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Signals from the Adipose Microenvironment and the Obesity-Cancer Link – A Systematic Review

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Abstract

Obesity and its associated metabolic dysregulation are established risk factors for many cancers. However, the biologic mechanisms underlying this relationship remain incompletely understood. Given the rising rates of both obesity and cancer worldwide, and the challenges for many people to lose excess adipose tissue, a systematic approach to identify potential molecular and metabolic targets is needed to develop effective mechanism-based strategies for the prevention and control of obesity-driven cancer. Epidemiological, clinical, and preclinical data suggest that within the growth-promoting, pro-inflammatory microenvironment accompanying obesity, crosstalk between adipose tissue (comprised of adipocytes, macrophages and other cells) and cancer-prone cells may occur via obesity-associated hormones, cytokines, and other mediators that have been linked to increased cancer risk and/or progression. We report here a systematic review on the direct "crosstalk" between adipose tissue and carcinomas in humans. We identified 4,641 articles with n=20 human clinical studies which are summarized as: (a) breast (n=7), (b) colorectal (n=4), (c) esophageal (n=2), (d) esophageal/colorectal (n=1), (e) endometrial (n=1), (f) prostate (n=4), and (g) ear-nose-throat (ENT) cancer (n=1). Findings from these clinical studies reinforce preclinical data and suggest organ-dependent crosstalk between adipose tissue and carcinomas via VEGF, IL-6, TNF-alpha and other mechanisms. Moreover, visceral white adipose tissue (VAT) plays a more central role as it is more bio-energetically active and is associated with a more pro-cancer secretome than subcutaneous adipose tissue (SAT). Efforts to eavesdrop and ultimately interfere with this cancer-enhancing crosstalk may lead to new targets and strategies for decreasing the burden of obesity-related cancers.

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INTRODUCTION

Obesity is a major global health challenge and is expected to further increase substantially over the next several decades (1). In the United States, 38% of adults are obese, defined as having a body mass index (BMI) >30 kg/m^2, and nearly 8% are extremely obese, with a BMI >40 kg/m^2 (2). A recent summary by the International Agency for Research on Cancer (IARC) reinforced obesity as a risk factor of many cancer types, including colorectal, postmenopausal breast, liver, endometrial, esophageal, kidney (renal cell), gastric, gall bladder, pancreatic, ovarian, thyroid, and multiple myeloma (3).

With cross-sectional studies investigating tumors in overweight or obese cancer patients, new knowledge can be gained on adipose-associated factors that drive tumor development and growth. The interactions between an evolving tumor and its microenvironment are known to involve a complex interplay among multiple cells, local and systemic secreted mediators and other components (4,5). In particular, emerging evidence suggests that non-cancer cell types in the tumor microenvironment, such as adipocytes and macrophages, interact to enhance inflammation, reprogram cancer cell metabolism, and affect processes involved in invasion, metastasis, and immune clearance, all of which can support tumor progression and impact patient outcome (6).

Adipose tissue classification

Adipose tissue can be classified into three different types: white (WAT), brown (BAT) and beige adipose tissue, whose presence differs with development, species, and anatomical location (7). While BAT and beige adipose tissue have been associated with thermoregulation, WAT is considered the key site for energy storage in the form of triacylglycerides (7). WAT can be further divided into distinct body compartments, which have differential impact on disease risk (8). Visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) are characterized by differences in cellular structure, molecular composition, and secretome, each of which may be altered by the degree of adiposity itself (8). VAT is generally considered to be bioenergetically more active and responsive to substrates of the electron transport chain than SAT due to a higher concentration of mitochondria. However, BAT has even higher mitochondrial density than VAT, so the differences in metabolic activity between VAT and SAT can be influenced by their brown or beige adipocyte content. VAT adipocytes are also more lipolytically active than SAT adipocytes and thus, contribute more to plasma free fatty acid levels, particularly in obese individuals. In addition, while pro-and anti-inflammatory mediators and immune cells (e.g. Tregs, TH2, eosinophils, ILC2s) maintain immune balance in the lean (healthy) state of adipose tissue (6), increased WAT mass accelerates chronic inflammation through at least three mechanisms: altered generation of secreted inflammatory factors, increased tissue inflammation (immune cell infiltration and formation of crown-like structures by macrophages surrounding dead or dying adipocytes), and adipose tissue remodeling (9).

