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REVIEW

The role of immune dysfunction in obesity-associated cancer risk, progression, and metastasis

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Abstract

Obesity has been linked to an increased risk of and a worse prognosis for several types of cancer. A number of interrelated mediators contribute to obesity's pro-tumor effects, including chronic adipose inflammation and other perturbations of immune cell development and function. Here, we review studies examining the impact of obesity-induced immune dysfunction on cancer risk and progression. While the role of adipose tissue inflammation in obesity-associated cancer risk has been well characterized, the effects of obesity on immune cell infiltration and activity within the tumor microenvironment are not well studied. In this review, we aim to highlight the impact of both adipose-mediated inflammatory signaling and intratumoral immunosuppressive signaling in obesity-induced cancer risk, progression, and metastasis.

Keywords Immunotherapy · Leptin · Chemoresistance

Introduction

Obesity and cancer

According to the Centers for Diseases Control and Prevention (CDC), approximately 40% of adults in the USA were considered obese in 2017 [1]. In the same year, the Organization for Economic Cooperation and Development predicted that this number will approach 50% by 2030 [2]. The CDC and the World Health Organization (WHO) define obesity as a body mass index (BMI) ≥ 30 kg/m^2 and severe obesity as ≥ 40 kg/m^2. However, the WHO has recommended defining obesity in Asian adults as BMI ≥ 27.5 kg/m^2 due to studies indicating a higher body fat percentage and higher rates of obesity-related health complications at lower BMIs in this population, relative to non-Hispanic whites [3, 4]. In concert with chronic adipose tissue inflammation, obesity increases the risk of several comorbidities such as heart disease, type 2 diabetes, and cancer. Obesity has been specifically associated with an increased risk of developing 13 cancers, including cancers of the esophagus (adenocarcinoma), gastric cardia, colon and rectum, liver, gallbladder, pancreas, postmenopausal breast, uterus, ovaries, kidneys, and thyroid as well as meningioma and multiple myeloma [5, 6]. It has been generally accepted that, with the exception of lung, brain/central nervous system, and malignant melanoma, obesity is also associated with increased mortality in most cancers, particularly liver, uterine, and kidney cancer [7]. However, there is a growing body of literature that supports the existence of an "obesity paradox" in cancer patients treated with immunotherapies, where obesity is associated with a better response to these treatments [8]. The effects of obesity on patient response to various cancer therapies will be described in more detail in the last section of this review.

Menopause, obesity, and associated cancer risks

Among women, menopause is also an important factor in susceptibility to certain cancers, and obesity interacts with this factor. Obesity has been shown to delay menopause, and a delay of 5 years increases postmenopausal breast cancer risk by 17% [9]. For ovarian and endometrial cancer, obesity increases risk regardless of menopausal status [10–12]. However, obesity protects against breast cancer in premenopausal women, particularly estrogen receptor positive disease, while the opposite is true in postmenopausal women [10, 13, 14]. One possible explanation for this contrast is that, while the ovaries produce estrogen prior to

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menopause, adipose tissue is the primary site of estrogen production in postmenopausal women due to their lack of ovarian aromatase activity and an increase in adipose tissue aromatase activity with age [15, 16]. In addition, increased inflammation due to adipose tissue dysfunction has been associated with increased adipose aromatase expression in obese postmenopausal women, suggesting that this inflammation contributes to estrogen-mediated breast cancer risk [17]. Postmenopausal obese women also have lower availability of sex hormone binding globulin (SHBG) [18], and weight is inversely proportional to SHBG [19, 20]. Reduced SHBG increases the levels of estradiol in circulation and therefore increases the risk of not just breast cancer but also endometrial cancer [21]. Additionally, hormone replacement therapy usage in postmenopausal women can contribute to an increased risk of certain subtypes of breast cancer [22]. However, this increased estrogen exposure has not been shown to significantly increase breast, endometrial, or ovarian cancer risk in obese postmenopausal women [23–27]. Finally, a change in fat distribution is observed in postmenopausal women, likely due to pro-androgen hormonal shifts, causing an accumulation of central fat compared to premenopausal women [28]. This central obesity has been linked to a greater risk of colorectal cancer in women [29].

WAT homeostasis and inflammation

Development of WAT inflammation

Obesity is often described as a state of chronic inflammation, primarily in the white adipose tissue (WAT). The WAT consists of a complex network of cells including adipocytes and immune cells like neutrophils, lymphocytes, and macrophages. One of the hallmarks of obesity-mediated inflammation is the presence of crown-like structures, which are the clusters of macrophages that form around dying/dead adipocytes in the WAT. This pathology is a defining feature of WAT inflammation. While it is commonly observed in obese patients, crown-like structures and WAT inflammation can also be seen in patients with normal BMI [30]. Homeostasis in the WAT of lean individuals is maintained by several anti-inflammatory cell types, such as the T regulatory (T_{reg}) population through the release of cytokines like interleukin (IL)-10 and IL-4. These T_{regs} are also responsible for maintaining insulin sensitivity in lean adipose tissue [31]. In addition, adipose stromal cells produce IL-33, which helps maintain the type 2 innate lymphoid cells that release type 2 cytokines like IL-4 and IL-5 [32]. Further, this environment supports the M2 macrophage phenotype, which suppresses the pro-inflammatory M1 phenotype [33]. The adipose tissue hypoxia and mechanical stress that results from obesity disrupts this balance and triggers nuclear factor kappa B (NF-κB)-related pathways, inducing inflammatory changes in the WAT [34–37].

Adipocytes secrete the adipokine leptin, which regulates metabolism and satiety through signaling to the hypothalamus [38, 39]. In the obese WAT, healthy expansion of the adipose tissue occurs through adipogenesis, wherein the preadipocytes become mature adipocytes. However, excess calorie intake can result in adipocyte hypertrophy or increased fat accumulation into mature adipocytes, which is marked by hypoxia and subsequent inflammation [40]. Additionally, patient-derived adipocytes show increased leptin and pro-inflammatory cytokine secretion with increased adipocyte size, while anti-inflammatory IL-10 and IL-1ra and adiponectin secretion are decreased [41–43]. Furthermore, hypoxia inhibits the differentiation of preadipocytes to mature adipocytes and promotes the synthesis of leptin and inflammatory cytokines by these preadipocytes [35]. Increased leptin production by the WAT and the stressed environment of the tissue results in the recruitment of pro-inflammatory factors to the region [44]. Inflammation in this region also induces T-cells to break out of the tolerogenic state and become more Th1-like, further exacerbating the inflammation [45, 46]. The increased production of leptin and inflammatory cytokines like tumor necrosis factor alpha (TNF-α) results in a persistent insult to the WAT that also promotes a paradoxical leptin resistance commonly observed in the obese WAT [47, 48]. This resistance plays a key role in promoting obesity, sustaining the stressful WAT environment and chronic inflammation. Although some studies show the presence of metabolically healthy obese individuals who do not present with adipose inflammation, they are still at increased risk for later insulin resistance, type II diabetes, and cardiovascular disease [40].

