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Mechanisms by which obesity regulates inflammation and anti-tumor immunity in cancer

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ABSTRACT

Obesity is associated with an increased risk for 13 different cancers. The increased risk for cancer in obesity is mediated by obesity-associated changes in the immune system. Obesity has distinct effects on different types of inflammation that are tied to tumorigenesis. For example, obesity promotes chronic inflammation in adipose tissue that is tumor-promoting in peripheral tissues. Conversely, obesity inhibits acute inflammation that rejects tumors. Obesity therefore promotes cancer by differentially regulating chronic versus acute inflammation. Given that obesity is chronic, the initial inflammation in adipose tissue will lead to systemic inflammation that could induce compensatory anti-inflammatory reactions in peripheral tissues to suppress chronic inflammation. The overall effect of obesity in peripheral tissues is therefore dependent on the duration and severity of obesity. Adipose tissue is a complex tissue that is composed of many cell types in addition to adipocytes. Further, adipose tissue cellularity is different at different anatomical sites throughout the body. Consequently, the sensitivity of adipose tissue to obesity is dependent on the anatomical location of the adipose depot. For example, obesity induces more inflammation in visceral than subcutaneous adipose tissue. Based on these studies, the mechanisms by which obesity promotes tumorigenesis are multifactorial and immune cell type-specific. The objective of our paper is to discuss the cellular mechanisms by which obesity promotes tumorigenesis by regulating distinct types of inflammation in adipose tissue and the tumor microenvironment.

1. Introduction

Obesity is a widespread chronic disease [1–10]. Obesity is a risk factor for cancer [11–20]. Specifically, obesity increases the risk for 13 different cancers [21]. The prevalence of worldwide obesity has approximately doubled since 1980 such that nearly one-third of the adult world population is now overweight or obese [4]. It is projected that nearly 60 % of the world's population will be overweight or obese by the year 2030 [4]. It is estimated that one in five men and women will develop cancer worldwide and that one in three adults will be overweight or obese, indicating that the majority of adults who will have cancer will also have obesity [4,12]. The global increase in obesity is hypothesized to contribute to the increasing incidence of early-onset cancers, such as colon cancer [22]. The increase in breast cancer incidence also coincides with the surge in obesity [23]. Obesity is positively associated with breast cancer risk in postmenopausal women and inversely correlated with breast cancer risk in premenopausal women [23]. The difference in obesity association with breast cancer based on menopausal age is in part due to estrogen synthesis by breast adipose tissue [23]. Obesity is also linked with increased risk and progression of breast cancer that is negative for the ER, progesterone receptor, and HER2 [24,25]. The increasing incidence of uterine cancer is hypothesized to be in part due to obesity [26–28]. The link between obesity and uterine cancer is especially strong considering obesity increases the risk for this hormone-responsive tumor by 7-fold [21]. Cancer is increased in obesity by several mechanisms, including the promotion of chronic inflammation, and the inhibition of acute inflammation that rejects tumors. Herein, we will review the cellular mechanisms that are involved in obesity-mediated chronic inflammation and suppression of acute inflammation that mediates anti-tumor immunity.

2. Adipokines

2.1. Cytokine effects of leptin

The term adipokine refers to a large group of bioactive molecules released from an adipocyte. Many adipokines have roles in cancer, and

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Abbreviations

APC	Antigen-Presenting Cells
ATP	Adenosine Triphosphate
BC	breast cancer
BRCA	Breast Cancer Associated Gene
CAA	Cancer Associated Adipocytes
CD4	Cluster of Differentiation 4
CD8	Cluster of Differentiation 8
CRC	colorectal carcinoma
CTRP3	Adipokine C1q/Tumor Necrosis Factor Related Protein 3
CTRP9	Adipokine C1q/Tumor Necrosis Factor Related Protein 9
DNA	Deoxyribonucleic Acid
ERK	Extracellular Signal Related Kinase
FGFB21	Fibroblast Growth Factor 21
GLP-1 –	Glucagon Like Peptide −1
HCC	hepatocellular carcinoma
HUVEC	Human Umbilical Vein Endothelial Cells
IGFBP2	Insulin-Like Growth Factor Binding Protein 2
IGF1	Insulin-Like Growth Factor 1
IL-1β	Interleukin 1 Beta
IL-2 –	Interleukin 2
IL-6 –	Interleukin-6
IL-10	Interleukin 10
IL-17 –	Interleukin 17
JAK	Janus Kinase
LepR	Leptin Receptor
MCP1	Monocyte Chemoattractant Protein 1
MDSCs	Myeloid Derived Suppressor Cells
MHC	Major Histocompatibility Complex
MMP2	Matrix Metalloproteinases 2
MMP9	Matrix Metalloproteinases 9
mTOR	Mammalian Target of Rapamycin
NASH	nonalcoholic steatohepatitis
NK	Natural Killer cells
PAI1 –	Plasminogen Activator Inhibitor 1
PD-1	Programmed Cell Death 1
PD-L1	Program Death Ligand 1
PHD3	Prolyl Hydroxylase 3
RANTES	Regulated on Activation Normal T Expressed and Secreted
RBP4	Retinol Binding Protein 4
RNA	Ribonucleic acid
SCC	squamous cell carcinoma
STAT	Signal Transducer and Activator of Transcription 3
TAMs	Tumor-Associated Macrophages
T_H1	T helper cell 1
T_H17	T helper cell 17
TME	Tumor Microenvironment
TNBC	Triple Negative Breast Cancer
TNFα –	Tumor Necrosis Factor Alpha
Tregs	T regulatory cells
VEGF	Vascular Endothelial Growth Factor

in this review, we have summarized their effects on cancer in Table 1. The adipokine leptin has been intensely studied, and we have reviewed its signaling mechanisms in more detail. The crystal structure of leptin is homologous to the long-chain helical cytokine family that induces IL-6 [29]. Leptin signals through its cell surface Jak-STAT linked receptor [30]. The binding of leptin to the leptin receptor (LepR), induces LepR dimerization and JAK2-mediated phosphorylation of specific residues in the intracellular domain of the LepR [30]. The phosphorylation of JAK2 sites in the LepR mediates the induction of STAT3 and ERK signaling in response to leptin [30]. Leptin acts on hypothalamic neurons to induce a satiety effect [31]. The increase in fat mass in obesity is correlated with an increase in serum leptin concentrations. The serum level of leptin in lean humans is 5 ng/mL and in obese humans, the levels of leptin can reach 100 ng/mL [32]. Overproduction of leptin leads to leptin resistance in obesity [31]. Clinically, leptin resistance causes overeating and obesity [31]. Leptin resistance may be cell-type specific. For example, obese levels of leptin are associated with the progression of breast cancer [33]. Leptin when applied to breast cancer cells in cell culture induces a concentration-dependent increase in signaling with a maximal effect observed in response to an obese concentration (100 ng/mL) of leptin [34]. Breast cancer cells also express leptin and the LepR [35]. The concentration of leptin in some tumors therefore might be higher than the concentration of leptin in blood. Most immune cell types in innate and adaptive T cell immunity express the leptin receptor (LepR) [36]. Broadly, the role of leptin in immunity is to boost inflammatory reactions. For instance, leptin augments TNFα and IL-1β production by human macrophages [37]. Leptin may also promote the initiation of cancer. For example, leptin stimulates an increase in DNA damage in normal breast epithelial cells obtained from women with a mutation in the BRCA gene [38]. The mechanism by which leptin promotes DNA damage is unknown.

3. Obesity-associated inflammation

Localized acute inflammation in adipose tissue is a beneficial mechanism that protects against determinantal deposition of lipids in peripheral tissues such as the liver [165]. In obesity, however, the chronic overfilling of adipocytes with triglycerides causes chronic low-grade inflammation in adipose tissue that leads to low-grade systemic inflammation [166,167]. The cytokines that emerge from adipose tissue modulate inflammatory pathways in peripheral organs [166]. Given that adipose tissue is in all tissues, chronic inflammation can occur in all tissues in response to obesity [166]. However, the severity of obesity-induced adipose tissue inflammation is dependent on the anatomical location of the adipose tissue in the body [168–170]. For example, in obesity, visceral fat has more inflammation than subcutaneous fat [171–176]. In humans, white adipocytes make up 98 % of total fat mass and the remaining adipocytes are brown adipocytes [177]. White adipocytes store and release energy and initiate inflammation in response to obesity. Brown adipocytes regulate thermogenesis and are less prone to obesity-associated inflammation [178–180]. In humans, body fat distribution is also linked with differences in risk for cardiovascular disease. The accumulation of abdominal fat promotes the risk of cardiovascular disease and insulin resistance. Conversely, gluteal-femoral subcutaneous fat protects against these obesity-associated diseases [181–188]. Visceral adipose tissue contains a greater percentage of hypertrophic adipocytes, and immune cells, and thus is more sensitive to obesity than subcutaneous adipose tissue. This difference could in part explain why the accumulation of visceral fat is more strongly associated with metabolic disease compared to an increase in the amount of subcutaneous adipose tissue [188]. Obesity also has distinct effects on different types of inflammation. For example, obesity promotes chronic inflammation in adipose tissue, yet inhibits acute inflammation in the tumor microenvironment (TME). In this review, we will discuss the cellular mechanisms by which obesity promotes low-grade inflammation, and inhibits acute inflammation in the TME.

3.1. Inflammation promotes cancer risk

There are several examples by which chronic inflammation promotes cancer and these studies support the hypothesis that obesity, by

Table 1
Summary table of the biomolecules secreted from adipose tissue, the effect obesity has on their secretion, and their role in cancer pathogenesis. Abbreviations: CRC- colorectal carcinoma, HCC- hepatocellular carcinoma, BC- breast cancer, NASH- nonalcoholic steatohepatitis, SCC- squamous cell carcinoma, TNBC- Triple Negative Breast Cancer, PD-L1- Program Death Ligand 1, mTOR- Mammalian Target of Rapamycin, HUVEC- human umbilical vein endothelial cells, RNA- Ribonucleic acid, DNA- Deoxyribonucleic Acid.

Adipokine Name	Obesity Effect	Effect on Cancer	Reference
Leptin	↑	- Increase cell proliferation in breast cancer - Increase cell invasion in CRC - promote secretion of exosomes	[39–44]
Adiponectin	↓	- Triggers cell death in BC - Suppress cell migration in prostate cancer cells	[40,45–47]
Visfatin	↑	- Promotes TNBC cell stemness - Anoikis resistance in ovarian cancer	[48–51]
Fetuin-A	↑	unknown	[52,53]
Plasminogen Activator Inhibitor 1 (PAI-1)	↑	- Marker of poor prognosis in breast and ovarian cancer - inhibits cell migration in pancreatic cancer, glioma, and melanoma	[54–59]
Resistin	↑	- Prostate cancer cell proliferation	[60–63]
Omentin-1	↓	- Inhibits proliferation and promotes apoptosis in CRC - promotes expression of tumor suppressive microRNA in CRC	[64–67]
Lipocalin-2	↑	- Inhibits ferroptosis in CRC - Promotes TME in hepatocellular carcinoma HCC	[68–71]
Asprosin	↑	- promote progress to invasive SCC	[72–74]
Neuregulin 4	↓	- serves as a hormonal checkpoint to prevent progression of NASH-HCC	[75–78]
Vaspin	↑	- Increase proliferation, migration and invasion of TNBC	[79–81]
Insulin-like Growth Factor Binding Protein-2 (IGFBP-2)	↓	- promotes metastasis of pancreatic cancer and chemotherapy resistance	[82–84]
Fibroblast Growth Factor 21 (FGF21)	↑	unknown	[85,86]
Retinol Binding Protein 4 (RBP4)	↑	- increases ovarian cancer migration	[87–89]
Adipokine C1q/Tumor Necrosis Factor Related Protein 3 (CTRP3)	Controversial	- promotes proliferation of osteosarcoma cells	[90–93]
Adipokine C1q/Tumor Necrosis Factor Related Protein 9 (CTRP9)	↑	unknown	[94,95]
Irisin	↑	- inhibit tumor development and induce apoptosis in prostate cancer	[96–100]
Apelin	↑	- promotes prostate cancer progression - increased tumor size, stage, and poor prognostic measure in BC	[101–104]
Angiopoietin like protein 2	↑	- increase breast cancer metastasis - chemotherapy resistance in CRC	[105–108]
Chemerin	↑	- promotes endothelial angiogenesis and migration of HUVEC cells	[109–111]
Progranulin	↑	- upregulates PDL-1 in breast cancer - promotes growth, migration, and invasion of CRC	[112–115]
Monocyte chemoattractant Protein 1 (MCP1/CCL2)	↑	- poor prognostic marker in multiple cancers including breast, lung, and prostate cancer - induce tamoxifen resistance	[112, 116–121]
Matrix Metalloproteinases 2 (MMP2)	↑	- promotes invasion and migration in bladder and prostate cancer	[122–125]
Matrix Metalloproteinases 9 (MMP9)	↑	- promotes invasion and migration in bladder and prostate cancer	[122–125]
Activin A	–	- increased invasion, migration and metastasis in prostate, BC, and squamous cell carcinoma SCC - induces apoptosis in HCC - suppresses angiogenesis and tumor growth in gastric cancer	[126–132]
Regulated on Activation, Normal T expressed and Secreted (RANTES/CCL5)	↑	- promotes immune cell infiltration of tumors - glioblastoma chemotherapy resistance	[133–136]
Insulin Like Growth Factor-1 (IGF-1)	Controversial	- increased tumor development, angiogenesis, and metastasis in CRC	[137–140]
Lysophosphatidic Acid	↑	- increase proliferation and migration of prostate cancer cells - suppress autophagy through activation of mTOR in prostate cancer	[141–144]
Vascular Endothelial Growth Factor (VEGF)	↑	- mediator of angiogenesis in cancer - suppress antitumor immune activity	[145–148]
Interleukin-1 beta (IL-1β)	↑	- marker of high-grade dysplasia or cancer - promote carcinogenesis	[149–152]