Consequently, the evidence has shown a stronger correlation between WAT and cancer risk compared to BAT and beige adipose tissue (10). Visceral fat area has also been found to be a predictive factor of poor survival and treatment outcomes for different cancer types, such as colon, esophageal, and renal cancers (11–14).

Adipose tissue-induced inflammation

Inflammation, a hallmark of cancer (4), has been linked to obesity and cancer in both epidemiological and preclinical research (15). Evidence from preclinical *in vitro* and *in vivo* studies is emerging that obesity-associated adipose-derived factors, including the cytokines interleukin (IL)-6, IL-8, monocyte chemotactic protein 1 (MCP-1), and tumor necrosis factor alpha (TNF-α), as well as infiltrating inflammation-inducing cells (e.g. macrophages) can influence cellular metabolism and promote cancer (see Figure 1) (16–22). This expanded, inflamed adipose tissue appears to increase cancer risk more prominently than obesity itself (6) and may stimulate the hallmark events involved in the development and progression of cancer (23) including cellular transformation; cell survival and proliferation; invasion; angiogenesis; and metastasis (24) (see Figure 1).

O'Flanagan et al has demonstrated that obesity enhances the development and metastatic spread of orthotopically transplanted metM-Wnt^{lung} cells, a triple negative breast cancer (TNBC) cell line that metastasizes to the lung (25). Pascual et al also showed that diet-induced obesity increases the metastatic potential of several types of cancer cells, including oral squamous cell carcinoma, melanoma, luminal breast cancer, bladder cancer and small cell lung carcinoma, in a CD36-dependent manner (26). Muller's group found a metabolic symbiosis between tumor-associated adipocytes and cancer cells involving transfer of triglyceride to the cancer cells, resulting in increased availability of free fatty acids for β-oxidation and enhanced metastatic potential (27). They also established that components of the adipocyte secretome, particularly IL-6, are able to stimulate the invasive capacity of breast cancer cells, independent of any effect on proliferation (28,29).

IL-6 regulates the inflammatory process by inducing the production of acute phase proteins and other inflammatory molecules (e.g. C-reactive protein (CRP), prostaglandins, and fibrinogen), the recruitment of CD3+ T lymphocytes and the proliferation of B-lymphocytes. Recent publications have demonstrated crosstalk between adipose tissue and breast as well as colon cancer cells through IL-6 (16–19,30). For example, Walter et al. have reported that IL-6 is secreted by adipose stromal cells (ASC) and promotes migration and invasion in breast cancer cells (30). A variety of signaling pathways have been investigated to elucidate how IL-6 induces cell proliferation. In colorectal cancer cell lines, for example, IL-6 triggers the phosphorylation of ERK, p38 (MAPK), MEK1/2, JAK2 and STAT3 – signaling molecules which control cell metabolism and proliferation (18). Obesity-associated systemic IL-6 also promotes ASC aromatase expression via direct effects and stimulation of breast cancer cell cyclooxygenase 2 (COX2) expression and prostaglandin E2 (PGE2) production (31). The subsequent elevation in estradiol levels promotes estrogen receptor positive breast cancer cell growth (17).

IL-8 shows chemotactic attributes and is particularly involved in the recruitment of leukocytes. Adipocytes in cancer stroma upregulate the expression of IL-8, which exerts its

effects via the PI3K, JAK/STAT3, ERK and MAPK signaling pathways, resulting in cell proliferation, survival, angiogenesis and invasion (20).

MCP-1, also known as chemokine (CC motif) ligand (CCL2), plays a key role in the recruitment and accumulation of proinflammatory macrophages in both adipose and tumor tissues (16). Studies demonstrated elevated adipose tissue MCP-1 in obese mice compared with lean controls, indicating MCP-1 is an important factor for enhanced macrophage recruitment into obesity-associated adipose tissue (32). Consistent with this observation, obesity-induced MCP-1 (and IL1-β) expression in mammary fat depots leads to increased macrophage recruitment (16).

TNF-α is a cytokine mainly secreted by macrophages, including those in the adipose tissue. In breast cancer cells lines, TNF-α can have either growth promoting or inhibiting properties depending on cell type (19). Reports also suggest that TNF-α contributes to cancer cell proliferation via MAPK and PI3K/AKT signaling pathways (19).