WAT inflammation and cancer

Chronic inflammation is associated with an increased risk of several cancers [49]. Dysfunctional adipose tissue also results in altered adipokine profiles, increased pro-inflammatory cytokines, and hypoxia, which can all promote tumor progression [50]. Many pathways involved in carcinogenesis are implicated in the inflammation process as well, including STAT3/5 as well as toll-like receptor (TLR) recognition initiated inflammasome activation [51–53]. Additionally, increased aromatase activity in the WAT due to increased adiposity is correlated with WAT inflammation[30]. In vitro, prostaglandin E2 (PGE2) production by breast cancer cells and macrophages was shown to be enhanced by obese patient-derived sera, and this PGE2 was shown to promote aromatase production in preadipocytes [54, 55]. Furthermore, WAT inflammation in obese women has been shown to correlate with metastatic progression in breast cancer [56]. M1 macrophage-derived TNF-α has also been shown

to promote ovarian cancer cell metastasis through the NF-κB pathway, and accumulation of these macrophages in the adipose tissue has been observed in obese individuals [57].

Leptin signaling

Leptin receptors and resistance

Leptin is a member of the adipokine family of hormones that work to regulate energy metabolism through interaction with the arcuate nucleus of the hypothalamus. It is primarily produced by adipocytes and signals satiety to the brain. Leptin interacts with cells through the leptin receptor, Ob-R, which is found on several cell types. Through RNA splicing, there are six isoforms of this receptor, with five forms predominating: the long Ob-Rb and four short forms (Ob-Ra, Ob-Rc, Ob-Rd, and Ob-Rf). The sixth form, Ob-Re, is a secretory form that lacks intracellular domains and has been mostly shown to provide a quenching effect on circulating leptin as a regulatory mechanism [58]. The long form, Ob-Rb, is found in the hypothalamus and on B and T lymphocytes where it influences their activity [59]. Ob-Rb differs from the other forms of Ob-R by also expressing suppressor of cytokine signaling (SOCS) motifs, which suppress leptin signaling. The commonly found short form of the leptin receptor, Ob-Ra, is expressed on multiple cell types, like those of the kidney and liver as well as macrophages. Signaling through the leptin receptor can take place via the JAK-STAT3/STAT5, PI3K/Akt, and MAPK (SHP2-dependent and SHP2-independent) pathways [58].

Obese individuals tend to have high levels of circulating leptin and present with "leptin resistance." While the mechanism of leptin resistance has not been clearly elucidated, some proposed mediators include decreased leptin permeability through the blood brain barrier due to increased leptin concentrations in the brain, downregulation of the Ob-Rb isoform in the presence of excess leptin, and delayed cell surface receptor expression [60, 61]. These mechanisms suggest that leptin resistance primarily affects the hypothalamic neurons, while leptin sensitivity may be retained in other cell types. It has been shown that neuronal deletion of SOCS3 restores leptin sensitivity in diet-induced obese mice [62].

Inflammatory role of leptin

Leptin has been shown to promote the production of IL-2 and interferon gamma (IFN-γ) in stimulated T cells while suppressing T_{reg} proliferation [63–65]. Leptin also skews the monocyte and macrophage populations to the pro-inflammatory type by stimulating the release of TNF-α and IL-6 in vitro [66, 67]. Furthermore, leptin and other adipokines have been shown to regulate the activity of inflammasomes, large multimolecular complexes that are key players in the innate immune system and the development of obesity-associated adipose tissue inflammation [68]. Leptin has specifically been linked to an inflammasome-mediated increase in macrophage production of IL-18 in vitro [69]. Although leptin has been shown to be involved in several pro-inflammatory processes, subphysiological to physiological doses of leptin have an anti-inflammatory effect through the reduction of circulating macrophage chemoattractant protein (MCP)-1 and IL-6, potentially by downregulating their mRNA expression in adipose tissues [70]. This anti-inflammatory effect has also been observed in glial cells as well as models of pancreatitis and acute colitis [71–73].

Leptin and cancer

Leptin is involved in many cancer-promoting mechanisms including proliferation, chemoresistance [74–76], and angiogenesis [77, 78]. In vitro studies have shown that leptin not only supports the proliferation of cancer cells through pathways like the Wnt pathway, but also promotes the expression of epithelial-to-mesenchymal transition-related genes through the PI3K/Akt pathway [79, 80]. Furthermore, leptin promotes the migration and invasion of several cancer types including breast, lung, prostate, and ovarian cancer. In addition to adipocytes and immune cells, cancer stem cells also express the leptin receptor, and in vitro leptin has been shown to promote cancer stem cell enrichment in breast cancer through the induction of stem cell transcription factors NANOG, OCT4, and SOX2 in a STAT3-dependent manner [81, 82]. Leptin from adipose stromal/stem cells in the tumor microenvironment can also promote the metastasis of estrogen receptor positive breast cancer [83].

Hyperinsulinemia and insulin resistance

Insulin is another hormone implicated in obesity-associated cancers. Insulin plays a key role in adipocyte maintenance through various mechanisms, including generation of adipocytes from preadipocytes as well as lipogenesis [84]. Chronic inflammation promotes insulin resistance in many obese individuals, as shown in studies assessing systemic inflammation and insulin resistance [85]. Insulin promotes triglyceride storage into adipocytes, which prevents their degradation by lipases into free fatty acids (FFA). These FFAs are often elevated in the plasma of obese patients and can cause insulin resistance in secondary sites like the skeletal muscles due to the accumulation of lipid products like fatty acyl-CoA, which interfere with the insulin signaling cascade [86]. FFAs can also act in a pro-inflammatory manner by binding the toll-like receptors TLR2 and TLR4, which then activate the NF-κB pathway to induce the

release of TNF-α and MCP-1 and therefore further increase pro-inflammatory immune cell infiltrations into the region [87]. The pro-inflammatory cytokine TNF-α has also been shown to induce insulin resistance via activation of inhibitor of nuclear factor kappa B kinase subunit beta (IKK-β) and subsequent serine phosphorylation of the insulin receptor, which interferes with insulin signaling [88].