(continued on next page)

Table 1 (*continued*)

Adipokine Name	Obesity Effect	Effect on Cancer	Reference
Interleukin-6 (IL-6)	↑	- promotes resistance to anti-PDL-1 immunotherapy - expansion of cancer stem cell population in BC	[82, 153–156]
Tumor Necrosis Factor alpha (TNF α)	↑	- breast cancer progression and metastasis - promotes epithelial to mesenchymal transition - promotes suppression of T-regulatory cells	[157–160]
Extracellular Vesicles - siRNA - microRNA - DNA - Lipids - Sphingolipids - Phosphatidylserine	Unknown	- promote cell to cell communication in breast cancer - influence tumor microenvironment	[161,162], [44,163, 164]

promoting low-grade inflammation, promotes tumorigenesis. For example, the presence of gut pathogens promotes inflammatory bowel disease, which increases the risk of colon cancer [189]. Human papillomavirus induces cervicitis and increases the risk of cervical cancer [189]. The risk for hepatocellular carcinoma is increased by hepatitis, which is caused by the hepatic B/C virus [189]. The Epstein-Barr virus induces mononucleosis and is a risk factor for Burkitt's lymphoma [189]. The hypothesis that chronic inflammation in obesity promotes cancer is supported by the link between cancer and other instances of inflammation, including chronic inflammation.

3.2. Obesity-associated mechanisms of chronic inflammation in adipose tissue

The inflammatory environment in adipose tissue is highly responsive to obesity. With obesity, the inflammatory milieu in adipose tissue moves from anti-inflammatory to pro-inflammatory. This regulation is mediated by changes in the numbers and activity of anti- and pro-inflammatory immune cells in adipose tissue in response to obesity. For example, regulatory T cells (Tregs) inhibit inflammation by releasing the anti-inflammatory cytokine, interleukin 10 (IL-10) [190]. During murine and human obesity, there is a reduction in Tregs and IL-10 in adipose tissue [190–193]. Macrophages are also responsive to obesity [194,195]. There is increased infiltration and phenotypic switching to proinflammatory M1-stage macrophages in adipose tissue in obesity [194–196]. M1-stage macrophages release tumor necrosis factor-α (TNF-α), interleukin 6 (IL-6), and IL-1β [197]. The recruitment of macrophages is due to chemokines released from necrotic adipocytes in obese adipose tissue [198]. The inflammatory activity of M1-macrophages in adipose tissue is further increased by leptin which is produced in greater amounts by adipocytes in obesity [37]. Obesity increases the number of inflammatory T helper 1 (T_H1), and T_H17 cells in part by upregulating major histocompatibility complex class II on adipocytes in adipose tissue [192]. The primary cytokine from T_H1 cells is interferon-gamma (INF-γ). INF-γ is also the primary cytokine that downregulates the number of Tregs, which stimulates more inflammation in adipose tissue in obesity [191]. T_H1 cells also release TNFα and IL-2 cytokines [199]. Cytotoxic CD8 T cells are also responsive to obesity. The induction and expansion of adipose tissue-resident CD8 T cells initiate the recruitment of proinflammatory M1-macrophages to adipose tissue in obesity [200,201]. T_H17 are inflammatory T cells that are increased in adipose tissue in obesity [202,203]. IL-17 is the proinflammatory cytokine that is primarily released by T_H17 cells [204]. Functionally, IL-17 activates neutrophils, which are the first immune cells to infiltrate adipose tissue in obesity [205]. IL-17 also inhibits adipocyte differentiation and therefore the increase in IL-17 in obesity disrupts adipose tissue [203]. Clinically, IL-17 could be linked to autoimmunity in obese humans [206]. Fig. 1 summarizes the mechanisms of obesity-associated inflammation in adipose tissue. Based on these studies, the accumulation of inflamed adipose tissue causes systemic inflammation that increases cancer risk in obesity.

4. Breast adipose tissue inflammation

Clinically, breast adipose tissue inflammation is measured by the number of tissue slides that are positive for the presence of macrophage crown-like structures surrounding dying adipocytes [207–210]. The density of crowns per tissue section is also reported [207–210]. The macrophages in crowns surrounding dying adipocytes are immunostained with an anti-CD68 antibody, which is a pan-marker of macrophages [207–210]. The presence of macrophage crown-like structures is a good readout of inflammation, given that the infiltration of macrophages is the first and most robust inflammatory response in adipose tissue in obesity [211,212]. Clinical studies show obesity is significantly associated with increased abundance of macrophage crowns in breast adipose tissue in women with breast cancer [207–210]. Obesity-associated systemic increases in leptin, IL-6, and triglycerides are also positively correlated with breast adipose tissue inflammation in women who underwent mastectomy for breast cancer treatment [209]. In women, breast adipose tissue inflammation is positively associated with faster relapse of metastatic breast disease [209]. The progression of benign breast disease to breast cancer is also significantly associated with breast adipose tissue inflammation [207]. The presence of crowns in breast adipose tissue was significantly higher in women with breast cancer compared with women who did not have cancer [210]. Women who were carriers of a BRCA mutation did not show increased breast adipose tissue inflammation [210]. Breast adipose tissue inflammation

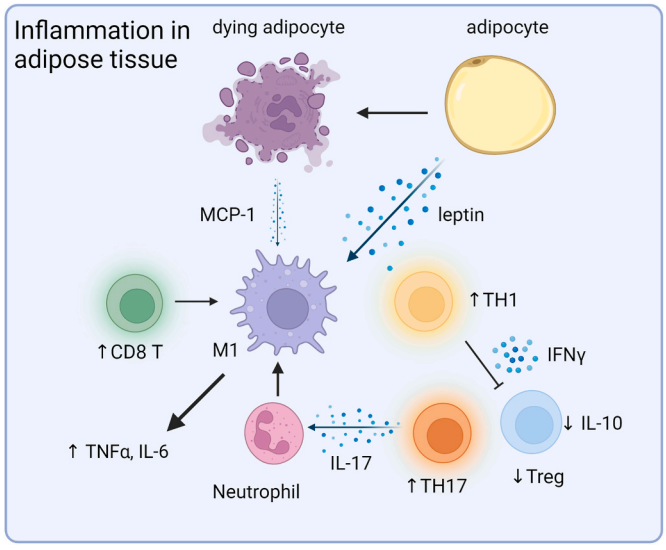

Fig. 1. Adipose tissue inflammation in obesity.
Adipose tissue is highly responsive to obesity-induced inflammation. The increase in MCP-1, leptin, cytotoxic CD8 T cells, and activated neutrophils recruit and polarize proinflammatory M1-macrophages in adipose tissue in obesity. There is increased development of proinflammatory TH1 and TH17 cells, which by releasing $INF_γ$ and IL-17 inhibit Tregs and stimulate neutrophils, respectively. Obesity-associated adipose tissue inflammation increases circulating TNF-α, IL-6, and leptin. MCP-1 = Monocyte Chemoattractant Protein 1, TNFα = Tumor necrosis factor-alpha, IL-6 = Interleukin-6, M1 = M1-stage Macrophage, IL-7 = Interleukin-17, TH17 = T helper 17, TH1 = T helper 1, Treg = Regulatory T cells, $INF_γ$ = Interferon-gamma, IL-10, Interleukin-10.

is not associated with breast tumor grade [208]. However, breast adipose tissue crowns occurred more frequently in women with luminal-B-like breast tumors [210]. The presence of breast adipose tissue crowns was associated with increased lymphovascular disease for triple-negative breast cancer (TNBC) [210]. The mechanisms that link luminal-B-like breast tumors and TNBC invasiveness with increased breast adipose tissue inflammation in women have not been published. Studies have asked if the presence of breast adipose tissue crowns is associated with breast cancer progression. The abundance of macrophage crowns in breast adipose tissue is not associated with disease-free progression or overall survival of breast cancer patients [208,210]. The role of race has also been investigated, and the results show that the number of breast adipose tissue crowns in African-American women was not significantly different than the number of breast adipose tissue crowns in White women with breast cancer [208]. The role of the tumor has been assessed and the results show the abundance of macrophage crowns in breast adipose tissue is higher in obese women with breast cancer compared with obese women who do have cancer [210]. This finding indicates the tumor secretes proinflammatory cytokines that act on breast adipose tissue. Combining multiple biomarkers for breast adipose tissue inflammation could be a more accurate predictor of cancer progression than just assessing the number of macrophage crowns in breast adipose tissue. A future study that combines multiple markers of breast adipose tissue inflammation could identify an improved strategy that might be significantly associated with disease-free survival and overall survival for breast cancer patients.

5. Anti-tumor immunity

The recognition and killing of cancer cells by T cells is a seven-step process [213,214]. The first step starts with the release of cancer-specific antigens by the tumor. The cancer antigens are detected and processed by antigen-presenting cells (APCs). Cancer-primed APCs activate T cells in the lymph node. Cancer-primed cytotoxic T cells ($CD8^+$ T cells) traffic in the bloodstream to the tumor. Cancer-activated $CD8^+$ T cells infiltrate the tumor and react with cancer cells that present antigens via the major histocompatibility complex (MHC). The final step is the killing of cancer cells by $CD8^+$ T cells. Natural killer (NK) cells also contribute to the killing of cancer cells through an MHC-independent mechanism [215]. Tumors evade anti-tumor immunity by down-regulating the expression of MHC and upregulating the expression of PD-L1 on cancer cells [216–218]. PD-L1 expressed on cancer cells binds to PD-1 expressed on T cells and this association between PD-L1 and PD-1 induces signaling in T cells that inhibits T cell effector activity [219–221]. Tregs and myeloid-derived suppressor cells (MDSCs) are immunosuppressive and they promote cancer by inhibiting anti-tumor immunity [222,223]. Consequently, increased numbers of Tregs and MDSCs in the tumor microenvironment are associated with poor cancer prognosis [224,225].

Upon entering a tumor, a subset of effector-like $CD8^+$ T cells differentiate into tissue-resident memory T cells [226]. Tissue-resident T cell markers are CD69 or CD103, which retain T cells in tissue through integrin interactions [226]. In peripheral tissues, memory resident T cells release granzyme B in response to antigen stimulation, which can eliminate pathogen-infected cells [226]. Tissue-resident T cells also release the pro-inflammatory cytokines INFγ, TNFα, and IL-2, which recruit additional inflammatory cells to the site of infection [226]. The release of granzyme B and proinflammatory cytokines by tumor resident T cells suppress tumor growth [226]. Tumor resident T cells are heterogeneous, with subsets expressing several T cell exhaustion and activation markers [226]. Clinically, increased number of resident $CD8^+$ T cells in tumors is associated with good cancer prognosis [226]. In the sections below, we will review how obesity inhibits anti-tumor immunity by acting on T cells, NK cells, and MDSCs.