Tumor infiltrating adipose stromal cells (ASC)

In addition to the pro-tumor para- or endocrine effects of inflammatory factors from dysfunctional adipose tissue, several studies have shown that ASC from the adipose actually infiltrate cancer lesions and contribute to a tumor-promoting microenvironment via paracrine and contact-dependent effects. Furthermore, the recruitment of ASC to tumors is enhanced by obesity. Kolonin and colleagues have published several pioneering studies in this area, first demonstrating that GFP-labeled ASC are recruited to tumors, but not other organs (33). They then found that obesity in mice is associated with increased tumor-infiltrating ASC that are traceable to an adipose tissue origin and that these ASC promote tumor growth in multiple cancer models by facilitating tumor vascularization (11–12). ASC migrate to tumors in response to tumor production of CXCL1 and CXCL8 (34). The application of these pre-clinical findings to human disease was evidenced by data indicating that obese prostate cancer patients have increased tumor CXCL1 expression, circulating ASC, and tumor-infiltrating ASC (34) and has been further demonstrated by studies indicating an increase in circulating mesenchymal stromal cells (which include ASC) in obese disease-free donors (35) and colorectal cancer patients (36) as well as an increase in circulating ASC in obese breast cancer survivors (37).

Others have similarly found that ASC play a key role in cancer progression via additional mechanisms, including the promotion of metastasis and alterations in extracellular matrix mechanics (38,39). In addition, obesity has been shown to promote a pro-fibrotic ASC phenotype, leading to a more fibrillar and stiffer extracellular matrix that enhances mammary tumor growth and the tumorigenic potential of pre-malignant human breast epithelial cells (40). These mechanisms may act in parallel to ASC's effects on tumor vascularization, suggesting that the obesity-associated elevation in tumor ASC may play a significant role in obesity-induced tumor progression via multiple mechanisms.

Adipokines and hormones

Leptin is a peptide hormone mainly produced within adipose tissue. Beside its neuroendocrine function controlling food intake, leptin can impact a wide range of biological activities including angiogenesis, bone formation and modulation of immune responses (41,42). The intensity of its production and secretion by adipocytes depends on the body energy status and is highly increased in obese individuals; the resulting leptin resistance causes hyperphagia and increases adipose tissue volume (43).

Obesity-associated hyperleptinemia also promotes chronic low-grade inflammation by stimulating the production of IL-1, IL-6, IL-12 and TNF-α (43,44). In a murine model of preneoplastic (Apc $^{Min/+}$; IMCE) colon epithelial cells, leptin treatment induced the production of IL-6 (18). Consequently, leptin seems to be an important initiating mediator in the pro-inflammatory cascade in adipose tissue (45). Multiple studies have reported that leptin-induced cell signaling cascades are associated with an enhanced risk for different types of cancer such as colorectal, hepatocellular, renal, breast, ovarian, endometrial and prostate (46).

Adiponectin, another major adipokine, antagonizes the oncogenic actions of leptin in several tissues. Also secreted by adipocytes, but at reduced levels in the obese versus non-obese state, adiponectin regulates the effects of insulin on adipocytes and attenuates inflammation (6,47). There is *in vitro* evidence of a protective effect of adiponectin on the development of cancer by inhibiting proliferation and metastasis (48–52). Particularly in breast cancer cells, it has been shown that adiponectin signaling results in antiproliferative responses (48–50). The peptide hormone stimulates AMPK and PPARα signaling and inhibits MAP-kinases pathways via two types of receptors (AdipoR1 and R2) (49,52).

Increased levels of the steroid hormone **estradiol** have been associated with breast and gynecologic cancers, such as cervical, endometrial and ovarian cancer. The conversion of androgen to estradiol by aromatase (a key step in estradiol synthesis) in adipose tissue is the major source of circulating estradiol in postmenopausal women (53). Estradiol's effects are mediated by ER's transcription factor activity as well as its stimulation of PI3K/Akt and MAPK signaling pathways (54). Several *in vitro* studies have demonstrated that obesity-associated factors (e.g. leptin, IL-6, TNF-α) increase the expression and activation of aromatase and estrogen receptors in ASCs and cancer cells (e.g. breast and endometrial) (55–60).