Conversely, insulin signaling has been linked to adipose tissue inflammation in obese individuals. Some studies report elevated adipose tissue inflammation and macrophage infiltration in diabetic patients receiving insulin [89]. In addition, a reduction in circulating insulin levels in obese mice resulted in a significant decrease in adipose tissue inflammation [90], likely by preventing insulin-induced (via ERK signaling) production of MCP-1 from adipocytes, which can occur even in the context of insulin resistance [91].

Insulin and cancer

Increased circulating insulin can contribute to carcinogenesis as in vitro studies show chronic exposure to insulin and glucose promotes proliferation and aberrant chromosomal alterations in melanocytes [92]. In colon cancer cells, chronic insulin exposure also results in increased chemoresistance to the drugs oxaliplatin and SN38 in vitro [93]. In addition, overexpression of insulin receptor substrate-1 (IRS-1) aids in cell proliferation and inhibits autophagy in fibroblasts [92, 94]. Hyperinsulinemia-induced increases in IRS-1, as seen in patients, also promote colon and endometrial cancer progression [95, 96]. Further, in humans and mouse models, hyperinsulinemia results in increased expression of insulin-like growth factor-1 [97], which has been shown to promote metastasis [98, 99]. Additionally, insulin resistance has been linked to an increased risk of breast, pancreatic, endometrial, colorectal, and prostate cancer [99–103].

Obesity-mediated immune cell dysfunction in the adipose tissue

Adipose tissue homeostasis maintained by suppressive immune cells like T_{reg} cells, regulatory B cells (B_{regs}), and M2-like macrophages is disturbed in obese conditions, with increased TNF-α and MCP-1 production by the adipocytes resulting in a pro-inflammatory immune profile [104]. In obese individuals, this chronic inflammation alters the immune profile to not only an inflammatory type but also a dysfunctional one as shown in Fig. 1. Chronic inflammation has been associated with an increased risk of several cancers like colon, pancreatic, and ovarian cancer [105], and pro-inflammatory alterations in the immune profile of WAT are also associated with higher cancer risk [106].

Adaptive immune cells

T cells

Obesity modulates the antigen specific adaptive population of the immune system. It accelerates T cell senescence in the visceral adipose tissue (VAT) of HFD-fed mice, resulting in T cells that resemble those typically found in aging VAT [107]. In human and murine adipose tissue, increased adiposity results in the activation of NF-κb pathways, which induce the expression of inflammatory cytokines that recruit Th1-like cells to the region [45, 108]. Th1 cells secrete additional IL-6 and IFN-γ in the WAT microenvironment, exacerbating the inflammation [46]. Increased leptin expression also aids in induction of pro-inflammatory cytokines from the T cells, which express the long form of the leptin receptor (Ob-Rb) [109]. In addition, leptin appears to be important in lymphocyte generation and development since leptin-deficient ob/ob [39] and leptin receptor-deficient *db/db* mice [110, 111] exhibit a significant reduction in functional T cells [112].

Obesity in mice has also been shown to predispose the T-cell type to Th17 due to increased IL-6 presence [113]. Th17 cells are a helper T cell type characterized by the production of the pro-inflammatory cytokine IL-17 and the transcription factor RAR-related orphan receptor gamma t (RORγt). T cells in obese mice selectively promote Th17 cells and these cells produce a greater amount of IL-17, which was abrogated in $IL6^{-/-}$ mice [113]. In addition to IL-6, Th17 cells are also induced through the IL-21 pathway. Obese mice show increased expression of IL-21 in the adipose tissue, which has been shown to promote IL-17 expression in Th17 cells in an autocrine process that is STAT3-dependent [114]. Furthermore, this population is maintained and supported by IL-23 secreted by adipose tissue dendritic cells (DCs) [115, 116]. In the adipose tissue, obesity results in increased fatty acid metabolism and acetyl CoA carboxylase 1 expression. This enzyme modulates RORγt function in Th17 cells, promoting their growth in obese individuals [117].

As the major T cell population in lean adipose tissue, T_{regs} are important for homeostasis through their anti-inflammatory actions. The VAT in mice contains more T_{regs} than the spleen, lung, and liver, but these numbers decline in obese mice, highlighting their importance in the adipose tissue [46]. The increased circulating leptin in obese mice can bind leptin receptors expressed on T_{reg} cells to suppress their proliferation and negatively regulate their anti-inflammatory activity [65]. Furthermore, these cells have decreased forkhead box P3 (FOXP3) expression and are in an anergic state, which can be reversed with a leptin monoclonal antibody. Monoclonal antibody blockade of leptin signaling also results in increased ERK1/2 phosphorylation, which restores