6. The roles of obesity in anti-tumor immunity

6.1. Upregulation of PD-1 on T cells in obesity

Upon their recruitment to the TME, CD8 T-cells become exhausted [227]. T cells that become exhausted are initially active, but their persistent overstimulation in the TME leads to their gradual loss of effector activity and their inability to kill cancer cells [227]. The upregulation of PD-1 on T cells is a marker of T cell exhaustion [228]. The PD-1 that is expressed on T cells binds to PD-L1, which is expressed on the surface of cancer cells. The binding of PD-1 to PD-L1 induces signaling in T cells that block T cell effector activity [221]. The hallmark of an exhausted CD8 T cell in the TME is the inability of the PD-1-expressing CD8 T cell to kill a cancer cell [221]. Consequently, obesity by increasing the expression of PD-1 on T cells facilitates T cell inactivation in the TME and this favors tumorigenesis [229]. Mechanistically, leptin acts on T cells to induce phosphorylated STAT3 signaling that upregulates the expression of PD-1 [229] (Fig. 2). Higher levels of leptin in obesity, therefore, drive the inactivation of $CD4^+$ helper T cells, and $CD8^+$ cytotoxic T cells [229]. The induction of PD-1 on T cells in response to obesity was confirmed in mice, primates, and humans and therefore this mechanism could promote tumorigenesis in obese patients [229]. The induction of PD-1 on $CD8^+$ T cells in response to obesity was associated with reduced $CD8^+$ T cell effector activity and reduced release of cytokines (IL-2 and interferon-gamma) [229]. Thus, the induction of PD-1 on T cells in obesity is linked to the functional suppression of $CD8^+$ T cells. RNA-seq experiments coupled with pathway analysis showed that $CD8^+$ T cells from obese mice exhibited gene expression changes significantly associated with metabolic alterations, and T cell hyporesponsiveness, such as T cell anergy [229]. Thus, the observed reduction in $CD8^+$ T cell activity in obesity is due to

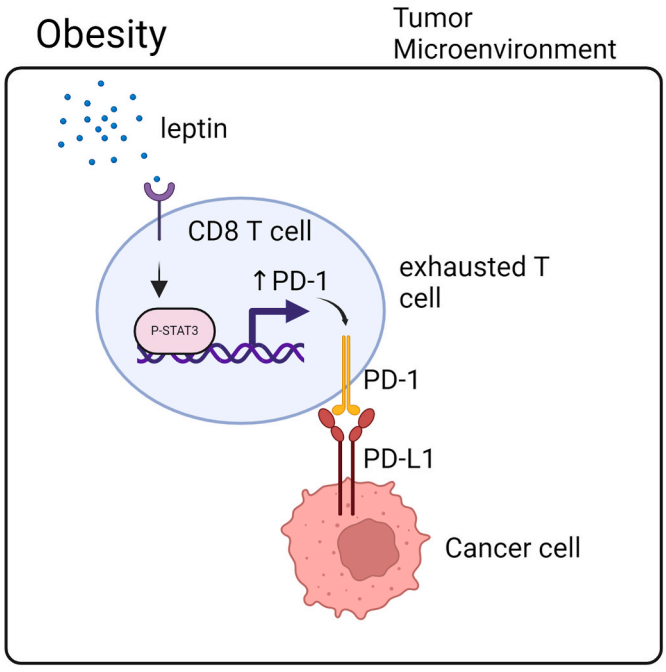

Fig. 2. T-cell exhaustion in obesity.
Increased leptin in obesity acts on cytotoxic CD8 T cells to induce signaling that promotes the phosphorylation of STAT3 (Tyr705) which in turn activates the STAT3 response element within the enhancer of the PD-1 gene which leads to increased PD-1 expression by T cells. The binding of T cell-expressed PD-1 to cancer cell-expressed PD-L1 induces signaling in CD8 T cells that inactivates the effector function of T cells, leading to an exhausted T cell state. P-STAT3 = Phosphorylated-Signal Transducer And Activator Of Transcription 3 (Tyr705), PD-1 = Programmed cell death protein 1, PD-L1 = Programmed Death-1 (PD-1) Ligand 1.

multiple changes in the T cell that inhibit T cell effector activity towards cancer cells [229]. Preclinically, the effect of PD-1 inhibitors on tumor growth in obese compared with lean mice was investigated [229]. Mechanistically, PD-1 antibodies, by binding to PD-1 on T cells, block PD-1 binding to PD-L1 on cancer cells [221]. PD-1 blocking drugs by preventing the binding of T cell PD-1 to cancer cell PD-L1 disinhibits the T cell, and the now active $CD8^+$ T cell kills cancer cells [221]. Of interest, is that inhibiting PD-1 with PD-1 antibody, inhibited the growth of melanoma and mammary tumors in obese mice more than it inhibited the growth of these tumors in lean mice [229]. A similar response has been reported in humans with melanoma, such that obese patients are more responsive to PD-1 inhibitors than lean patients [229]. From an immunity standpoint, the PD-1 inhibitor not only inhibited the growth of tumors in obese mice, but it also increased the number of activated $CD8^+$ T cells, and M1-phase macrophages, and reduced the number of immunosuppressive MDSCs in the TME and peripheral tissues [230]. These findings show that blocking PD-1 activity in obese mice with cancer, restored several aspects of anti-tumor immunity and that this was correlated with a reduction in the growth of tumors in obese mice, and the anti-tumor effect was stronger in obese, than lean mice [229]. The greater efficacy of blocking PD-1 translates to humans, given that the efficacy of PD-1 inhibitors in obese humans with cancer is better than the efficacy of PD-1 inhibitors in lean humans with cancer [231]. This human response has been shown for melanoma, lung cancer, and renal cancer in human obesity [231]. Mechanistically, it is hypothesized that $CD8^+$ T cells are more responsive to PD-1 blockers in obesity because $CD8^+$ T cells are more suppressed by PD-1 signaling in obese compared with lean mice or humans [231].

6.2. Obesity inhibits the acquisition of free fatty acids by T cells in the TME

There is competition between T cells and cancer cells for nutrients in the TME [232]. Cancer cells out-compete T cells for nutrients by upregulating the expression of nutrient transporters and increasing their utilization of nutrients [232]. This, in turn, establishes a gradient by which nutrients flow from the tumor interstitium into cancer cells, instead of moving into T cells [232]. The reduced flow of nutrients into T cells prevents the expansion and effector activity of T cells in the TME and this compromises anti-tumor immunity and the tumor evades the immune system. Prior reports have focused on the reduced flow of glucose and amino acids into T cells due to enhanced uptake of these nutrients by cancer cells [232]. In obesity, however, the gradient is free fatty acids, such that these lipids flow into and are rapidly utilized by cancer cells. In contrast, the movement of free fatty acids into $CD8^+$ T cells in the TME is suppressed [233]. The reduced flow of lipids into $CD8^+$ T cells is associated with reduced $CD8^+$ T cell infiltration in tumors and poor $CD8^+$ T cell effector activity in obese mice compared with lean mice with tumors [233]. Interestingly, this process of free fatty acids preferentially being moved into cancer cells at the expense of $CD8^+$ T cells is induced by the downregulation of prolyl hydroxylase 3 (PHD3) in cancer cells in obesity [233] (Fig. 3). In lean mice, PHD3 is highly expressed in cancer cells, and it blocks the movement of free fatty acids into the mitochondria; therefore, lipids are not readily utilized by cancer cells in lean mice, and this allows lipids to distribute into $CD8^+$ T cells within the TME, and this is associated with improved anti-tumor immunity in lean mice [233]. However, in obesity, PHD3 is downregulated in cancer cells [233] (Fig. 3). In response to PHD3 downregulation, free fatty acids flow into the mitochondria of cancer cells in obesity, and this increased utilization of free fatty acids by the mitochondria for fatty acid oxidation drives a gradient by which free fatty acids in the tumor interstitium are transported into cancer cells, not $CD8^+$ T cells, and this is associated with inhibited $CD8^+$ T cell effector activity in the tumors of obese mice [233]. Interestingly, genetically preventing the downregulation of PHD3 in cancer cells in obesity inhibits lipid uptake by cancer cells, restores $CD8^+$ T cell effector activity,

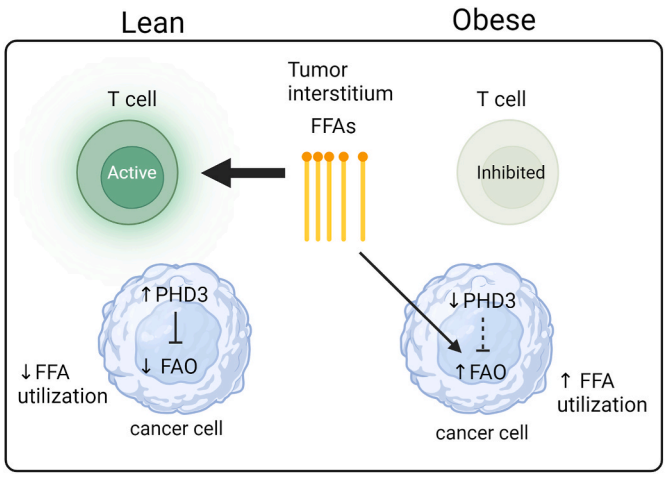

Fig. 3. T cell inactivation in obesity.
There is a competition between T cells and cancer cells for limiting amounts of FFAs in the tumor interstitium. In lean mice, reduced utilization of FFAs by cancer cells due to upregulation of PHD3 promotes the flow of FFAs into T cells. In obese mice, reduced PHD3 promotes FFA utilization by cancer cells, which diverts the flow of FFAs away from T cells. PHD3 = Prolyl hydroxylase 3, FFA = Free Fatty Acids, FAO = Fatty Acid Oxidation.

and inhibits the growth of tumors in obese mice [233]. Clinically, analysis of the Cancer Genome Atlas showed the levels of PHD3 were negatively correlated with BMI in the context of cancer [233]. These findings provide the premise for a future study investigating what factor (s) in obesity reduce PHD3 expression in cancer cells. Hypothetically, preventing obesity-stimulated downregulation of PHD3 in cancer cells would inhibit tumor growth by restoring anti-tumor immunity. In addition to altering fatty acid and lipid metabolism, obesity decreases amino acid metabolism in tumor-resident $CD8^+$ T cells in MC38 colon tumors [234]. This is secondary to reduced activity of the amino acid transporter, SLC7A5, on tumor resident T cells in response to obesity [234]. Conversely, leucine uptake by breast cancer cells is stimulated by obesity-associated breast adipokines [235]. Increased leucine uptake by breast cancer cells is mediated by increased SLC7A5 activity in response to obesity-associated adipokines [235]. These findings show that tumor-associated T-cell activity and cellular metabolism are interconnected and dysfunctional in obesity.