IGF-1 is a growth factor with similar molecular structure and signaling pathways to insulin and is mutagenic in many cancer cell lines (21,61). For example, crosstalk between leptin and IGF-1 has been reported to induce invasion and migration of breast cancer cells (21). Findings from fatless A-Zip/F1 transgenic mice, which lack white adipose tissue and have alipotrophic diabetes, suggest that leptin and adiponectin may be less critical to tumorigenesis when insulin and/or IGF-1 are elevated. Tumor growth in these mice following topical application of a carcinogen or crossbreeding with a transgenic model of breast cancer was enhanced despite the total lack of adipose tissue and associated adipokines (62).

The present report systematically reviews the evidence regarding crosstalk between the adipose tissue (as an entity, comprised of adipocytes, macrophages and others cells) and carcinomas. We characterize the dimensions of this crosstalk in the context of mechanisms highlighted above. In contrast to prior reviews, we describe the direct interactions that occur between tumor cells and adipose tissue compartments in multiple cancer types, where adipose tissue can be adjacent to the tumor or part of the peritumoral microenvironment. Our focus on cross-sectional studies investigating the adipose-tumor crosstalk provides insight into direct adipose-stroma-associated factors that drive tumor development and growth.

METHODS

We conducted a systematic literature search in PubMed/Medline covering publications from January 1946 to March 2017 with the goal to identify literature characterizing crosstalk between adipose tissue and carcinomas.

Two researchers (CH and MD) independently performed two searches with the following search terms: 1) (adipose OR fat OR obese) AND (tissue OR cell) AND (cancer OR tumor) AND (crosstalk OR microenvironment OR paracrine OR milieu OR interaction), and 2) adipose tissue in cancer patients. The queries resulted in 4,641 paper publications.

At the identification stage, abstracts were read, and the articles were selected according to the following inclusion criteria: English language, prospective human clinical studies, adults (>18 years), and solid tumor types (in addition to “cancer” overall, we searched specifically for e.g., breast, gastrointestinal, reproductive, melanoma and renal cancer).

At the screening stage, articles were screened based on the following criteria: crosstalk (e.g. paracrine influence, adipocytes as cancer microenvironment) between adipose tissue and carcinoma in cancer patients. Studies investigating solely the systematic effects of secreted products of either adipose tissue or carcinoma (e.g. inflammation markers, adipokines, hormones measured in plasma or serum) were not included. Because the diverse publications on this topic could not be identified with simple search terms, we used the above described broad search strategy. The primary reasons for exclusion were (1) no cancer patients, (2) animal study, (3) intervention study, (4) review.

Finally, n=20 primary research publications of human clinical studies were found to be directly relevant as describing adipose tissue/tumor interactions and are summarized in Table 1: (a) breast cancer (n=7), (b) colorectal cancer (n=4), (c) esophageal cancer (n=2), (d) esophageal and colorectal cancer (n=1), (e) endometrial (n=1), (f) prostate cancer (n=4), and (g) ear-nose-throat (ENT) cancer (n=1). Disagreements relating to data extraction were discussed between authors and resolved. The overall process is outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA) flow diagram (Figure 2) (63).

RESULTS

1. Adipose tissue in cancer – human clinical studies

N=20 studies have been identified that were conducted in patients with different cancer types (breast, colorectal, esophageal, endometrial, prostate, and ENT) to investigate the crosstalk between patients' adipose tissue and carcinomas (see Table 1) (8,64–75).

The majority of human studies have been conducted in breast cancer patients (n=7) (66,68,70,75–78). Other studies have been implemented in cancers of the gastrointestinal tract (colorectal cancer (n=4) (8,64,71,73), esophageal cancer (n=2) (65,79), combined (colorectal and esophageal) (n=1) (80)), reproductive cancer (endometrial (n=1) (72), prostate (n=4) (69,74,81,82)), or ENT tract (tongue (n=1) (83)).

1.1. Breast cancer—The tumor stroma - consisting of immune cells, fibroblasts, extracellular matrix and other cells - may have profound tumor-promoting effects and plays an important role when investigating the tumor microenvironment. Of interest, while the risk for breast cancer is increased for obese postmenopausal women, premenopausal obese women have a lower incidence of breast cancer (84). Adipocytes comprise about 90% of the normal breast tissue and thus, the question of adipocytes contributing directly to tumor progression as part of the tumor stroma has been addressed in several studies (66,68,70,75,76). Breast cancer stroma can be classified into adipose stroma cancer (>50% of cells are adipocytes), and fibrous stroma cancer (100% of cells are fibroblasts) or a combination of both stroma types (<100% of cells are fibroblasts, <50% are adipocytes) (76).