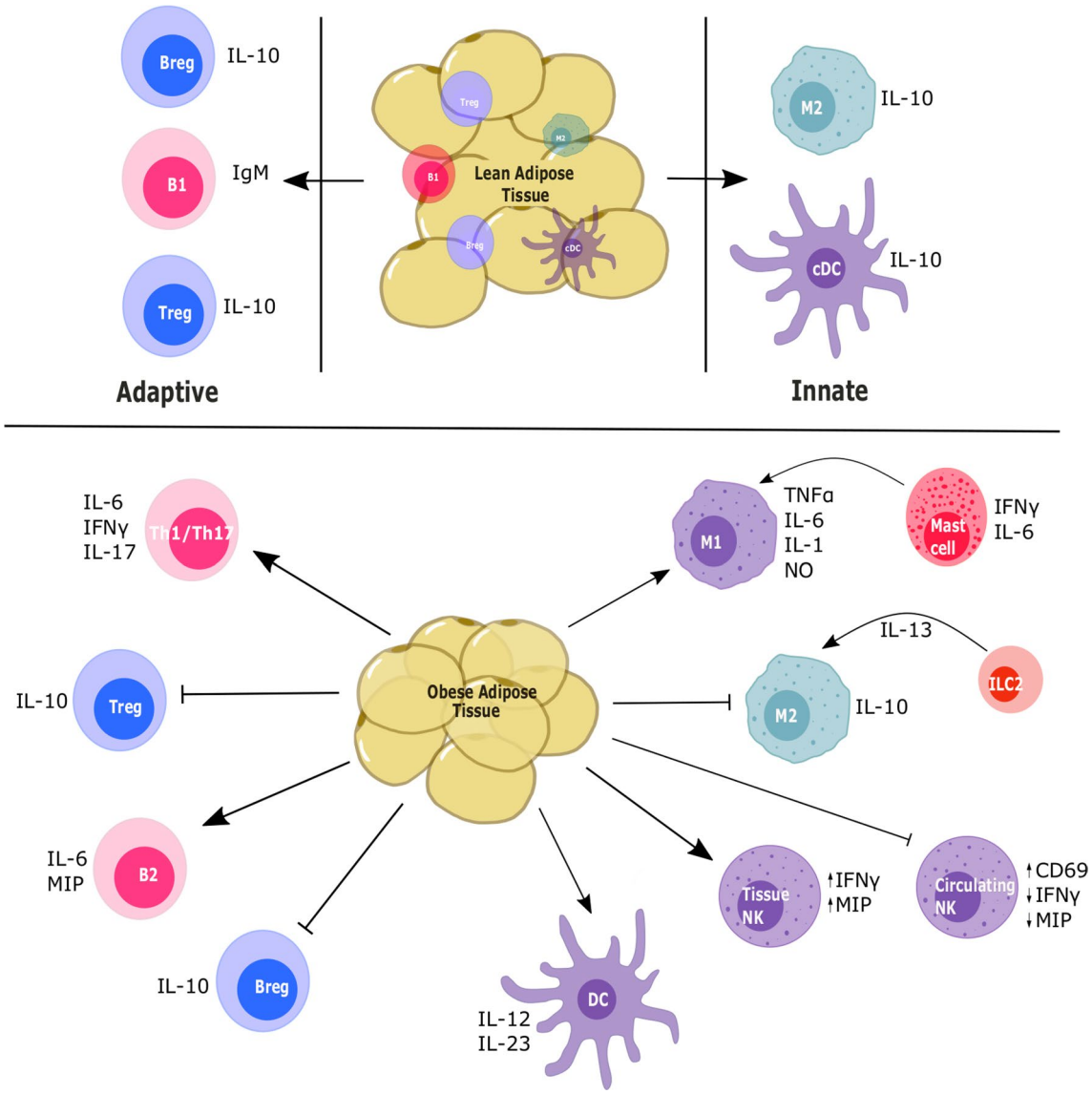

Fig. 1 Schematic showing the immune profile of the lean and obese adipose tissue. The immune profile of the obese adipose tissue is generally skewed toward the inflammatory phenotype due to the presence of cytokines like IL-6 and TNF-α secreted by the adipose tissue as a result of mechanical stress, hypoxia, and necrosis

T_{reg} cell responsiveness [65]. Adipocyte-derived IL-21 also suppresses T_{reg} accumulation in the VAT, and IL-21 knockout improved T_{reg} numbers, reduced body weight, and improved insulin sensitivity in HFD-fed mice [118].

B cells

Obesity also affects B-lymphocyte development and function. B cells express the leptin receptor (Ob-Rb) [59] and respond to leptin by upregulating expression of the pro-inflammatory cytokines IL-6 and TNF-α as well as anti-inflammatory IL-10 [119]. Leptin plays an important role in not only T cell development but hematopoiesis in general, and this has been shown through reduced B cell numbers in both *db/db* and *ob/ob* mice [120, 121].

B cells promote inflammation by modulating T-cell function through release of pro-inflammatory cytokines like IL-6 and macrophage inflammatory protein 2 (MIP-2, also known as CXCL2) [122]. While the role of B cells in adipose tissue is not clearly understood, obesity-associated inflammation has been linked with suppressed B cell responses through leptin-mediated STAT3 induction of TNF-α [123], which in unstimulated B cells results in preactivation and lack of response to further antigenic stimulation [124]. Further, B cells derived from obese individuals showed impaired IL-6 secretion and increased immunoglobulin IgM levels upon

stimulation, and an impaired response was also observed in B cells from HFD-fed mice [125]. However, others have shown that B cells accumulate in the VAT of obese individuals and are responsible for the activation of inflammatory macrophages and T cells here as well production of IgG autoantibodies, promoting insulin resistance [126]. Additionally, depletion of B cells in HFD-fed mice led to a decreased inflammatory profile, improved insulin sensitivity, and alterations in the IgG profile [126].

An anti-inflammatory regulatory B-cell type (B_{regs}), similar to T_{regs}, can also be found in the adipose tissue. These B_{regs} constitutively produce IL-10, which inhibits adipose tissue inflammation. In diet-induced obese mice, deletion of IL-10 from B cells results in increased $CD8^+$ T cell and M1 macrophage infiltration in the adipose tissue and reduced insulin sensitivity [127]. Further, decreased frequencies of B_{regs} were observed in the adipose tissue and peripheral blood of overweight and obese individuals compared to normal weight individuals [128].

Innate immune cells

Macrophages

In the adipose tissue, resident macrophages are found in the M2-like state, maintaining homeostasis [129]. Obesity affects this homeostasis, as seen with the WAT inflammation mentioned previously. Important to this process is the formation of crown-like structures (CLS) in the adipose tissue where, due to mechanical stress and hypoxia in the adipocytes, M1-like macrophages surround dead or dying adipocytes [85, 130]. In mice and human subjects, CLS are responsible for the release of several types of damage-associated molecular patterns, which bind with nod-like receptors on the macrophages, activating NF-κb-mediated release of MCP-1 [131] and TNF-α [132] and thereby promoting regional inflammation. Although it is a marker for DCs, CD11c expression is observed on M1-like macrophages that accumulate in the adipose tissue of obese mice but not in lean mice [133, 134]. In addition, obesity-induced leptin resistance enhances the release of FFAs, which bind TLRs on the macrophages and therefore promote the expression of pro-inflammatory genes, further contributing to WAT inflammation [135, 136]. Macrophages and monocytes also express the leptin receptor and produce pro-inflammatory cytokines like TNF-α and IL-6 in response to leptin [66, 137, 138]. Macrophage production of several other pro-inflammatory factors, such as IL-1β, nitric oxide (NO) and IFN-γ, can also be induced by leptin in vitro [138, 139]. Furthermore, obesity-associated TNF-α release in mice has been associated with an increase in circulating monocytes, which contribute to insulin resistance and subsequent hyperinsulinemia [140]. Studies have also shown that higher plasma levels of MCP-1 in the leptin receptor-deficient *db/db* mouse model of obesity or adipocyte specific-MCP-1 overexpressing mice results in increased macrophage recruitment into adipose tissues, which promotes insulin resistance [141, 142].