6.3. Natural killer (NK) cells

NK cells are inhibited in obesity [236,237]. In the context of cancer, NK cells synapse with a tumor cell, and polarize their cytolytic granules to release a payload of proteases and hydrolases onto cancer cells, which kills the cancer cell [238]. In obesity, NK cells synapse with tumor cells, yet they fail to polarize and, therefore, fail to release their cytolytic granules onto cancer cells, and the cancer cell is not lysed [236]. This defect in the polarization of lytic granules is linked to a defect in glycolysis and oxidative metabolism in NK cells in obesity [236]. The defect in glycolysis and oxidative metabolism is due to the accumulation of triglyceride storage droplets in the cytoplasm of NK cells in murine and human obesity [236,237]. In obesity, NK cells accumulate cytoplasmic lipid droplets via a transcriptional mechanism that promotes lipid absorption and synthesis [237]. In NK cells, excess lipid accumulation in the cytoplasm inhibits the activity of mTOR and destabilizes P300 and cMYC protein [237]. The mTOR pathway, P300, and cMYC drive metabolism in NK cells [236,237]. The metabolic defect in NK cells in obesity is therefore linked to the loss of mTOR, P300, and cMYC [236,237]. The mechanisms that reduce NK activity in obesity are summarized in Fig. 4. Clinically, bariatric surgery improved NK cell activity in humans [239]. Glucagon-like-peptide-1 agonist (GLP-1) treatment in

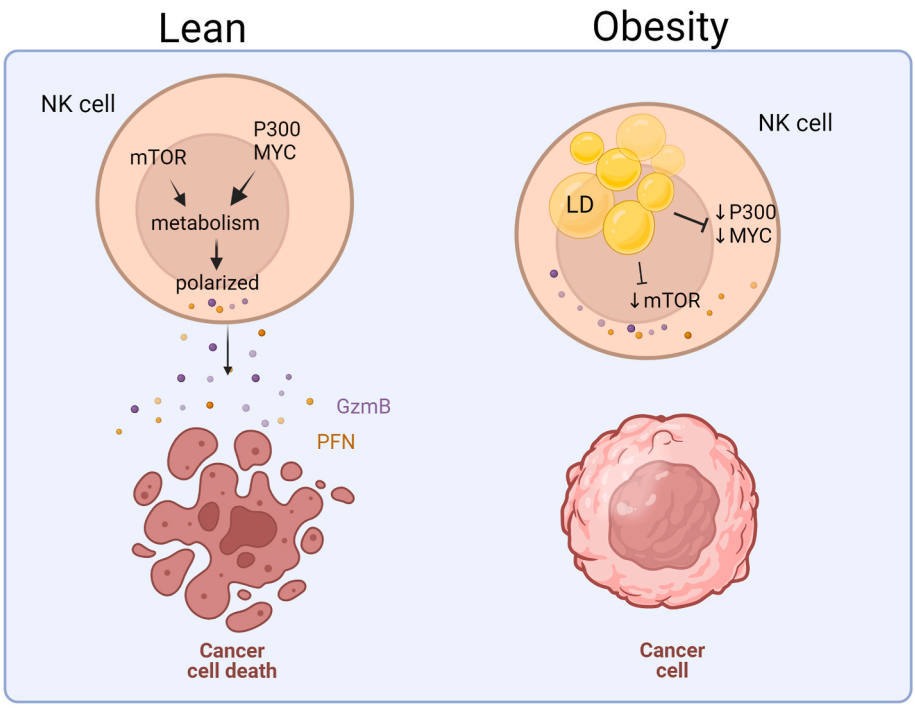

Fig. 4. Inhibition of NK cells in obesity.
In lean mice, mTOR signaling, P300, and MYC transcriptional proteins mediate the increase in cellular metabolism that is needed for NK polarization and the release of cytotoxic enzymes onto cancer cells. In obese mice, the uptake of lipids by NK cells leads to the formation of cytoplasmic lipid droplets (LDs) that inhibit mTOR signaling and destabilize P300 and MYC. This compromises cellular metabolism that is needed for the polarization and release of cytolytic enzymes by NK cells onto cancer cells. NK = Natural Killer, mTOR = mechanistic target of rapamycin, P300 = E1A Binding Protein P300, MYC = MYC Proto-Oncogene, BHLH Transcription Factor, GzmB = Granzyme B, PFN = Profilin 1, LD = lipid droplet.

humans also boosted NK activity [240]. These clinical findings are encouraging and suggest that moving to a low-fat diet and losing weight might be lifestyle changes that improve NK activity.

6.4. *Myeloid-derived suppressor cells (MDSCs)*

Chronic inflammation, infections, and cancer induce granulocytes and monocytes to develop into MDSCs [222,223]. MDSCs inhibit inflammation and suppress anti-tumor immunity [222,223]. Obesity-associated leptin expands the number of MDSCs in peripheral blood and the TME in mice [241]. Tumor-associated MDSCs express PD-L1, which inhibits the activity of tumor-associated $CD8^+$ T cells [241]. Clinically, obese women with TNBC had increased circulating MDSCs compared with lean women with TNBC [242]. In obese mice, renal tumors had increased MDSCs compared with renal tumors in lean mice [243]. Renal tumors in obese mice produced increased concentrations of C–C Motif Chemokine Ligand 2, which is an MDSC chemoattractant [243]. In obese mice, an increase in the number of MDSCs in the peritoneal cavity is associated with increased ovarian tumor burden [244]. In mice and humans, obesity-stimulated MDSC is associated with increased progression of oral squamous cell carcinoma [245]. In mice, obesity is broadly associated with an increase in the number of myeloid cells and a decrease in the number of lymphoid cells being produced in bone marrow [246]. In murine obesity, a subset of monocytes develops into APCs that activate neutrophils that travel to the lung and release neutrophil extracellular traps that "trap" metastatic mammary cancer cells in the lung [246]. This monocyte-neutrophil-based mechanism could, in part explain why breast cancer metastasis is increased in obesity [246].

6.5. *Macrophages*

Macrophages are the most abundant immune cell type in adipose tissue and within the TME [247,248]. Macrophages respond to tissue signals to polarize towards an anti-inflammatory or proinflammatory activation state [249]. Macrophages in adipose tissue in obesity are classically M1 activated and release proinflammatory cytokines that drive chronic inflammation and cancer susceptibility [248]. Conversely, macrophages within the TME are alternatively polarized towards an M2 phenotype that produces cytokines that mediate antitumor immunity within the TME [247]. Consequently, TAMs that are M2-activated are associated with poor cancer prognosis [247]. Classically activated M1 macrophages also populate the TME and suppress cancer development by producing proinflammatory cytokines and presenting antigens to cytotoxic T cells [247]. Preclinical findings show a high-fat diet is associated with enhanced infiltration of M2-like macrophages and regulatory T cells into prostate tumors in mice [250]. Preclinical findings also show that high-fat diet-induced obesity correlates with upregulated expression of PD1 on TAMs, which reduces antigen presentation and phagocytic activity in murine MC38 colorectal tumors [251]. The obesity suppressive effects on TAMs were reversed by anti-PD1 antibody treatment [251]. Clinically, obesity is associated with an increase in the percentage of immunosuppressive M2-activated macrophages in breast adipose tissue [252]. These findings show that obesity regulation of TAMs promotes cancer development. The obesity signal that regulates TAMs, however, is unknown.

7. Cancer-associated adipocytes

Adipocytes in direct contact with cancer cells exhibit morphological, functional, and de-differentiation processes that are unique compared with adipocytes that are located far from the tumor—and because these changes are unique, adipocytes that are in direct contact with cancer cells are referred to as being cancer-associated adipocytes (CAAs) [253–255]. CAAs undergo lipolysis in the TME [253,255]. In CAAs, this is mediated by the activation of hormone-sensitive lipase by

cancer-secreted factors [254,256]. The induction of hormone-sensitive lipase in CCAs is partially mediated by adrenergic receptors in ovarian, but not breast cancer [254,256]. Free fatty acids are steadily liberated from lipid droplets by adipose tissue lipase expressed by cancer cells [254–257]. In cancer cells, free fatty acids are oxidized, which is not coupled to ATP synthesis but is essential for cancer cell invasiveness [256]. The flow of free fatty acids from adipocytes to cancer is enhanced in obesity [257].

In mice, in vivo adipocyte tracing studies show CAAs do not undergo apoptosis; instead, they transition to a fibroblast-like morphology [255]. This transition of an adipocyte to fibroblast-like cells is viewed as a de-differentiation process [253,255]. CAAs can re-differentiate to an adipocyte if removed from the tumor and placed in cell culture [255]. Thus, cancer-secreted factors maintain CAAs [255]. An interesting question is whether delipidation occurs first, which triggers de-differentiation, or if de-differentiation triggers delipidation, or the two processes are independent responses to direct interaction with cancer cells. In mice, genetically blocking adipocyte lipolysis prevents cancer-induced adipocyte de-differentiation in the context of mammary cancer [255]. This finding suggests that adipocyte delipidation leads to adipocyte de-differentiation in response to direct contact with cancer cells [255]. Mice with adipocytes that are refractory to lipolysis are also protected from tumorigenesis because implanted mammary tumors in these mice fail to grow and are significantly smaller than tumors implanted in mice with adipocytes that undergo lipolysis in response to being in direct contact with cancer cells [255]. Independent of lipid transfer, the de-differentiation of adipocytes in response to cancer cells might benefit the tumor by increasing total cellular heterogeneity within the TME [255] (Fig. 5). Specifically, cells that were adipocytes but are no longer adipocytes because they are in contact with cancer cells are a heterogeneous population of six different cell types in various stages of cellular transition that resemble inflammatory cells, macrophages, myofibroblasts, adipocyte progenitor cells, and mesenchymal cells in the murine TME [255] (Fig. 5). Single-cell RNA-seq studies show that these tumor-stimulated adipocyte-derived cells respond to hypoxia and alter pathways involved in the extracellular matrix and inflammation [255]. This heterogenous adipocyte response to cancer may be one mechanism by which de-differentiation of adipocytes promotes tumorigenesis by increasing cell heterogeneity in the tumor microenvironment [255] (Fig. 5). Targeting adipocytes in direct contact with cancer cells could foster new cancer therapies in obesity.

8. Conclusions and future directions

In obesity, chronic overfilling of adipocytes with lipids exceeds capillary support to adipose tissue, which in turn leads to the death of adipocytes that, in the process of dying, release chemokines and cytokines that recruit M1-stage macrophages to adipose tissue that mediate chronic low-level inflammation and skew T cell differentiation towards proinflammatory T_H1 and T_H17 T cells (Section 2). The inflammation is more severe in visceral adipose tissue. However, there is also an increase in low-grade inflammation in peripheral tissues that are prone to cancer, such as the breast, in obesity. There are many examples where obesity inhibits anti-tumor immunity, including exhaustion and lipid deprivation of $CD8^+$ T cells, inactivation of NK cells, and increased numbers of MDSCs (Section 6). Although obesity affects anti-tumor immunity through several mechanisms, it is not clear which perturbations are the most important for cancer progression and which mechanisms are cancer-type-specific. Many anti-tumor immunity mechanisms have been established in mouse models of obesity with correlates to human data. It will be essential to translate these findings to human cancer in obesity. The risk of cancer in obesity for many cancers is associated with a low hazard ratio [21]. Thus, obesity alone is not a promising biomarker for cancer. However, combining obesity with other cancer biomarkers might identify a subset of obese patients who are at high risk for aggressive cancer.

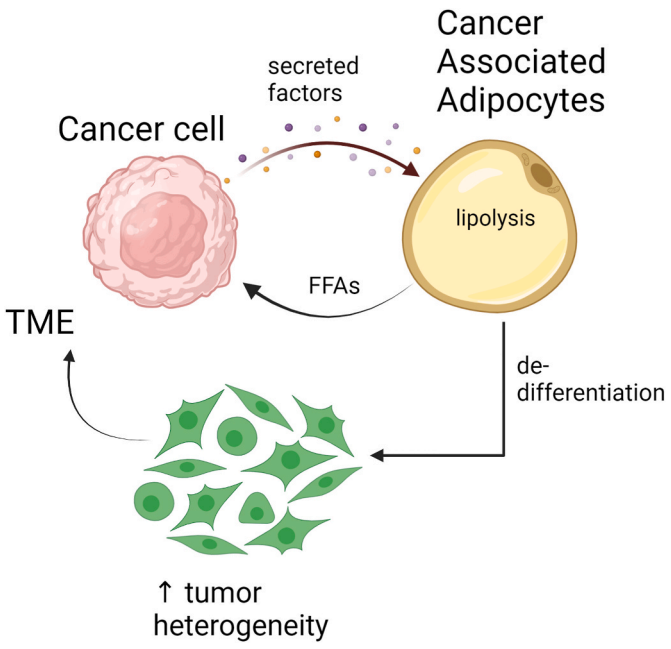

Fig. 5. Cancer-associated adipocytes
Cancer-associated adipocytes are in direct contact with cancer cells. Cancer cell-secreted factors act on adipocytes to induce lipolysis and the liberated FFAs are transferred to cancer cells for metabolism. Delipidation of adipocytes triggers de-differentiation into multiple cell types, including myofibroblasts, immune-like cells, and adipocyte progenitor cells that collectively increase cellular heterogeneity within the tumor microenvironment (TME), which promotes tumorigenesis. FFAs = Free fatty acids, TME = tumor microenvironment.

Given that obesity is a heterogeneous condition, a better understanding of which associated comorbidities drive T-cell dysfunction could lead to better-targeted interventions for cancer therapy. Identifying the obesity signal that drives T cell dysfunction could foster the development of novel therapeutic approaches to restore tumor-associated T cell function in obesity. Although the link between dysfunctional tumor-infiltrating T cells and obesity is relatively well characterized, less is known about how obesity regulates immunosurveillance of early cancer development. A more precise understanding of the mechanisms of T-cell responsiveness to immune checkpoint therapy in obesity may identify biomarkers that better predict patient response to immune-based treatment for cancer therapy [258]. Considering the sensitivity of tumor-associated T cells to diet, a better understanding of the mechanism could lead to therapies that incorporate diet to improve anti-tumor immunity [259].