The most recent study collected benign breast tissue of n=83 postmenopausal women who were recently diagnosed with invasive breast cancer (75). Mullooly et al focused on the association between crown-like structures and steroid hormones in breast adipose tissue (75). In about 36% of the tissue samples crown-like structures were detected, and the frequency was increased in obese individuals (75). Women with a high ratio of estrone:androstendione were more likely to exhibit crown-like structures; individual hormone levels or tumor characteristics were not associated (75).

Another study investigated the association between the densities of tumor-associated macrophages with or without crown-like structures with patient survival (78). Further, the authors assessed whether there are differences between the racial/ethnicity groups (Caucasian, black, non-black Latinas). Densities of tumor-associated macrophages in black breast cancer patients were the highest (mean=142.21 cells/mm^2) compared to Caucasian (62.72 cells/mm^2) and non-black Latinas (110.16 cells/mm^2) (78). Caucasian patients presented with a significantly lower density of tumor-associated macrophages than the other ethnicities ($p<0.0001$) (78). Tumor-associated macrophages detected in the tissue of black patients showed a higher proliferation activity of tumor-associated macrophages and survival rates for black patients were lower than for other ethnicities (78).

In a large study, n=939 breast cancer cases were classified depending on the adipose tissue and fibroblast content within the tumor stroma into adipose stroma type and fibrous stroma

type (76). The differences between these two cancer types were investigated regarding the breast cancer subtypes, molecular tumor characteristics and the patients' outcome (76). Cases with cancer of 'adipose stroma type' showed higher expression of cancer-associated and fibroblast-related proteins (e.g. fibroblast activation protein α (FAPα), prolyl 4-hydroxylase) compared to cases with 'fibrous stroma type'. For example, FAPα, which is reported to be involved in extracellular matrix-modulation and tumor cell invasion, was higher expressed in stroma ($p<0.001$) and tumor ($p<0.001$) cells in 'adipose stroma type' patients (76). Furthermore, among cases of 'adipose stroma type', high tumor expression of prolyl 4-hydroxylase was associated with longer disease-free survival ($p=0.03$) (76). However, stromal expression of prolyl 4-hydroxylase was associated with shorter disease-free ($p=0.005$) and overall ($p<0.001$) survival (76). Taken together, the results show that breast cancer of 'adipose stroma type' present a distinct expression profile that may lead to an increase in cancer growth, invasion and metastasis compared to the 'fibrous stroma type'.

Recently, Iyengar et al focused on breast WAT-induced inflammation which was defined by the presence of crown-like structures within WAT (66). Using biospecimens from two cohorts (cohort 1, prospective (n=100), cohort 2, retrospective (n=127)), they reported that 52 of 100 (52%) and 52 of 127 (41%) patients had breast WAT inflammation, respectively (66). Cohort 1 patients with WAT inflammation experienced increased levels of insulin, glucose, leptin, CRP, and IL-6 and lower high-density lipoprotein cholesterol and adiponectin ($p<0.05$). In cohort 2 WAT-induced inflammation correlated with hyperlipidemia, hypertension and diabetes ($p<0.05$). In both cohorts, WAT inflammation was associated with reduced recurrence-free survival suggesting that WAT inflammation may, at least in part, explain the relationship between metabolic syndrome and worse breast cancer prognosis (66).

The same study presented results on the association between breast WAT inflammation and menopausal status or BMI in n=237 breast cancer patients (77). They reported a significant association between breast tissue-associated crown-like structures (CLS-B) or the crown-like structures' density (CLS-B/cm^2) (indicating WAT inflammation) with menopausal status ($p=0.008$ and $p<0.001$) and BMI (both $p<0.001$) (77). Furthermore, the average size of adipocytes was correlated with crown-like structures in breast tissue ($p<0.001$) (77).