Dendritic cells

DCs are critical antigen presenting cells responsible for T cell activation. In lean mice, conventional DCs in the adipose tissue promote a tolerogenic state through IL-10 production as well as upregulating Wnt and PPARγ pathways, which regulate adipocyte differentiation and limit T cell activation [143, 144]. These lean adipose tissue anti-inflammatory DCs have not been identified in humans, but adipose tissue resident DCs have been found to contribute to inflammation and insulin resistance through the induction of Th17 cells in both mice and humans [145]. In humans, a positive correlation was observed between BMI and CD11c + CD1c + DCs, which induced Th17 responses ex vivo. $CD11c^{high}F4/80^{low}$ DCs from mice also induced Th17 cells [146]. DCs also express the leptin receptor, and leptin promotes a pro-inflammatory DC phenotype [147]. In contrast, DCs obtained from leptin-deficient *ob/ob* and leptin receptor-deficient *db/db* mice have impaired functioning due to reduced expression of co-stimulatory molecules and inability to stimulate allogeneic T cells [148, 149]. In vitro, leptin has been shown to stimulate increased DC production of IL-12, but not IL-10 or transforming growth factor beta (TGF-β). IL-12 favors the polarization of CD4 + T cells to the pro-inflammatory Th1 and Th17 type [150].

Natural killer cells

Natural killer (NK) cells, while part of the innate system, exhibit lymphoid-like features due to shared lineage with T and B lymphocytes. Obese patients have been shown to have significantly lower levels of circulating NK cells compared to lean controls [151]. Further, circulating NK cells from obese patients show increased activation through CD69 upregulation, but they are functionally impaired with decreased IFN-γ and macrophage inflammatory protein (MIP)-1β production [152]. Furthermore, obesity reduces circulating NK cell degranulation, despite increased CD69 levels, suggesting greater activation and exhaustion of these cells in comparison to lean controls [153]. NK cells from obese individuals also have decreased oxidative phosphorylation and glycolytic activity upon cytokine stimulation [154]. This metabolic dysfunction results in decreased cytotoxic function in terms of perforin and granzyme activity as well as decreased anti-tumor activity. However, a subsequent study found no difference in the total NK cell population between obese and normal weight humans, but did note that the low cytotoxic $CD56^{bright}$ NK cell population was

increased in obese individuals compared to the cytotoxic CD56^{dim} phenotype [155].

Other cell types

Additionally, other innate cells are involved in maintaining adipose tissue homeostasis. Innate lymphoid cells have been shown to promote an anti-inflammatory Th2 environment by sustaining the alternatively activated macrophage population [156]. Neutrophils express the short form of the leptin receptor (Ob-Ra). However, leptin only plays an indirect role in neutrophil migration and activation in vivo, which is directly mediated by the release of TNF-α from monocytes and chemokine (C-X-C motif) ligand 1 (CXCL1) from peritoneal cells [157, 158]. In pancreatic cancer, tumor-associated neutrophils are recruited by adipocyte-derived IL-1β and activated pancreatic stellate cells, which release additional IL-1β to further increase neutrophil recruitment and therefore promote cancer progression and chemoresistance [159].

Another immune population, the mast cell, also expresses the leptin receptor [160] and is increased in the WAT of obese individuals. These cells have been shown to promote obesity and glucose intolerance, as well as adipose tissue apoptosis and angiogenesis, through release of IL-6 and IFN-γ [161]. Further, leptin-deficient (*ob/ob*) mast cells were shown to play a protective role when administered to wild-type diet-induced obese mice, mitigating obesity and diabetes by aiding in polarization of WAT macrophages to the anti-inflammatory M2-type [162].

Obesity-mediated immune cell dysfunction in the tumor microenvironment

The tumor microenvironment is generally considered to be immunosuppressive due to the presence of IL-10 and TGF-β and the suppressive properties of various cell types like myeloid-derived suppressor cells (MDSCs), M2 macrophages and T_{regs} in addition to the cancer cells as shown in Fig. 2. In the obese tumor microenvironment, the involvement of the adipose tissue and adipokines like leptin and adiponectin can influence the immune profiles as well.

