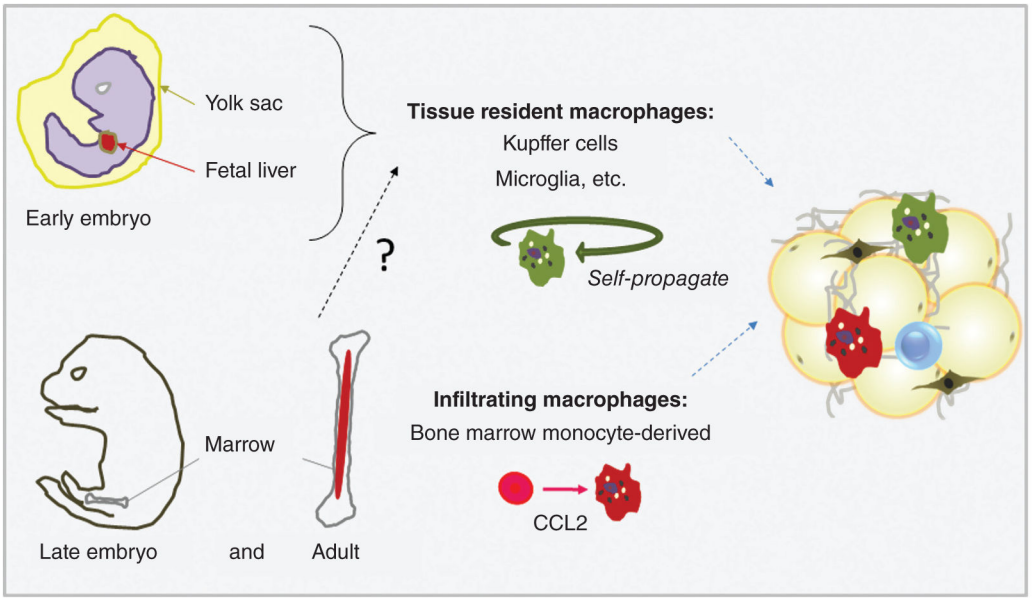

Figure 19. Adipose tissue macrophage ontogeny

Lineage tracing studies have revealed multiple embryonic sources for tissue-resident macrophages (e.g., Kupffer cells, microglia) including the yolk sac and fetal liver. However, the contribution of bone marrow monocyte-derived macrophages to tissue-resident populations remains ambiguous. Moreover, the relative contribution of yolk sac, fetal liver, and bone marrow-derived macrophages within adipose tissue depots has not been established, although the overall proportion of inflammatory, bone-marrow derived macrophages increases in obese adipose.

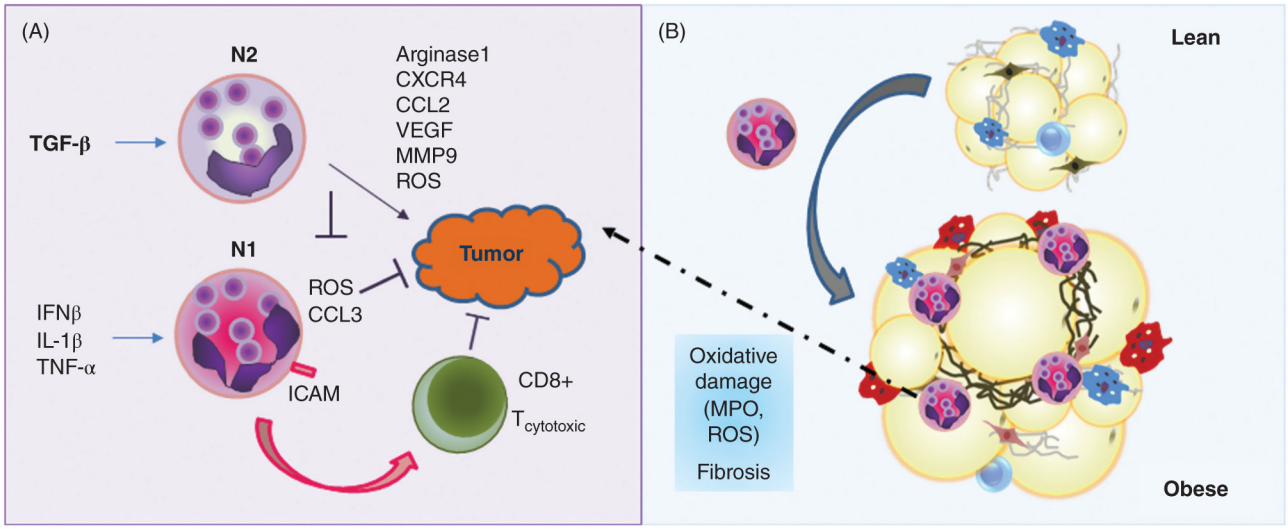

Figure 20. Tumor-Associated Neutrophils have N1 and N2-like phenotypes

(A) Neutrophil content and phenotype is both pro- and anti-tumoral with cytokines such as IFNβ, IL-1β, TNF-α activating the N1 or proinflammatory phenotype and TGF-B driving the N2 immunomodulatory phenotype. The N1 neutrophil releases reactive oxygen species (ROS) and proteins that increase cell recruitment and extravasation [ICAM and CCL3 (MIP-1-alpha)]. N1 neutrophils support cytotoxic CD8+ T cell activity. N2 neutrophils have a less segmented nucleus than typical and secretes many angiogenic and immunosuppressive mediators, expressing arginase 1 for example. ROS secreted by both N1 and N2 may both promote genotoxicity in tumor initiation, or in contrast, can be cytotoxic to growing tumors. The timing and phenotype of neutrophil influx in obesity and tumor progression warrants further study. (B) Neutrophils infiltrate adipose early during progression to obesity. Neutrophil production of ROS, for example, through myeloperoxidase (MPO) expression, contributes to oxidative stress and fibrotic changes.