In a small study, Savolainen-Peltonen et al examined the concentrations of estrone, estradiol, and estradiol fatty acyl ester and the mRNA expression of estrogen-converting enzymes in subcutaneous breast adipose tissue (70). Samples were collected from postmenopausal women either with ER-positive breast cancer (n=14) or undergoing breast reduction mammoplasty (controls) (n=14) (70). The concentration of estradiol in breast subcutaneous adipose tissue was reduced in women with cancer compared to controls ($p=0.002$) (70). Expression of *17β-hydroxysteroid dehydrogenase type 12* was also lower in the adipose tissue of breast cancer patients compared to controls ($p=0.018$) (70). This suggests that estradiol metabolism may be differentially regulated in the adipose tissue of women with breast cancer.

Confirming their initial results of links between adiposity and inflammation in a mouse model (85), Morris et al showed in breast tissue of n=30 breast cancer patients that the

severity of breast inflammation, defined as the crow-like structures of the breast index (CLS-B) (number of breast WAT slides with evidence of crown-like structures/ number of breast WAT slides examined), correlated with BMI ($p<0.001$) and adipocyte size ($p=0.01$) (68). In addition, increased NF-kB binding activity and elevated aromatase expression and enzyme activity were found in the inflamed breast tissue of overweight and obese women (68).

In summary, the current evidence on the local interaction between breast WAT and breast cancer cells supports the hypothesis that adipose tissue inflammation, defined by presence of crown-like structures, is a key player in cancer growth and progression. However, the involvement of steroid hormones as drivers of tumor progression represents an additional important aspect of the adipose-cancer link, particularly in hormone-dependent cancers, such as breast or endometrial cancer (17,86–88).

1.2. Colorectal cancer—Four studies were identified that have investigated the crosstalk between adipose tissue and colorectal cancer (8,64,71). Nested in the international cohort study ColoCare, Liesenfeld et al used a multi-omic approach to investigate differences between VAT compared with SAT in patients with colorectal cancer (8). They comprehensively assessed differences in metabolic, lipidomic, and transcriptomic profiles in paired human VAT and SAT samples and their association with colorectal cancer tumor stage (8). Mass spectrometry was used to measure 1,065 metabolites in adipose tissue and 1,810 metabolites in serum of n=59 patients, and parallel genome-wide gene expression data were used to perform integrated analyses of candidate metabolites (8). Compared with SAT, VAT was characterized by elevated markers of inflammatory lipid metabolism, phospholipases (PLA2G10), free arachidonic acid, and prostaglandin synthesis-related enzymes (PTGD/PTGS2S) (8). Several lipids showed a linear association with increasing tumor stage (not significant after correction for multiple testing) (8).

In the same year, Amor et al collected visceral adipose tissue of n=18 colorectal cancer patients and n=18 health controls (73). Participants were classified into four groups: i) obese with cancer, ii) lean with cancer, iii) obese without cancer, and iv) lean without cancer (73). Tissue samples were divided into peritumoral and non-tumoral fat. Their results showed that the secretion activity of peritumoral adipose tissue in cancer patients was higher compared to the control groups and non-tumoral tissue samples (73). Tissue samples from obese cancer patients had also an increased rate of secretion compared to lean patients (73).

Another study examined regional differences (peritumoral and distant from neoplasia) in the expression of lipogenic enzymes (e.g. lipoprotein lipase and fatty acid synthase) and their influence on events which sustain colorectal cancer growth (64). The evaluation of n=32 adipose tissue samples of colorectal cancer patients (adjacent [not defined] and distant [about 10 cm]) to neoplasia showed that lipoprotein lipase, as well as fatty acid synthase were less expressed in adipose tissue adjacent to the tumor compared to adipose tissue distant from the cancer (64). The results underline the influence of cancer cells on environmental adipose tissue’s lipid metabolism, demonstrating a cancer-induced impairment in the formation and lipid storing capacity of adjacent adipose tissue in patients with colorectal cancer (64).

In a small case-control study, differences in VAT gene expression of proinflammatory and angiogenesis-related factors between 11 colorectal cancer patients and 18 healthy individuals were assessed (71). Gene expression of *lipocalin-2, osteopontin, chitinase-3 like-1, TNF-α, HIF1A* and *VEGFA* was significantly elevated in VAT of colorectal cancer patients. These results suggest that inflammatory factors in VAT of colorectal cancer patients are elevated and may accelerate cancer development or progression (71).