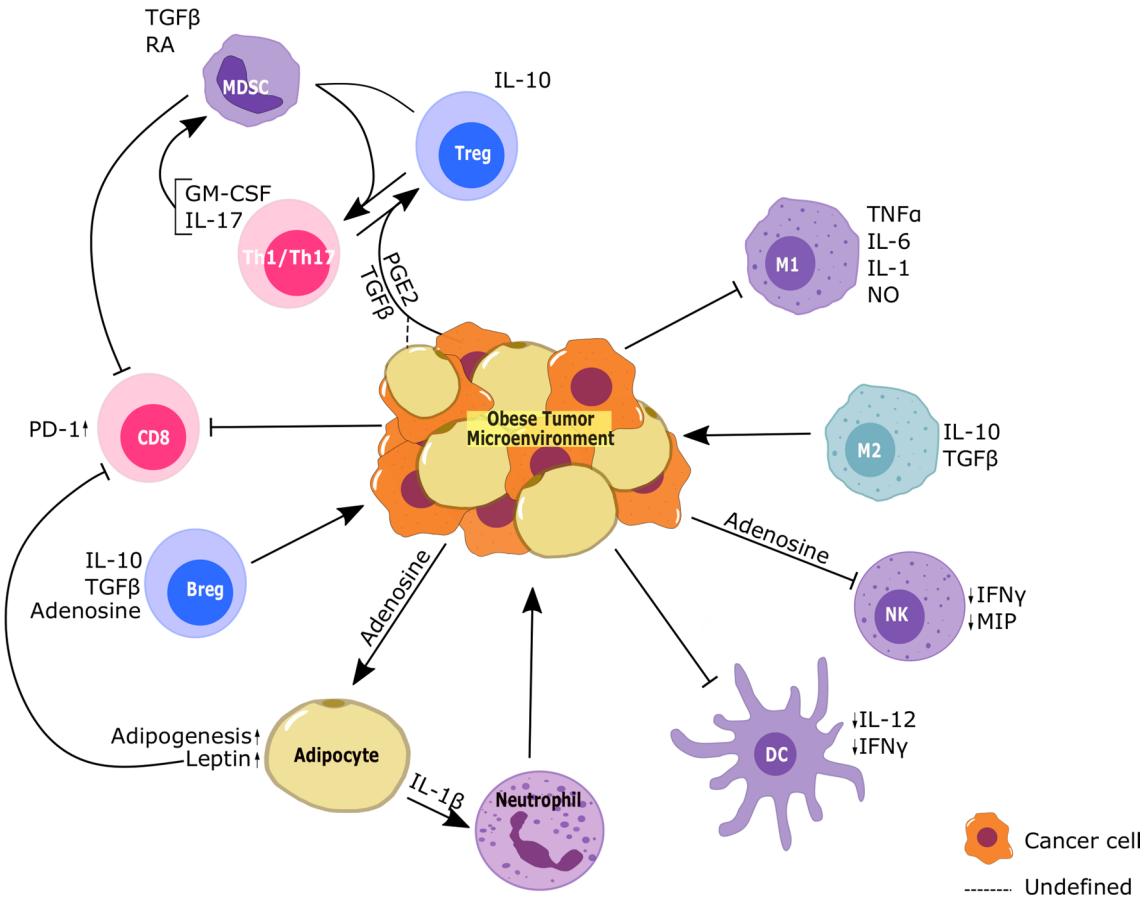

Fig. 2 Schematic showing the immune profile of the obese tumor microenvironment. Unlike the adipose tissue, due to the immunosuppressive factors from the cancer cells, the obese tumor microenvironment is infiltrated by mostly suppressive populations such as M2 macrophages, MDSCs, and T_{regs}

Adaptive immune cells

T cells

Obesity has been shown to promote immune exhaustion through upregulation of PD-1 on CD8 + T cells, as seen in the tumors of HFD-fed mice [163]. This effect has been beneficial in mouse models of breast cancer, lung cancer, and melanoma as well as colorectal cancer patients in their response to PD-1/PD-L1 blockade [164]. Further, treatment with anti-PD-1 antibodies in esophageal cancer not only improved the killing capacity of the T cells but also reduced the number of PD-1 + T cells in the tumors [165]. Increased T cell PD-1 expression has been linked to leptin signaling through an indirect mechanism involving the STAT3 pathway as leptin resistant *db/db* T cells had decreased PD-1 expression compared to wild-type T cells after adoptive transfer into tumor bearing diet-induced obese $Rag2^{-/-}$ mice [164].

Th17 and Treg: the inflammatory environment in obesity favors the generation of Th17 cells through the release of not only IL-23 from the adipose DCs but also through IL-1β released from adipose macrophages [166]. While Th17 is generally an inflammatory T cell type, Th17 cells in the tumor microenvironment often promote tumor progression by inducing infiltration of pro-tumor immunosuppressive MDSCs [167] as well as angiogenesis and chemoresistance through granulocyte–macrophage colony stimulation factor (GM-CSF) and IL-17 secretion and stimulation of vascular endothelial growth factor (VEGF) production [168–170].

In colorectal cancer patients, Foxp3 + IL-17 + T cells are present in the microenvironment that not only express high levels of TGF-β and RORγt, but can also promote the induction of cancer initiating cells ex vivo [171]. These T cells have immunosuppressive effects in colon cancer patients despite releasing high levels of IL-17 [172]. Further, Foxp3 + RORγt + regulatory T cells also have immunosuppressive activity as seen in pancreatic cancer patient samples through suppression of T cell proliferation. However, they can also be pro-inflammatory through release of TGF-β and IL-6, which promote IL-17 production from T cells, and through their own production of IL-17 [173]. MDSCs have been shown to promote the induction of T_{regs} and the transdifferentiation of Th17 to T_{regs} through TGF-β and retinoic acid [174]. In the tumor microenvironment of an ovarian cancer mouse model, tumor-derived TGF-β and PGE2 were also shown to promote the transdifferentiation of Th17 cells to suppressive T_{regs}, and these Th17-T_{reg} subsets have been identified in patient samples [175]. The enzyme cyclooxygenase-2 (COX2), which is responsible for the production of prostaglandins like PGE2, is highly expressed in adipose tissue [176], and COX2 signaling is also upregulated in the subcutaneous adipose tissue of obese individuals [177]. Hence, adipocyte-derived PGE2 could contribute to the generation of an immunosuppressive T cell population. Further, adipocyte-derived TGF-β, which has been shown to be increased in the adipose tissue of *ob/ob* and *db/db* mice [178], can also contribute to this Th17-T_{reg} subset.

B cells

Tumor-infiltrating B cells are generally associated with a positive outcome in anti-tumor immunity [179] and are comprised of activated B cells [180, 181]. B cells are recruited to the tumor microenvironment through the action of CXCL13, produced by the tumor cells. This chemokine is also produced by mature adipocytes [182].

However, several studies in mice have shown that B_{reg} infiltration into tumors causes immunosuppression through IL-10 production and therefore promotes tumor growth [183]. B_{reg} cells have also been shown to promote tumor growth in head and neck cancer patients through an increase in the production of adenosine seen ex vivo [184], which suppresses the cytotoxicity of NK cells. However, the role of tumor-infiltrating B cells in the obese TME has not been fully characterized.

Innate immune cells

Macrophages

Obesity results in the increased recruitment of macrophages to the tumor microenvironment, which are then polarized to the M2-like tumor-associated macrophages (TAMs) that promote an immunosuppressive tumorigenic environment [185]. Although M2 to M1 polarization does occur in the adipose tissue, this skewing has not been observed in tumors, where M2-like TAM cells predominate [135, 163]. TAMs contribute to cancer progression through the release of TGF-β, promoting cancer growth and suppressing immune response [186, 187]. Angiogenesis is an important factor in breast cancer progression, and macrophages have also been implicated via in vitro studies in the promotion of stromal vascularization and angiogenesis through CXCL12 when recruited and activated by adipocyte-derived MCP-1 and IL-1β [188]. Of note, exosomes derived from melanoma cells were shown to be able to generate a hybrid M1/M2 macrophage type in vitro with upregulation of both types of macrophage markers. These macrophages were associated with pro-tumor activity [189].