CRediT authorship contribution statement

Cora E. Miracle: Writing – review & editing, Writing – original draft. **Chelsea L. McCallister:** Writing – review & editing, Writing – original draft. **Richard D. Egleton:** Writing – review & editing, Writing – original draft. **Travis B. Salisbury:** Writing – review & editing, Writing – original draft.

Declaration of competing interest

The authors declare they have no competing interests.

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References

[1] B.A. Swinburn, et al., The global obesity pandemic: shaped by global drivers and local environments, Lancet 378 (9793) (2011) 804–814.
[2] B.L. McKenzie, A.C. Pinho-Gomes, M. Woodward, Addressing the global obesity burden: a gender-responsive approach to changing food environments is needed, Proc. Nutr. Soc. (2024) 1–9.
[3] Y.Z. Ge, et al., The age-related obesity paradigm: results from two large prospective cohort studies, J Cachexia Sarcopenia Muscle 15 (1) (2024) 442–452.
[4] Y.C. Chooi, C. Ding, F. Magkos, The epidemiology of obesity, Metabolism 92 (2019) 6–10.
[5] A.B. Pulungan, et al., Childhood obesity as a global problem: a cross-sectional survey on global awareness and national Program implementation, J Clin Res Pediatr Endocrinol 16 (1) (2024) 31–40.
[6] V. Sethi, et al., Prevalence of overweight and obesity and associated demographic and health factors in India: findings from Comprehensive National Nutrition Survey (CNNS), Pediatr Obes 19 (4) (2024) e13092.
[7] N. Tumas, S.R. López, Double burden of underweight and obesity: insights from new global evidence, Lancet 403 (10431) (2024) 998–999.
[8] H. Gou, et al., Prediction models for children/adolescents with obesity/overweight: a systematic review and meta-analysis, Prev. Med. 179 (2024) 107823.
[9] Y. Zhang, et al., General or central obesity and mortality among US hispanic and latino adults, JAMA Netw. Open 7 (1) (2024) e2351070.
[10] Worldwide trends in underweight and obesity from 1990 to 2022: a pooled analysis of 3663 population-representative studies with 222 million children, adolescents, and adults, Lancet 403 (10431) (2024) 1027–1050.
[11] M. Arnold, et al., Obesity and cancer: an update of the global impact, Cancer Epidemiol 41 (2016) 8–15.
[12] F. Bray, et al., Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA Cancer J Clin 44 (3) (2024) 229–263.
[13] D.J.H. Tan, et al., Rising global burden of cancer attributable to high BMI from 2010 to 2019, Metabolism 152 (2024) 155744.
[14] R. Sharma, Burden of stomach cancer incidence, mortality, disability-adjusted life years, and risk factors in 204 countries, 1990-2019: an examination of global burden of disease 2019, J. Gastrointest. Cancer. 55 (2) (2024) 787–799.
[15] A. Afshin, et al., Health effects of overweight and obesity in 195 countries over 25 years, N. Engl. J. Med. 377 (1) (2017) 13–27.
[16] P. Gona, et al., Trends in the burden of most common obesity-related cancers in 16 Southern Africa development community countries, 1990-2019. Findings from the global burden of disease study, Obes Sci Pract 10 (1) (2024) e715.
[17] W. Li, W. Wang, Contribution of high body mass index to the global burden of esophageal cancer: a population-based study from 1990 to 2019, Dig. Dis. Sci. 69 (4) (2024) 1125–1134.
[18] J. Huang, et al., Global incidence and mortality trends of corpus uteri cancer and associations with gross domestic product, human development index, lifestyle, and metabolic risk factors, Int. J. Gynaecol. Obstet. 162 (3) (2023) 998–1009.
[19] D.Q. Huang, et al., Changing global epidemiology of liver cancer from 2010 to 2019: NASH is the fastest growing cause of liver cancer, Cell Metabol. 34 (7) (2022) 969–977.e2.
[20] S. Safiri, et al., Global, regional, and national burden of cancers attributable to excess body weight in 204 countries and territories, 1990 to 2019, Obesity 30 (2) (2022) 535–545.
[21] B. Lauby-Secretan, et al., Body fatness and cancer–viewpoint of the IARC working group, N. Engl. J. Med. 375 (8) (2016) 794–798.
[22] F.A. Sinicrope, Increasing incidence of early-onset colorectal cancer, N. Engl. J. Med. 386 (16) (2022) 1547–1558.
[23] S. Harborg, et al., New horizons: epidemiology of obesity, diabetes mellitus, and cancer prognosis, J. Clin. Endocrinol. Metab. 109 (4) (2024) 924–935.
[24] A.C. Garrido-Castro, N.U. Lin, K. Polyak, Insights into molecular classifications of triple-negative breast cancer: improving patient selection for treatment, Cancer Discov. 9 (2) (2019) 176–198.
[25] L. Yin, et al., Triple-negative breast cancer molecular subtyping and treatment progress, Breast Cancer Res. 22 (1) (2020) 61.
[26] S.J. Henley, et al., Uterine cancer incidence and mortality - United States, 1999-2016, MMWR Morb. Mortal. Wkly. Rep. 67 (48) (2018) 1333–1338.
[27] A. Mazidimoradi, et al., The global incidence, mortality, and burden of uterine cancer in 2019 and correlation with SDI, tobacco, dietary risks, and metabolic risk factors: an ecological study, Health Sci Rep 7 (1) (2024) e1835.
[28] M. Wang, et al., Global cervical cancer incidence by histological subtype and implications for screening methods, J Epidemiol Glob Health 14 (1) (2024) 94–101.
[29] F. Zhang, et al., Crystal structure of the obese protein leptin-E100, Nature 387 (6629) (1997) 206–209.
[30] R.A. Saxton, et al., Structural insights into the mechanism of leptin receptor activation, Nat. Commun. 14 (1) (2023) 1797.
[31] C.J. Rosen, Antagonizing the leptin receptor in obesity, N. Engl. J. Med. 388 (24) (2023) 2291–2293.
[32] L. Oksanen, et al., Markers for the gene ob and serum leptin levels in human morbid obesity, Hum. Genet. 99 (5) (1997) 559–564.
[33] Y. Gui, et al., The association between obesity related adipokines and risk of breast cancer: a meta-analysis, Oncotarget 8 (43) (2017) 75389–75399.
[34] N.K. Saxena, et al., leptin-induced growth stimulation of breast cancer cells involves recruitment of histone acetyltransferases and mediator complex to CYCLIN D1 promoter via activation of Stat3, J. Biol. Chem. 282 (18) (2007) 13316–13325.
[35] C. Garofalo, et al., Increased expression of leptin and the leptin receptor as a marker of breast cancer progression: possible role of obesity-related stimuli, Clin. Cancer Res. 12 (5) (2006) 1447–1453.
[36] A. Abend Bardagi, et al., Leptin's immune action: a review beyond satiety, Immunol. Invest. 52 (1) (2023) 117–133.
[37] D. Flores Gomez, et al., The effect of leptin on trained innate immunity and on systemic inflammation in subjects with obesity, J. Leukoc. Biol. 115 (2) (2024) 374–384.
[38] P. Bhardwaj, et al., Obesity promotes breast epithelium DNA damage in women carrying a germline mutation in BRCA1 or BRCA2, Sci. Transl. Med. 15 (684) (2023) eade1857.
[39] Y. Zhang, et al., Positional cloning of the mouse obese gene and its human homologue, Nature 372 (6505) (1994) 425–432.
[40] F. Jaleel, et al., Comparison of adiponectin, leptin and blood lipid levels in normal and obese postmenopausal women, J. Pakistan Med. Assoc. 56 (9) (2006) 391–394.
[41] M.N. Dieudonne, et al., Leptin mediates a proliferative response in human MCF7 breast cancer cells, Biochem. Biophys. Res. Commun. 293 (1) (2002) 622–628.
[42] S. Attoub, et al., Leptin promotes invasiveness of kidney and colonic epithelial cells via phosphoinositide 3-kinase-, rho-, and rac-dependent signaling pathways, Faseb. J. 14 (14) (2000) 2329–2338.
[43] C. Garofalo, E. Surmacz, Leptin and cancer, J. Cell. Physiol. 207 (1) (2006) 12–22.
[44] C. Giordano, et al., Leptin modulates exosome biogenesis in breast cancer cells: an additional mechanism in cell-to-cell communication, J. Clin. Med. 8 (7) (2019).
[45] K. Maeda, et al., cDNA cloning and expression of a novel adipose specific collagen-like factor, apM1 (AdiPose Most abundant Gene transcript 1), Biochem. Biophys. Res. Commun. 221 (2) (1996) 286–289.
[46] D.V. Pham, P.H. Park, Adiponectin triggers breast cancer cell death via fatty acid metabolic reprogramming, J. Exp. Clin. Cancer Res. 41 (1) (2022) 9.
[47] E. Kashiwagi, et al., The role of adipocytokines and their receptors in prostate cancer: adiponectin may protect against progression, Anticancer Res. 44 (4) (2024) 1369–1376.
[48] S. Zvonic, et al., Secretome of primary cultures of human adipose-derived stem cells: modulation of serpins by adipogenesis, Mol. Cell. Proteomics 6 (1) (2007) 18–28.
[49] Y.F. Chiang, et al., The adipokine visfatin modulates cancer stem cell properties in triple-negative breast cancer, Biomedicines 11 (2) (2023).
[50] J. Gogola-Mruk, et al., Visfatin induces ovarian cancer resistance to anoikis by regulating mitochondrial activity, Endocrine 80 (2) (2023) 448–458.
[51] A. Kaminska, et al., An evaluation of visfatin levels in obese subjects, Endokrynol. Pol. 61 (2) (2010) 169–173.
[52] I. Jialal, R. Pahwa, Fetuin-A is also an adipokine, Lipids Health Dis. 18 (1) (2019) 73.
[53] J.M. Brix, et al., Elevated Fetuin-A concentrations in morbid obesity decrease after dramatic weight loss, J. Clin. Endocrinol. Metab. 95 (11) (2010) 4877–4881.
[54] T. Funahashi, et al., Role of adipocytokines on the pathogenesis of atherosclerosis in visceral obesity, Intern. Med. 38 (2) (1999) 202–206.
[55] I. Shimomura, et al., Enhanced expression of PAI-1 in visceral fat: possible contributor to vascular disease in obesity, Nat. Med. 2 (7) (1996) 800–803.
[56] K. Annecke, et al., uPA and PAI-1 in breast cancer: review of their clinical utility and current validation in the prospective NNBC-3 trial, Adv. Clin. Chem. 45 (2008) 31–45.
[57] S. Mashiko, et al., Inhibition of plasminogen activator inhibitor-1 is a potential therapeutic strategy in ovarian cancer, Cancer Biol. Ther. 16 (2) (2015) 253–260.
[58] M. Inoue, et al., Plasminogen activator inhibitor-1 (PAI-1) gene transfection inhibits the liver metastasis of pancreatic cancer by preventing angiogenesis, Oncol. Rep. 14 (6) (2005) 1445–1451.
[59] K.A. Rubina, et al., Increased expression of uPA, uPAR, and PAI-1 in psoriatic skin and in basal cell carcinomas, Arch. Dermatol. Res. 309 (6) (2017) 433–442.
[60] S. Verma, et al., Resistin promotes endothelial cell activation: further evidence of adipokine-endothelial interaction, Circulation 108 (6) (2003) 736–740.
[61] H.J. Kim, et al., Expression of resistin in the prostate and its stimulatory effect on prostate cancer cell proliferation, BJU Int. 108 (2 Pt 2) (2011) E77–E83.
[62] C.W. Liu, et al., Resistin stimulates PC-3 prostate cancer cell growth through stimulation of SOCS3 and SOCS5 genes, Exp. Biol. Med. 248 (20) (2023) 1695–1707.
[63] M. Degawa-Yamauchi, et al., Serum resistin (FIZZ3) protein is increased in obese humans, J. Clin. Endocrinol. Metab. 88 (11) (2003) 5452–5455.
[64] R.Z. Yang, et al., Identification of omentin as a novel depot-specific adipokine in human adipose tissue: possible role in modulating insulin action, Am. J. Physiol. Endocrinol. Metab. 290 (6) (2006) E1253–E1261.
[65] M. Sperling, et al., Association of serum omentin-1 concentration with the content of adipose tissue and glucose tolerance in subjects with central obesity, Biomedicines 11 (2) (2023).
[66] H. Ji, et al., The effect of omentin-1 on the proliferation and apoptosis of colon cancer stem cells and the potential mechanism, J BUON 24 (1) (2019) 91–98.
[67] L. Hou, et al., Effect of omentin-1 on cancer stem cell surface markers and tumour-suppressive miRNA expression in a high-glucose environment associated with colorectal cancer, J. Pakistan Med. Assoc. 72 (3) (2022) 430–435.