In summary, the inflammatory features of the adipose tissue environment embedding the colon and rectum seem to play a crucial role when investigating the tumor-promoting effects of adipose tissue. Only one study considered the reciprocal influence of the tumor on the surrounding adipose tissue. Focusing on only lipogenic enzymes, this study illustrates that the adipose tissue – tumor interaction needs to be considered in both directions.

1.3. Esophageal cancer—A recent study reported that esophageal peritumoral adipose tissue and its secretion of tumor-promoting factors are directly correlated with increased tumor growth (65). Studying the morphological, histological, and molecular characteristics of peritumoral and omental adipose tissue in esophageal cancer patients (n=60), the study was designed to investigate whether adipose depot-specific differences affect tumor behavior (65). Only in peritumoral adipose tissue, increased adipocyte size was directly associated with *leptin* expression, angiogenesis (CD31), and lymph angiogenesis (podoplanin) (65). Thus, peritumoral adipose tissue may directly accelerate the progression of esophageal cancer by secreting paracrine factors; the adipokine leptin seems to be a key player in this crosstalk (65).

Lysaght et al performed flow cytometry to assess the activation of T cells and cytokine production in VAT (omental adipose tissue) of n=35 esophageal cancer patients (79). A large number of lymphocytes was observed in the omentum (79). Both CD4(+) and CD8(+) T cells showed significantly increased expression of the T cell activation markers CD69 ($p< 0{\cdot}001$) and CD107a (CD8(+) T cells: $p<0{\cdot}01$) compared with blood, as well as reduced CD62L expression ($p<0.05$). Similarly, higher proportions of CD45RO(+) T cells compared with CD45RA(+) T cells were present. Interferon γ was significantly elevated in VAT, compared to blood and subcutaneous adipose tissue ($p<0.01$) (79). Overall, this study confirmed that VAT is a major source of activated proinflammatory lymphocytes, which may help fuel chronic inflammation (79).

Although the number of studies in esophageal cancer are limited, they highlight two important aspects. First the theme of inflammatory mechanisms as a key player in the adipose-cancer link is also prominent in this cancer type; second, the fascinating work by Travellin et al (65) highlights the role of peritumoral adipocytes as a carcinogenic driver in esophageal cancer and possibly beyond.

1.4. Colorectal and esophageal cancer (combined)—In 2011, one study investigated the differences in cytokine and adipokine expression of VAT and SAT from normal-weight and centrally obese gastrointestinal cancer patients (including colorectal and esophageal cancer) and their effects on colorectal and esophageal cancer cell lines (80). They observed a higher *IL-6, VEGF* and *LEP* gene expression in VAT compared to SAT and

a higher IL-6 and VEGF protein secretion from VAT into conditioned media compared to SAT (80). Adipose-tissue conditioned media from centrally obese patients induced significantly more proliferation in both esophageal and colorectal cancer cell lines, compared to adipose-tissue conditioned media from non-obese patients. Greater proliferation of cancer cell lines was observed after culture with VAT-conditioned media, compared to SAT-conditioned media. (80). This study illustrates the elevated expression of inflammatory and angiogenesis-related factors in VAT compared to SAT of cancer patients and translates it directly back to impact gastrointestinal cancer cell lines. In particular the link via VEGF highlights a potential mechanism whereby VAT from centrally obese patients may drive carcinogenic progression (80).

1.5 Endometrial cancer—To identify obesity-related endometrial cancer genes via microarray analysis in endometrial and adipose tissues, Modesitt et al collected endometrial tissue, VAT and SAT in n=8 (n=4 with endometrial cancer, n=4 without endometrial cancer) individuals undergoing hysterectomy (72). The authors noted no differences in hormone/metabolite levels between groups (72). Gene set enrichment analysis contrasting patients with and without endometrial cancer showed that endometrial, VAT and SAT displayed 40, 47, and 38 alternatively regulated gene set pathways, respectively (72). Eighteen pathways were regulated in opposite directions between VAT and SAT (72).

The results from this pilot study suggest that SAT and VAT have opposite patterns of gene expression in obese patients with and without endometrial cancer and may provide new potential targets for cancer treatment and prevention for obese women. However, considering the small sample size of this first study, more research is needed.