Dendritic cells

DCs play an important role in antigen presentation and T cell education. In the tumor microenvironment of diet-induced obese mice, there is an increase in the inhibitory type of DC,

which suppresses T cell proliferation [190]. Further, these cells also produce less IL-12 and TNF-α than DCs in normal weight mice, which contributes to their impaired functionality and results in reduced T cell function [190].

Natural killer cells

NK cells express both long and short forms of the leptin receptor [191]. Leptin plays an important role in the development of NK cells, as leptin receptor deficiency in *db/db* mice decreases NK cell numbers in the liver, spleen, lung, and peripheral blood and also impairs the activation of these cells [192]. Interestingly, leptin treatment in a hepatocellular carcinoma mouse model suppressed tumor progression through the increased proliferation and activation of NK cells [193]. However, obesity in humans results in significantly reduced hepatic NK cell numbers as well as Ob-Rb expressing NK cells [194]. Resistance to leptin signaling through suppressed downstream JAK/STAT signaling has also been implicated in the NK cell dysfunction in diet-induced obese rat models [195]. This suggests that while leptin promotes NK cell activity, obesity results in dysfunctional NK cells, leading to impaired tumor immunity. Dysfunctional NK cells have also been implicated in promoting metastasis in *db/db* and *ob/ob* mice due to their lack of leptin signaling [196].

In addition to increased leptin and hyperinsulinemia, obesity also results in increased circulating levels of adenosine [197]. Adenosine is implicated in dampening immune responses and, like adipocytes and B_{reg} cells, cancer cells produce adenosine through CD73 and CD39 activity. NK cells recruited to the tumor microenvironment express the A2a receptor, which binds adenosine, and this results in decreased cytotoxic functionality [198].

Metastatic microenvironment

The metastatic potential of tumors is influenced by several factors, including mutational burden of the tumor, expression of genes promoting metastasis, and the cancer type, as some cancers are more susceptible to metastasis [199, 200]. However, obesity has also been shown to contribute to increased metastasis in several cancers such as breast, prostate, and colorectal cancer [201].

The innate immune population of myeloid-derived cells are seen as key players in metastasis due to their pro-angiogenic (VEGF) actions and pro-inflammatory actions (TNF-α) [202]. Comparison of the primary tumors and metastatic lesions in murine breast cancer models show an increase in polymorphonuclear neutrophils in the latter, while the primary tumors show increased inflammatory monocytes [203]. In the breast cancer 4T1 mouse model, HFD diet-fed mice showed decreased survival through increased tumor volumes as well as lung and liver metastasis [204]. Further, in vitro studies show increased proliferation, migration, and invasion capacity of the cancer cells when treated with cytokines elevated specifically in the HFD-fed mice, such as macrophage colony-stimulating factor (M-CSF) [204]. In breast cancer, obesity also results in increased neutrophil count causing neutrophilia, which has been shown to promote lung metastasis through the release of GM-CSF and IL-5 by the lung neutrophils [205]. In obesity resistant mice, HFD was sufficient to promote tumor growth and lung metastasis in colon cancer through expression of genes regulating inflammation and proliferation [206]. These mice also show increased macrophage infiltration into the adipose tissue [206].

The tumor metabolite sphingosine-1 phosphate (S1P), formed by the phosphorylation of sphingosine by sphingosine kinase 1, is upregulated by HFD in both syngeneic and spontaneous tumor models of breast cancer [207]. S1P results in increased macrophage recruitment to the lungs, a common site of breast cancer metastasis, and IL-6 produced by the infiltrating cells helps promote lung metastasis. The role of IL-6 in promoting breast cancer metastasis has also been shown in other studies [208, 209]. HFD also increases circulating cholesterol, and its derivative 27-hydroxycholesterol has been shown to increase the neutrophil count (IL-17 responders) as well as γδ-T cells (IL-17 producers) in metastatic sites while decreasing the CD8 + T cell count [210].

Obesity's implications for current therapies

Chemotherapy and adipose tissue-mediated chemoresistance

Several studies have also shown that increased adiposity results in poorer response to chemotherapy. In a retrospective study of breast cancer patients enrolled in the BIG 2–98 adjuvant clinical trial comparing docetaxel-based and non-docetaxel-based chemotherapy, BMI > 30 kg/m^2 was associated with lower overall and disease-free survival rates in those receiving docetaxel-based therapies [211]. Excess visceral adipose tissue in postmenopausal breast cancer patients has been linked to decreased chemosensitivity [212–214]. In vitro studies have shown that adipose stromal cells can promote chemoresistance in prostate cancer cells by inducing the expression of epithelial-to-mesenchymal transition-related genes like *Cdh2, fibronectin, vimentin, Zeb2*, and *Slug1* [215]. In ovarian cancer, adipocytes have been shown to promote chemoresistance through upregulation of genes involved in apoptosis like Bcl_{xl} [216]. Adipocyte-derived leptin can also promote resistance to the taxane chemotherapy paclitaxel in breast cancer cells via increased fatty acid oxidation [217]. Further, adipocytes can metabolize

chemotherapy drugs, rendering them inactive, as seen in the conversion of daunorubicin to inactive daunorubicinol [218]. Prevention of doxorubicin uptake through its accumulation into cytoplasmic vesicles and eventual expulsion via upregulation of transport proteins like major vault protein has also been observed in co-cultures of adipocytes and breast cancer cells [219]. Fatty acid synthase (FASN) is an important enzyme in de novo lipogenesis and is upregulated in several cancers. Melanoma tumors from HFD-fed mice had increased FASN expression compared to normal diet mice, while conditioned media from obese patient-derived adipose macrophages (but not monocyte-derived macrophages) stimulates FASN expression in breast cancer and colon cancer cells [220, 221]. This FASN overexpression promotes resistance to the chemotherapy drug cisplatin in breast and ovarian cancers, which can be overcome by treatment with the FASN inhibitor C75 [222, 223]. However, FASN expression in renal cancer was shown to be inversely correlated with obesity, and high BMI was determined to be a prognostic factor for longer survival and response to targeted therapy. These findings highlight the importance of varying BMI considerations for different cancers [224]. Overall, excess adipose tissue surrounding solid tumors like breast cancer can make it challenging to effectively target the cancer cells, which are being affected by the fatty acids, adipokines, and multiple other factors produced by that adipose tissue.