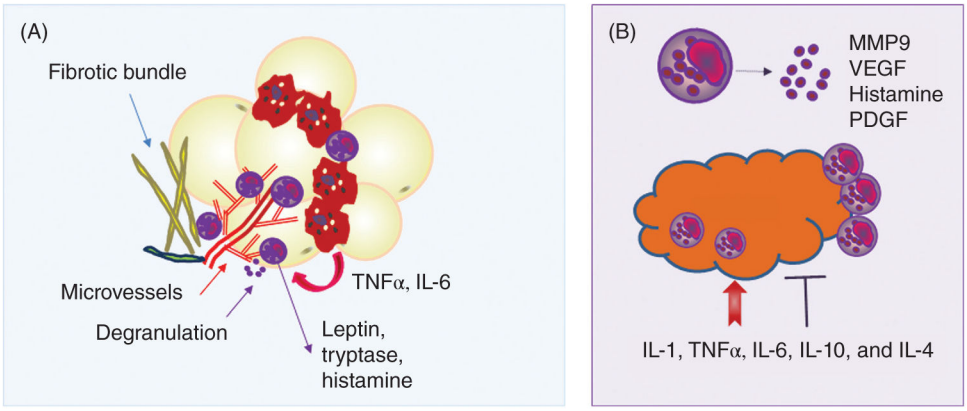

Figure 21. Mast cells: Unappreciated players in adipose and tumor biology

(A) Mast cell content in adipose tissue increases with obesity, with mast cells localized to blood vessels and/or within fibrotic bundles. Obesity is also associated with increased mast cell degranulation, an indicator of a mast cell activation. (B) In cancer, mast cells contribute to tumor progression through release of proangiogenic factors (MMP9, VEGF), immunosuppressive mediators (histamine), or growth factors such as PDGF. Mast cells also secrete cytokines that may promote (arrow) or inhibit (line) tumor progression. Mast cell influence on tumor progression appears to be dependent upon mast cell localization as peri-*versus* intratumoral.

Table 1

Abbreviations Used in Text

Abbreviation	Explanation
AMPK	AMP-activated protein kinase
Ang-2	Angiopoietin-2
APC	Antigen-presenting cell
ASC	Adipose stromal cell, Adipose-derived stem cell
ASCO	American Society of Clinical Oncology
α-SMA	Alpha smooth muscle actin
ATGL	Adipocyte triglyceride lipase
ATM	Adipose tissue macrophages
BAI	Body Adiposity Index
BMI	Body mass index
CAA	Cancer-associated adipocytes
CAFs	Cancer-associated fibroblasts
CCK	Cholecystokinin
CLS	Crown like structure
COX-2	Cyclooxygenase-2
CPT1	Carnitine palmitoyltransferase 1
DAMPs	Damage-associated molecular patterns
DCIS	Ductal carcinoma in situ
ECM	Extracellular matrix
EMT	Epithelial-to-mesenchymal transition
FACS	Fluorescence activated cell sorting
FGF-2	Fibroblast growth factor 2
GEMM	Genetically engineered mouse model
HGF	Hepatocyte growth factor
HIF-1, HIF-1α	Hypoxia-inducible factor, 1α subunit
IDC	Invasive ductal carcinoma
IGF-1	Insulin-like growth factor-1
IL-6	Interleukin-6
ILCs	Innate lymphoid cells
ILC2s	Innate lymphoid type 2 cells
LVD	Lymphatic vessel density
M1, M2	Macrophage phenotypes
MCP-1/CCL2	Monocyte-chemoattractant protein, also called CC chemokine ligand 2
MMP	Matrix metalloprotease
MMTV-PyMT	Mouse mammary tumor virus, Polyoma middle T antigen
N1, N2	Subtypes of tumor-associated neutrophils (see TAN)
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NHANES	United States National Health and Nutrition Examination Survey
NK	cells Natural killer cells

Abbreviation	Explanation
PAI-1	Plasminogen activator inhibitor-1
PD-1	Programmed Death-1
PDGF	Platelet-derived growth factor
PD-L1	Programmed death-1 ligand
PGE_2	Prostaglandin E2
PIN	Prostatic intraepithelial neoplasia
PPARγ	Peroxisome proliferator-activated receptor gamma
TAM	Tumor-associated macrophage
TAN	Tumor-associated neutrophil
TCR	T cell receptor
TDLU	Terminal ductal lobular unit
TEB	Terminal end bud
TGF-β	Transforming growth factor beta
Th1, Th2,	Th17 T helper cell subtypes
TNBC	Triple negative breast cancer
TNFα	Tumor necrosis factor alpha
Tregs	Regulatory T cells
VEGF	Vascular endothelial growth factor