[68] Q.W. Yan, et al., The adipokine lipocalin 2 is regulated by obesity and promotes insulin resistance, Diabetes 56 (10) (2007) 2533–2540.
[69] T. Auguet, et al., Upregulation of lipocalin 2 in adipose tissues of severely obese women: positive relationship with proinflammatory cytokines, Obesity 19 (12) (2011) 2295–2300.
[70] N. Chaudhary, et al., Lipocalin 2 expression promotes tumor progression and therapy resistance by inhibiting ferroptosis in colorectal cancer, Int. J. Cancer 149 (7) (2021) 1495–1511.
[71] P. Shen, et al., A biomimetic liver cancer on-a-chip reveals a critical role of LIPOCALIN-2 in promoting hepatocellular carcinoma progression, Acta Pharm. Sin. B 13 (11) (2023) 4621–4637.
[72] C. Romere, et al., Asprosin, a fasting-induced glucogenic protein hormone, Cell 165 (3) (2016) 566–579.
[73] D. Lv, et al., A study of the relationship between serum asprosin levels and MAFLD in a population undergoing physical examination, Sci. Rep. 14 (1) (2024) 11170.
[74] E. Inan Yuksel, et al., Role of asprosin and meteorin-like peptide in progression of actinic keratosis to squamous cell carcinoma, Biotech. Histochem. 99 (2) (2024) 61–68.
[75] G.X. Wang, et al., The brown fat-enriched secreted factor Nrg4 preserves metabolic homeostasis through attenuation of hepatic lipogenesis, Nat. Med. 20 (12) (2014) 1436–1443.
[76] R. Wang, et al., Differences in neuregulin 4 expression in children: effects of fat depots and obese status, Endocr. Res. 45 (3) (2020) 190–201.
[77] C. Cai, et al., Association of circulating neuregulin 4 with metabolic syndrome in obese adults: a cross-sectional study, BMC Med. 14 (1) (2016) 165.
[78] P. Zhang, et al., Neuregulin 4 suppresses NASH-HCC development by restraining tumor-prone liver microenvironment, Cell Metabol. 34 (9) (2022) 1359–1376 e7.
[79] K. Hida, et al., Visceral adipose tissue-derived serine protease inhibitor: a unique insulin-sensitizing adipocytokine in obesity, Proc. Natl. Acad. Sci. U. S. A. 102 (30) (2005) 10610–10615.
[80] R. Feng, et al., Higher vaspin levels in subjects with obesity and type 2 diabetes mellitus: a meta-analysis, Diabetes Res. Clin. Pract. 106 (1) (2014) 88–94.
[81] X.H. Cao, et al., Vaspin accelerates the proliferation, invasion and metastasis of Triple-Negative breast cancer through MiR-33a-5p/ABHD2, Cancer Med. 12 (4) (2023) 4530–4542.
[82] M.A. Peter, et al., Regulation of insulin-like growth factor-I (IGF-I) and IGF-binding proteins by growth hormone in rat white adipose tissue, Endocrinology 133 (6) (1993) 2624–2631.
[83] K. Al-Regaiey, et al., Effects of gastric sleeve surgery on the serum levels of GH, IGF-1 and IGF-binding protein 2 in healthy obese patients, BMC Gastroenterol. 20 (1) (2020) 199.
[84] H. Liu, et al., Silencing IGFBP-2 decreases pancreatic cancer metastasis and enhances chemotherapeutic sensitivity, Oncotarget 8 (37) (2017) 61674–61686.
[85] M. Mraz, et al., Serum concentrations and tissue expression of a novel endocrine regulator fibroblast growth factor-21 in patients with type 2 diabetes and obesity, Clin. Endocrinol. 71 (3) (2009) 369–375.
[86] R.Y. Gao, et al., Serum fibroblast growth factor 21 levels are positively associated with metabolic syndrome in patients with type 2 diabetes, Internet J. Endocrinol. 2019 (2019) 5163245.
[87] C. Tsutsumi, et al., Retinoids and retinoid-binding protein expression in rat adipocytes, J. Biol. Chem. 267 (3) (1992) 1805–1810.
[88] P.A. Nono Nankam, M. Bluher, Retinol-binding protein 4 in obesity and metabolic dysfunctions, Mol. Cell. Endocrinol. 531 (2021) 111312.
[89] Y. Wang, Y. Wang, Z. Zhang, Adipokine RBP4 drives ovarian cancer cell migration, J. Ovarian Res. 11 (1) (2018) 29.
[90] G.W. Wong, et al., A family of Acrp30/adiponectin structural and functional paralogs, Proc. Natl. Acad. Sci. U. S. A. 101 (28) (2004) 10302–10307.
[91] H. Akiyama, et al., Elevated expression of CTRP3/cartducin contributes to promotion of osteosarcoma cell proliferation, Oncol. Rep. 21 (6) (2009) 1477–1481.
[92] T. Chen, et al., Serum CTRP3 levels in obese children: a potential protective adipokine of obesity, insulin sensitivity and pancreatic beta cell function, Diabetes Metab Syndr Obes 12 (2019) 1923–1930.
[93] S.M. Masoodian, et al., Increased mRNA expression of CTRP3 and CTRP9 in adipose tissue from obese women: is it linked to obesity-related parameters and mRNA expression of inflammatory cytokines? Rep Biochem Mol Biol 9 (1) (2020) 71–81.
[94] G.W. Wong, et al., Identification and characterization of CTRP9, a novel secreted glycoprotein, from adipose tissue that reduces serum glucose in mice and forms heterotrimers with adiponectin, Faseb. J. 23 (1) (2009) 241–258.
[95] R.M. Wolf, et al., C1q/TNF-Related protein-9 (CTRP9) levels are associated with obesity and decrease following weight loss surgery, J. Clin. Endocrinol. Metab. 101 (5) (2016) 2211–2217.
[96] P. Bostrom, et al., A PGC1-alpha-dependent myokine that drives brown-fat-like development of white fat and thermogenesis, Nature 481 (7382) (2012) 463–468.
[97] A. Roca-Rivada, et al., FNDC5/irisin is not only a myokine but also an adipokine, PLoS One 8 (4) (2013) e60563.
[98] J.M. Moreno-Navarrete, et al., Irisin is expressed and produced by human muscle and adipose tissue in association with obesity and insulin resistance, J. Clin. Endocrinol. Metab. 98 (4) (2013) E769–E778.
[99] A. Saeedi Sadr, et al., The effect of irisin on proliferation, apoptosis, and expression of metastasis markers in prostate cancer cell lines, Oncol Ther 10 (2) (2022) 377–388.
[100] J. Jia, et al., Relationship between circulating irisin levels and overweight/obesity: a meta-analysis, World J Clin Cases 7 (12) (2019) 1444–1455.
[101] K. Tatemoto, et al., Isolation and characterization of a novel endogenous peptide ligand for the human APJ receptor, Biochem. Biophys. Res. Commun. 251 (2) (1998) 471–476.
[102] C. Mund, et al., Study of serum apelin and insulin resistance in type 2 diabetes mellitus patients with or without obesity, Cureus 15 (8) (2023) e43401.
[103] T.H. Lin, et al., Apelin promotes prostate cancer metastasis by downregulating TIMP2 via increases in miR-106a-5p expression, Cells 11 (20) (2022).
[104] D. Hu, et al., Apelin is associated with clinicopathological parameters and prognosis in breast cancer patients, Arch. Gynecol. Obstet. 306 (4) (2022) 1185–1195.
[105] M. Tabata, et al., Angiopoietin-like protein 2 promotes chronic adipose tissue inflammation and obesity-related systemic insulin resistance, Cell Metabol. 10 (3) (2009) 178–188.
[106] A. Muramoto, et al., Angiopoietin-like protein 2 sensitively responds to weight reduction induced by lifestyle intervention on overweight Japanese men, Nutr. Diabetes 1 (11) (2011) e20.
[107] M. Endo, et al., Tumor cell-derived angiopoietin-like protein ANGPTL2 is a critical driver of metastasis, Cancer Res. 72 (7) (2012) 1784–1794.
[108] H. Horiguchi, et al., Angiopoietin-like protein 2 renders colorectal cancer cells resistant to chemotherapy by activating spleen tyrosine kinase-phosphoinositide 3-kinase-dependent anti-apoptotic signaling, Cancer Sci. 105 (12) (2014) 1550–1559.
[109] K.B. Goralski, et al., Chemerin, a novel adipokine that regulates adipogenesis and adipocyte metabolism, J. Biol. Chem. 282 (38) (2007) 28175–28188.
[110] Y. Li, B. Shi, S. Li, Association between serum chemerin concentrations and clinical indices in obesity or metabolic syndrome: a meta-analysis, PLoS One 9 (12) (2014) e113915.
[111] N. Nakamura, et al., Chemerin promotes angiogenesis in vivo, Phys. Rep. 6 (24) (2018) e13962.
[112] A. Tonjes, et al., Adipokine pattern in subjects with impaired fasting glucose and impaired glucose tolerance in comparison to normal glucose tolerance and diabetes, PLoS One 5 (11) (2010) e13911.
[113] H. Qu, H. Deng, Z. Hu, Plasma progranulin concentrations are increased in patients with type 2 diabetes and obesity and correlated with insulin resistance, Mediat. Inflamm. 2013 (2013) 360190.
[114] W. Fang, et al., Progranulin induces immune escape in breast cancer via up-regulating PD-L1 expression on tumor-associated macrophages (TAMs) and promoting CD8(+) T cell exclusion, J. Exp. Clin. Cancer Res. 40 (1) (2021) 4.
[115] J. Zhao, et al., Effect of progranulin on migration and invasion of human colon cancer cells, J Coll Physicians Surg Pak 28 (8) (2018) 607–611.
[116] R. Nosalski, T.J. Guzik, Perivascular adipose tissue inflammation in vascular disease, Br. J. Pharmacol. 174 (20) (2017) 3496–3513.
[117] V. Catalan, et al., Proinflammatory cytokines in obesity: impact of type 2 diabetes mellitus and gastric bypass, Obes. Surg. 17 (11) (2007) 1464–1474.
[118] K. Izumi, et al., Serum chemokine (CC motif) ligand 2 level as a diagnostic, predictive, and prognostic biomarker for prostate cancer, Oncotarget 7 (7) (2016) 8389–8398.
[119] D. Li, et al., Tumor-associated macrophages secrete CC-chemokine ligand 2 and induce tamoxifen resistance by activating PI3K/Akt/mTOR in breast cancer, Cancer Sci. 111 (1) (2020) 47–58.
[120] L. Li, et al., High levels of CCL2 or CCL4 in the tumor microenvironment predict unfavorable survival in lung adenocarcinoma, Thorac Cancer 9 (7) (2018) 775–784.
[121] M. Xu, et al., Role of the CCL2-CCR2 signalling axis in cancer: mechanisms and therapeutic targeting, Cell Prolif. 54 (10) (2021) e13115.
[122] A. Bouloumie, et al., Adipocyte produces matrix metalloproteinases 2 and 9: involvement in adipose differentiation, Diabetes 50 (9) (2001) 2080–2086.
[123] G. Derosa, et al., Matrix metalloproteinase-2 and -9 levels in obese patients, Endothelium 15 (4) (2008) 219–224.
[124] H. Kanayama, Matrix metalloproteinases and bladder cancer, J. Med. Invest. 48 (1–2) (2001) 31–43.
[125] D. Karmakar, et al., E2F5 promotes prostate cancer cell migration and invasion through regulation of TFPI2, MMP-2 and MMP-9, Carcinogenesis 41 (12) (2020) 1767–1780.
[126] E.K. Oikonomou, C. Antoniades, The role of adipose tissue in cardiovascular health and disease, Nat. Rev. Cardiol. 16 (2) (2019) 83–99.
[127] L. Sylow, et al., Circulating follistatin and activin A and their regulation by insulin in obesity and type 2 diabetes, J. Clin. Endocrinol. Metab. 105 (5) (2020).
[128] M. Nomura, et al., Activin type IB receptor signaling in prostate cancer cells promotes lymph node metastasis in a xenograft model, Biochem. Biophys. Res. Commun. 430 (1) (2013) 340–346.
[129] M. Kalli, et al., Activin A signaling regulates IL13Ralpha2 expression to promote breast cancer metastasis, Front. Oncol. 9 (2019) 32.
[130] K.P. Chang, et al., Overexpression of activin A in oral squamous cell carcinoma: association with poor prognosis and tumor progression, Ann. Surg Oncol. 17 (7) (2010) 1945–1956.
[131] A. Zauberman, M. Oren, D. Zipori, Involvement of p21(WAF1/Cip1), CDK4 and Rb in activin A mediated signaling leading to hepatoma cell growth inhibition, Oncogene 15 (14) (1997) 1705–1711.
[132] H. Kaneda, et al., Activin A inhibits vascular endothelial cell growth and suppresses tumour angiogenesis in gastric cancer, Br. J. Cancer 105 (8) (2011) 1210–1217.
[133] R. Madani, et al., RANTES release by human adipose tissue in vivo and evidence for depot-specific differences, Am. J. Physiol. Endocrinol. Metab. 296 (6) (2009) E1262–E1268.