Another major challenge to effective chemotherapy treatment in obese cancer patients is under-dosing. Previously, up to 40% of obese patients were under-dosed because clinicians did not use patients' actual body weights to calculate doses, resulting in a variation of up to 25% in calculated doses for patients at the same body weight. The under-dosing was largely due to concerns about increased susceptibility to chemotherapy toxicity in obese patients, though there was no evidence of elevated short- or long-term toxicity with chemotherapy doses based on their full weight. The American Society of Clinical Oncology published practice guidelines in 2012 indicating that obese patients' full weight should be used for dose calculations since toxicity concerns are limited and under-dosing results in greater risks [225]. Further, several clinical trials are currently being conducted to assess obese patients' response to chemotherapy drugs for various cancers, which will help shed light on the efficacy of these drugs in the context of obesity (Table 1).

Endocrine therapy

In prostate and breast cancer, endocrine therapies such as androgen agonists and aromatase inhibitors (AI) are commonly administered to control tumor growth. AIs like anastrozole, letrozole, and exemestane are used in breast cancer to decrease estrogen production. However, increased adiposity results in a greater concentration of circulating estradiol in obese postmenopausal patients due to greater aromatase activity in their adipose tissue, leading to concerns regarding the effectiveness of AIs in obese breast cancer patients [226]. Trials involving AIs versus tamoxifen (ATAC, BIG 1–98, TEAM, ABCSG-12) have in some cases suggested that AIs can be more beneficial than tamoxifen in women with higher BMI, but results are inconsistent [226, 227].

Immunotherapies

In more recent years, immune-based targeted approaches to cancer therapy have emerged. Some examples include chimeric antigen receptor (CAR), monoclonal antibody, and cytokine therapies.

In CAR-based therapies, patients' immune cells are genetically modified to express a cancer antigen specific receptor, enhancing their anti-tumor ability. However, the increased cytotoxicity of CAR-based therapy, particularly in CAR-T cells, can produce a severe immune reaction in which too many cytokines are released too quickly, known as a cytokine storm. Given the underlying chronic inflammation present in most obese patients, these individuals may be at particularly high risk of adverse side effects from such CAR-based therapies. In addition, monoclonal antibody treatment in aged mice with increased adiposity and pre-existing inflammation has been shown to further increase inflammation as well as morbidity, relative to young lean mice [228, 229].

While monoclonal antibody therapies such as epidermal growth factor receptor (EGFR) and cytotoxic

Table 1 Clinical trials assessing drug efficacy in obese (BMI ≥ 30 kg/m^2) cancer patients

Cancer	Drug	Study summary	Sex	Trial number
Multiple, advanced	Xeloda (Capecitabine)	Capecitabine pharmacokinetics in patients dosed as per ideal vs actual body weight	A	NCT01828554
Colorectal	Metformin	Assessment of metformin in reduction of pS6Serine235 expression on mucosal tissue	A	NCT01312467
Breast cancer	Doxorubicin, Cyclophosphamide	Assessment of drug plasma clearance between normal weight and obese patients	F	NCT01537029
Endometrial cancer	Metformin	Assessment of effects of metformin administration prior to hysterectomy	F	NCT01877564

T-lymphocyte-associated protein 4 (CTLA-4) blockade (panitumumab and ipilimumab, respectively) have recommended doses based on weight, it has been suggested that fixed dosing be used for cost-effectiveness due to the potency of these therapies [230, 231]. The safety of αPD-1 treatment in obese patients has been prospectively assessed in esophageal cancer, where it was shown to be safe due to a lack of extratumoral pro-inflammatory T cell phenotype rescue in the αPD-1-treated patients [165]. In addition, recent retrospective studies of patients treated with αPD-1/PD-L1 and/or CTLA-4 checkpoint inhibitors have shown improved clinical outcomes in patients with BMI ≥ 25, compared to those with BMI < 25. These studies, which included patients with non-small cell lung cancer, melanoma, and several other cancer types, also found no issues with elevated toxicity in the overweight/obese patients [232–234]. As previously mentioned, obesity has been shown to increase PD-1 expression on cytotoxic CD8 T cells, which promotes tumor progression but also greatly aids in αPD-1/PD-L1 therapy effectiveness in mice and patients [164]. This enhanced efficacy was demonstrated in male patients with metastatic melanoma that received combinations of immunotherapy (trametnib, vemurafenid, nivolumab, cobimetinib, ipilimumab, pembrolizumab, and atezolizumab), as improved survival was observed in the obese men compared to lean men, but this effect was not seen in female patients [235]. For additional information, Deshpande et al. [236] recently published a review extensively detailing the effects of obesity, as well as lifestyle factors and diabetes, on response to checkpoint inhibitors.

Cytokines such as IL-2, IL-7, and IL-15 have also been used as immunotherapeutic agents. Combination therapy of IL-2 with αCD40 in aging obese mice has been shown to exacerbate inflammation, leading to death [228, 229]. However, more studies are needed to determine the safety of interleukin-based cancer therapies in the context of obesity.

Concluding remarks

Obesity-associated chronic adipose inflammation and dysfunction in the development and activity of several types of tumor-infiltrating immune cells have been shown to promote cancer growth as well as metastasis. Immunotherapy-based rescue of the dysfunctional immune cells, alone or in combination with other therapies, could aid in the treatment of obesity-associated cancers. However, additional studies will be needed to evaluate the efficacy and safety of these therapies for specific obesity-associated cancers. Further, obese status needs to be considered during administration for effective dosage to prevent under-dosing as well as overactivation of the immune system. More in vivo model data are also required to properly evaluate the impact of obesity on the immune microenvironment of tumors, as the role of some tumor-infiltrating immune cell types remains poorly characterized. As the rate of obesity continues to increase across the globe, greater understanding of the impact of obesity on the tumor microenvironment will help inform the development of improved treatment regimens, which are urgently needed to reduce the burden of obesity on cancer mortality.

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