[134] E. Maury, et al., Adipokines oversecreted by omental adipose tissue in human obesity, Am. J. Physiol. Endocrinol. Metab. 293 (3) (2007) E656–E665.
[135] D. Dangaj, et al., Cooperation between constitutive and inducible chemokines enables T cell engraftment and immune attack in solid tumors, Cancer Cell 35 (6) (2019) 885–900 e10.
[136] X.N. Zhang, et al., Pericytes augment glioblastoma cell resistance to temozolomide through CCL5-CCR5 paracrine signaling, Cell Res. 31 (10) (2021) 1072–1087.
[137] E. Lengyel, et al., Cancer as a matter of fat: the crosstalk between adipose tissue and tumors, Trends Cancer 4 (5) (2018) 374–384.
[138] Y. Wu, et al., Circulating insulin-like growth factor-I levels regulate colon cancer growth and metastasis, Cancer Res. 62 (4) (2002) 1030–1035.
[139] P. Juiz-Valina, et al., Altered GH-IGF-1 Axis in severe obese subjects is reversed after bariatric surgery-induced weight loss and related with low-grade chronic inflammation, J. Clin. Med. 9 (8) (2020).
[140] J. Frystyk, et al., Free insulin-like growth factors in human obesity, Metabolism 44 (10 Suppl 4) (1995) 37–44.
[141] C. Pages, et al., Lysophosphatidic acid synthesis and release, Prostag. Other Lipid Mediat. 64 (1–4) (2001) 1–10.
[142] S. Fayyaz, et al., Lysophosphatidic acid inhibits insulin signaling in primary rat hepatocytes via the LPA3 receptor subtype and is increased in obesity, Cell. Physiol. Biochem. 43 (2) (2017) 445–456.
[143] R. Guo, et al., Expression and function of lysophosphatidic acid LPA1 receptor in prostate cancer cells, Endocrinology 147 (10) (2006) 4883–4892.
[144] G.E. Genc, et al., Lysophosphatidic acid represses autophagy in prostate carcinoma cells, Biochem. Cell. Biol. 97 (4) (2019) 387–396.
[145] R. Schlich, et al., VEGF in the crosstalk between human adipocytes and smooth muscle cells: depot-specific release from visceral and perivascular adipose tissue, Mediat. Inflamm. 2013 (2013) 982458.
[146] S. Miyazawa-Hoshimoto, et al., Elevated serum vascular endothelial growth factor is associated with visceral fat accumulation in human obese subjects, Diabetologia 46 (11) (2003) 1483–1488.
[147] S. Ghalehbandi, et al., The role of VEGF in cancer-induced angiogenesis and research progress of drugs targeting VEGF, Eur. J. Pharmacol. 949 (2023) 175586.
[148] D.P. Berger, et al., Vascular endothelial growth factor (VEGF) mRNA expression in human tumor models of different histologies, Ann. Oncol. 6 (8) (1995) 817–825.
[149] M. Pardo, et al., Obesidomics: contribution of adipose tissue secretome analysis to obesity research, Endocrine 41 (3) (2012) 374–383.
[150] L.F. Palomera, et al., Serum levels of interleukin-1 beta associate better with severity of simple steatosis than liver function tests in morbidly obese patients, J. Res. Med. Sci. 23 (2018) 93.
[151] A.V. Maker, et al., Cyst fluid interleukin-1beta (IL1beta) levels predict the risk of carcinoma in intraductal papillary mucinous neoplasms of the pancreas, Clin. Cancer Res. 17 (6) (2011) 1502–1508.
[152] J.A. Del Campo, P. Gallego, L. Grande, Role of inflammatory response in liver diseases: therapeutic strategies, World J. Hepatol. 10 (1) (2018) 1–7.
[153] V. Mohamed-Ali, et al., Subcutaneous adipose tissue releases interleukin-6, but not tumor necrosis factor-alpha, in vivo, J. Clin. Endocrinol. Metab. 82 (12) (1997) 4196–4200.
[154] L. Roytblat, et al., Raised interleukin-6 levels in obese patients, Obes. Res. 8 (9) (2000) 673–675.
[155] M.A. Huseni, et al., CD8(+) T cell-intrinsic IL-6 signaling promotes resistance to anti-PD-L1 immunotherapy, Cell Rep Med 4 (1) (2023) 100878.
[156] H. Korkaya, et al., Activation of an IL6 inflammatory loop mediates trastuzumab resistance in HER2+ breast cancer by expanding the cancer stem cell population, Mol. Cell 47 (4) (2012) 570–584.
[157] G.S. Hotamisligil, N.S. Shargill, B.M. Spiegelman, Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance, Science 259 (5091) (1993) 87–91.
[158] P. Dandona, et al., Tumor necrosis factor-alpha in sera of obese patients: fall with weight loss, J. Clin. Endocrinol. Metab. 83 (8) (1998) 2907–2910.
[159] D. Cruceriu, et al., The dual role of tumor necrosis factor-alpha (TNF-alpha) in breast cancer: molecular insights and therapeutic approaches, Cell. Oncol. 43 (1) (2020) 1–18.
[160] Y. Qu, et al., The effects of TNF-alpha/TNFR2 in regulatory T cells on the microenvironment and progression of gastric cancer, Int. J. Cancer 150 (8) (2022) 1373–1391.
[161] Z.B. Deng, et al., Adipose tissue exosome-like vesicles mediate activation of macrophage-induced insulin resistance, Diabetes 58 (11) (2009) 2498–2505.
[162] M.L. Liu, et al., Cholesterol-induced membrane microvesicles as novel carriers of damage-associated molecular patterns: mechanisms of formation, action, and detoxification, Arterioscler. Thromb. Vasc. Biol. 32 (9) (2012) 2113–2121.
[163] Y. Kim, O.K. Kim, Potential roles of adipocyte extracellular vesicle-derived miRNAs in obesity-mediated insulin resistance, Adv. Nutr. 12 (2) (2021) 566–574.
[164] L. Rios-Colon, et al., The role of exosomes in the crosstalk between adipocytes and liver cancer cells, Cells 9 (9) (2020).
[165] I. Wernstedt Asterholm, et al., Adipocyte inflammation is essential for healthy adipose tissue expansion and remodeling, Cell Metabol. 20 (1) (2014) 103–118.
[166] A. Gilani, et al., Adipose signals regulating distal organ health and disease, Diabetes 73 (2) (2024) 169–177.
[167] M. Recarte, et al., Improvement of low-grade inflammation in patients with metabolically healthy severe obesity after primary bariatric surgery, Obes. Surg. 33 (1) (2023) 38–46.
[168] M. Norreen-Thorsen, et al., A human adipose tissue cell-type transcriptome atlas, Cell Rep. 40 (2) (2022) 111046.
[169] M.P. Emont, et al., A single-cell atlas of human and mouse white adipose tissue, Nature 603 (7903) (2022) 926–933.
[170] J. Vijay, et al., Single-cell analysis of human adipose tissue identifies depot and disease specific cell types, Nat. Metab. 2 (1) (2020) 97–109.
[171] M.M. Ibrahim, Subcutaneous and visceral adipose tissue: structural and functional differences, Obes. Rev. 11 (1) (2010) 11–18.
[172] H.S. Park, K. Lee, Greater beneficial effects of visceral fat reduction compared with subcutaneous fat reduction on parameters of the metabolic syndrome: a study of weight reduction programmes in subjects with visceral and subcutaneous obesity, Diabet. Med. 22 (3) (2005) 266–272.
[173] F. Greco, et al., Fat matters: exploring cancer risk through the lens of computed tomography and visceral adiposity, J. Clin. Med. 13 (2) (2024).
[174] K. Mitsushio, et al., Interrelationships among accumulations of intra- and peri-organ fat, visceral fat, and subcutaneous fat, Diabetes 73 (7) (2024) 1122–1126.
[175] M.J. Lee, J. Kim, The pathophysiology of visceral adipose tissues in cardiometabolic diseases, Biochem. Pharmacol. 222 (2024) 116116.
[176] F. Xu, et al., The relationship between fat distribution and diabetes in US adults by race/ethnicity, Front. Public Health 12 (2024) 1373544.
[177] K. Ziqubu, et al., Brown adipose tissue-derived metabolites and their role in regulating metabolism, Metabolism 150 (2024) 155709.
[178] A.M. Cypess, et al., Identification and importance of brown adipose tissue in adult humans, N. Engl. J. Med. 360 (15) (2009) 1509–1517.
[179] K.A. Virtanen, et al., Functional brown adipose tissue in healthy adults, N. Engl. J. Med. 360 (15) (2009) 1518–1525.
[180] S. Enerbäck, The origins of brown adipose tissue, N. Engl. J. Med. 360 (19) (2009) 2021–2023.
[181] Z. Qiu, et al., Associations of regional body fat with risk of cardiovascular disease and mortality among individuals with type 2 diabetes, J. Clin. Endocrinol. Metab. 00 (2024) 1–10.
[182] D. Zheng, et al., Association between visceral adiposity index and risk of diabetes and prediabetes: results from the NHANES (1999-2018), PLoS One 19 (4) (2024) e0299285.
[183] D. Salihefendic, M. Zildzic, I. Masic, The importance of the quantity and the distribution assessment of fat tissue in a diagnosis of insulin resistance, Med. Arch. 74 (6) (2020) 439–443.
[184] G.H. Goossens, The metabolic phenotype in obesity: fat mass, body fat distribution, and adipose tissue function, Obes. Facts 10 (3) (2017) 207–215.
[185] Y. Matsuzawa, T. Funahashi, T. Nakamura, The concept of metabolic syndrome: contribution of visceral fat accumulation and its molecular mechanism, J. Atherosclerosis Thromb. 18 (8) (2011) 629–639.
[186] S.K. Fried, Adipose 'neighborhoods' collaborate to maintain metabolic health, Curr. Opin. Genet. Dev. 81 (2023) 102079.
[187] S. Dhokte, K. Czaja, Visceral adipose tissue: the hidden culprit for type 2 diabetes, Nutrients 16 (7) (2024).
[188] M. Alser, K. Naja, M.A. Elrayess, Mechanisms of body fat distribution and gluteal-femoral fat protection against metabolic disorders, Front. Nutr. 11 (2024) 1368966.
[189] G. Multhoff, M. Molls, J. Radons, Chronic inflammation in cancer development, Front. Immunol. 2 (2011) 98.
[190] D. Bradley, et al., Adipose tissue T regulatory cells: implications for health and disease, Adv. Exp. Med. Biol. 1278 (2021) 125–139.
[191] D. Bradley, et al., Interferon gamma mediates the reduction of adipose tissue regulatory T cells in human obesity, Nat. Commun. 13 (1) (2022) 5606.
[192] T. Deng, et al., Class II major histocompatibility complex plays an essential role in obesity-induced adipose inflammation, Cell Metabol. 17 (3) (2013) 411–422.
[193] M. Feuerer, et al., Lean, but not obese, fat is enriched for a unique population of regulatory T cells that affect metabolic parameters, Nat. Med. 15 (8) (2009) 930–939.
[194] C.N. Lumeng, et al., Increased inflammatory properties of adipose tissue macrophages recruited during diet-induced obesity, Diabetes 56 (1) (2007) 16–23.
[195] C.N. Lumeng, J.L. Bodzin, A.R. Saltiel, Obesity induces a phenotypic switch in adipose tissue macrophage polarization, J. Clin. Invest. 117 (1) (2007) 175–184.
[196] A. Castoldi, et al., The macrophage switch in obesity development, Front. Immunol. 6 (2015) 637.
[197] C. Yunna, et al., Macrophage M1/M2 polarization, Eur. J. Pharmacol. 877 (2020) 173090.
[198] T. Chavakis, V.I. Alexaki, A.W. Ferrante Jr., Macrophage function in adipose tissue homeostasis and metabolic inflammation, Nat. Immunol. 24 (5) (2023) 757–766.
[199] F. Gao, B. Litchfield, H. Wu, Adipose tissue lymphocytes and obesity, J Cardiovasc Aging 4 (1) (2024).
[200] S. Nishimura, et al., CD8+ effector T cells contribute to macrophage recruitment and adipose tissue inflammation in obesity, Nat. Med. 15 (8) (2009) 914–920.
[201] S. Kiran, et al., High fat diet-induced CD8(+) T cells in adipose tissue mediate macrophages to sustain low-grade chronic inflammation, Front. Immunol. 12 (2021) 680944.
[202] A. Eljaafari, et al., Adipose tissue-derived stem cells from obese subjects contribute to inflammation and reduced insulin response in adipocytes through differential regulation of the Th1/Th17 balance and monocyte activation, Diabetes 64 (7) (2015) 2477–2488.
[203] S.H. Lee, et al., IL-17 axis accelerates the inflammatory progression of obese in mice via TBK1 and IKBKE pathway, Immunol. Lett. 184 (2017) 67–75.

[204] Y. Chen, et al., Adipose tissue dendritic cells enhances inflammation by prompting the generation of Th17 cells, PLoS One 9 (3) (2014) e92450.
[205] E. Uribe-Querol, C. Rosales, Neutrophils actively contribute to obesity-associated inflammation and pathological complications, Cells 11 (12) (2022).
[206] G. Matarese, The link between obesity and autoimmunity, Science 379 (6639) (2023) 1298–1300.
[207] J.M. Carter, et al., Macrophagic "Crown-like structures" are associated with an increased risk of breast cancer in benign breast disease, Cancer Prev. Res. 11 (2) (2018) 113–119.
[208] M.L. Maliniak, et al., Detection of crown-like structures in breast adipose tissue and clinical outcomes among African-American and White women with breast cancer, Breast Cancer Res. 22 (1) (2020) 65.
[209] N.M. Iyengar, et al., Systemic correlates of white adipose tissue inflammation in early-stage breast cancer, Clin. Cancer Res. 22 (9) (2016) 2283–2289.
[210] M.C. Zwager, et al., Presence of crown-like structures in breast adipose tissue; differences between healthy controls, BRCA1/2 gene mutation carriers and breast cancer patients, Breast Cancer Res. Treat. 204 (1) (2024) 27–37.
[211] S. Cinti, et al., Adipocyte death defines macrophage localization and function in adipose tissue of obese mice and humans, J. Lipid Res. 46 (11) (2005) 2347–2355.
[212] I. Murano, et al., Dead adipocytes, detected as crown-like structures, are prevalent in visceral fat depots of genetically obese mice, J. Lipid Res. 49 (7) (2008) 1562–1568.
[213] I. Mellman, et al., The cancer-immunity cycle: indication, genotype, and immunotype, Immunity 56 (10) (2023) 2188–2205.
[214] D.S. Chen, I. Mellman, Oncology meets immunology: the cancer-immunity cycle, Immunity 39 (1) (2013) 1–10.
[215] N.D. Huntington, J. Cursons, J. Rautela, The cancer-natural killer cell immunity cycle, Nat. Rev. Cancer 20 (8) (2020) 437–454.
[216] D.S. Vinay, et al., Immune evasion in cancer: mechanistic basis and therapeutic strategies, Semin. Cancer Biol. 35 (Suppl) (2015) S185–s198.
[217] K. Dhatchinamoorthy, J.D. Colbert, K.L. Rock, Cancer immune evasion through loss of MHC class I antigen presentation, Front. Immunol. 12 (2021) 636568.
[218] P. Sharma, et al., Primary, adaptive, and acquired resistance to cancer immunotherapy, Cell 168 (4) (2017) 707–723.
[219] L. Ai, A. Xu, J. Xu, Roles of PD-1/PD-L1 pathway: signaling, cancer, and beyond, Adv. Exp. Med. Biol. 1248 (2020) 33–59.
[220] Q. Tang, et al., The role of PD-1/PD-L1 and application of immune-checkpoint inhibitors in human cancers, Front. Immunol. 13 (2022) 964442.
[221] R. Liu, H.F. Li, S. Li, PD-1-mediated inhibition of T cell activation: mechanisms and strategies for cancer combination immunotherapy, Cell Insight 3 (2) (2024) 100146.
[222] S.A. Lasser, et al., Myeloid-derived suppressor cells in cancer and cancer therapy, Nat. Rev. Clin. Oncol. 21 (2) (2024) 147–164.
[223] O. Goldmann, et al., Mechanisms underlying immunosuppression by regulatory cells, Front. Immunol. 15 (2024) 1328193.
[224] C. Tay, A. Tanaka, S. Sakaguchi, Tumor-infiltrating regulatory T cells as targets of cancer immunotherapy, Cancer Cell 41 (3) (2023) 450–465.
[225] L. van Vlerken-Ysla, et al., Functional states of myeloid cells in cancer, Cancer Cell 41 (3) (2023) 490–504.
[226] S. Yenyuwadee, et al., The evolving role of tissue-resident memory T cells in infections and cancer, Sci. Adv. 8 (33) (2022) eabo5871.
[227] J.S. Yi, M.A. Cox, A.J. Zajac, T-cell exhaustion: characteristics, causes and conversion, Immunology 129 (4) (2010) 474–481.
[228] L.M. McLane, M.S. Abdel-Hakeem, E.J. Wherry, CD8 T cell exhaustion during chronic viral infection and cancer, Annu. Rev. Immunol. 37 (2019) 457–495.
[229] Z. Wang, et al., Paradoxical effects of obesity on T cell function during tumor progression and PD-1 checkpoint blockade, Nat. Med. 25 (1) (2019) 141–151.
[230] A.K. Pingili, et al., Immune checkpoint blockade reprograms systemic immune landscape and tumor microenvironment in obesity-associated breast cancer, Cell Rep. 35 (12) (2021) 109285.
[231] M.J. Woodall, et al., The effects of obesity on anti-cancer immunity and cancer immunotherapy, Cancers 12 (5) (2020).
[232] W. Palm, C.B. Thompson, Nutrient acquisition strategies of mammalian cells, Nature 546 (7657) (2017) 234–242.
[233] A.E. Ringel, et al., Obesity shapes metabolism in the tumor microenvironment to suppress anti-tumor immunity, Cell 183 (7) (2020) 1848–1866.e26.
[234] L. Dyck, et al., Suppressive effects of the obese tumor microenvironment on CD8 T cell infiltration and effector function, J. Exp. Med. 219 (3) (2022).
[235] C. Thompson, et al., The adipose tissue-derived secretome (ADS) in obesity uniquely induces L-type amino acid transporter 1 (LAT1) and mTOR signaling in estrogen-receptor-positive breast cancer cells, Int. J. Mol. Sci. 22 (13) (2021).
[236] X. Michelet, et al., Metabolic reprogramming of natural killer cells in obesity limits antitumor responses, Nat. Immunol. 19 (12) (2018) 1330–1340.
[237] D. Jiao, et al., Lipid accumulation-mediated histone hypoacetylation drives persistent NK cell dysfunction in anti-tumor immunity, Cell Rep. 42 (10) (2023) 113211.
[238] I. Prager, C. Watzl, Mechanisms of natural killer cell-mediated cellular cytotoxicity, J. Leukoc. Biol. 105 (6) (2019) 1319–1329.
[239] C.M. Moulin, et al., Bariatric surgery reverses natural killer (NK) cell activity and NK-related cytokine synthesis impairment induced by morbid obesity, Obes. Surg. 21 (1) (2011) 112–118.
[240] C. De Barra, et al., Glucagon-like peptide-1 therapy in people with obesity restores natural killer cell metabolism and effector function, Obesity 31 (7) (2023) 1787–1797.
[241] V.K. Clements, et al., Frontline Science: high fat diet and leptin promote tumor progression by inducing myeloid-derived suppressor cells, J. Leukoc. Biol. 103 (3) (2018) 395–407.
[242] W. Liu, et al., Obesity correlates with the immunosuppressive ILC2s-MDSCs axis in advanced breast cancer, Immun Inflamm Dis 12 (3) (2024) e1196.
[243] M. Hale, et al., Obesity triggers enhanced MDSC accumulation in murine renal tumors via elevated local production of CCL2, PLoS One 10 (3) (2015) e0118784.
[244] A.A. Shea, et al., Obesity modulates the cellular and molecular microenvironment in the peritoneal cavity: implication for ovarian cancer risk, Front. Immunol. 14 (2023) 1323399.
[245] J. Peng, et al., Diet-induced obesity accelerates oral carcinogenesis by recruitment and functional enhancement of myeloid-derived suppressor cells, Cell Death Dis. 12 (10) (2021) 946.
[246] S.A.C. McDowell, et al., Obesity alters monocyte developmental trajectories to enhance metastasis, J. Exp. Med. 220 (8) (2023).
[247] Y. Pan, et al., Tumor-associated macrophages in tumor immunity, Front. Immunol. 11 (2020) 583084.
[248] L. Russo, C.N. Lumeng, Properties and functions of adipose tissue macrophages in obesity, Immunology 155 (4) (2018) 407–417.
[249] A. Sica, A. Mantovani, Macrophage plasticity and polarization: in vivo veritas, J. Clin. Invest. 122 (3) (2012) 787–795.
[250] N. Boufaied, et al., Obesogenic high-fat diet and MYC cooperate to promote lactate accumulation and tumor microenvironment remodeling in prostate cancer, Cancer Res. 84 (11) (2024) 1834–1855.
[251] J.E. Bader, et al., Obesity induces PD-1 on macrophages to suppress anti-tumour immunity, Nature 630 (8018) (2024) 968–975.
[252] N.L. Springer, et al., Obesity-associated extracellular matrix remodeling promotes a macrophage phenotype similar to tumor-associated macrophages, Am. J. Pathol. 189 (10) (2019) 2019–2035.
[253] B. Dirat, et al., Cancer-associated adipocytes exhibit an activated phenotype and contribute to breast cancer invasion, Cancer Res. 71 (7) (2011) 2455–2465.
[254] K.M. Nieman, et al., Adipocytes promote ovarian cancer metastasis and provide energy for rapid tumor growth, Nat. Med. 17 (11) (2011) 1498–1503.
[255] Q. Zhu, et al., Adipocyte mesenchymal transition contributes to mammary tumor progression, Cell Rep. 40 (11) (2022) 111362.
[256] Y.Y. Wang, et al., Mammary adipocytes stimulate breast cancer invasion through metabolic remodeling of tumor cells, JCI Insight 2 (4) (2017) e87489.
[257] S. Balaban, et al., Adipocyte lipolysis links obesity to breast cancer growth: adipocyte-derived fatty acids drive breast cancer cell proliferation and migration, Cancer Metabol. 5 (2017) 1.
[258] K.I. Farag, A. Makkouk, L.A. Norian, Re-evaluating the effects of obesity on cancer immunotherapy outcomes in renal cancer: what do we really know? Front. Immunol. 12 (2021) 668494.
[259] C.L. McIntyre, A. Temesgen, L. Lynch, Diet, nutrient supply, and tumor immune responses, Trends Cancer 9 (9) (2023) 752–763.