1.6. Prostate cancer—While visceral obesity has been associated with worse prognosis for prostate cancer patients, peri-prostatic adipose tissue may lead to an increase in the aggressive growth of this disease (69,74,81,82). A recent study analyzed the expression of IL-6, leptin and adiponectin in peri-prostatic adipose tissues specimens from n=30 prostate patients and n=10 non-cancer controls (82). IL-6, leptin and adiponectin gene expression was higher in the samples from prostate cancer patients compared to controls ($p<0.001$) (82). Further, IL-6 expression in adipose tissue was associated with increased aggressiveness of prostate cancer ($p=0.001$) (82).

One study collected peri-prostatic and subcutaneous adipose tissue in n=40 prostate cancer patients (81). In culture with either prostate cancer cells or endothelial cells, the peri-prostatic adipose tissue showed higher proliferative effects compared to SAT (81). Furthermore, this result was more significant in samples of obese patients (BMI≥30 kg/m^2) compared to overweight (25–30 kg/m^2) or lean (<25 kg/m^2) patients (81).

Ribeiro et al (69) conducted a study with n=18 peri-prostatic adipose tissue samples, which were categorized into three groups based on post-surgical diagnosis and pathological analysis. Differentially expressed genes in the peri-prostatic tissue were investigated by microarrays (69). In the tissues of obese and overweight individuals an increased expression of genes were observed that are involved in adipogenic, proliferative and mild immunoinflammatory processes (e.g. *LEP, ANGPT1*) (69). In patients with prostate cancer

the expression profile of peri-prostatic adipose tissue was consistent with hypercellularity and reduced immunosurveillance (69). The authors concluded that their findings are consistent with peri-prostatic adipose tissue among obese individuals providing a favorable environment for prostate cancer progression (69).

In 2009, another study collected peri-prostatic adipose tissue samples from n=7 patients undergoing surgery treatment (74). Analyzing the cytokine expression in the tissue samples, their results showed a 375 times higher expression of IL-6 in the per-prostatic adipose tissue compared to the patients serum sample (74). Further, the phosphorylation cell signaling of STAT3 in peri-prostatic adipose tissue was greater with high grade tumors (74).

All studies of prostate cancer collected peri-prostatic adipose tissue and suggest that altered adipose tissue metabolism in obese individuals forms a more auspicious microenvironment for prostate cancer development. An increase in cell proliferation and expression of proliferative genes, as well as IL-6 has been detected in expanded peri-prostatic adipose tissue of obese individuals. However, the results need to be confirmed in studies with larger sample sizes.

1.7. Ear-nose-throat (ENT) cancer—To assess the association between WAT inflammation of the tongue environmental adipose tissue and squamous cell carcinoma (SCC) of the tongue, Iyengar et al. analyzed n=125 tissue samples from oral cancer patients (83). The presence of dead or dying adipocytes surrounded by macrophages forming crown-like structures was defined as WAT inflammation (83). Thirty-nine percent of the patients presented WAT inflammation, and this was statistically significant associated with BMI, increased tumor thickness, and vascular invasion ($p<0.05$) (83). The cancer-specific survival rate was with 59% (95% CI, 46–76%) lower for patients presenting WAT inflammation compared to patients without (82%; 95% CI, 72–92%) (83). In n=70 patients with early stage SCC (without lymph node involvement, no indication for adjuvant therapy) tongue WAT inflammation was significant associated with both decreased cancer-specific and overall survival ($p<0.05$) (83).

The results of this study suggest that inflammation of neck and tongue WAT plays an important role in the development and growth of oral cancers. However, considering that this is the first study of this cancer type, further investigations are needed to confirm the results.

CONCLUSIONS

Obesity is an established risk and progression factor for many cancers (e.g. breast, colorectal, esophageal), but the underlying mechanisms are incompletely understood. A potential crosstalk between adipose tissue and carcinomas may contribute importantly to the observed associations between obesity and increased cancer risk and/or progression.

In vitro and *in vivo* studies have shown that adipose tissue is enriched for hormones, cytokines and other mediators (e.g., leptin, adiponectin). This milieu has already been characterized as a growth-promoting and pro-inflammatory microenvironment. More recent investigations have used a set of multi-omic techniques, including transcriptomics and metabolomics, yielding novel signals, as well as integrated effects on pathways (10). They

also demonstrated clear distinctions of the adipose tissue type (visceral vs. subcutaneous) by these –omic characterizations.

Here, results of n=20 human clinical studies indicate that a) there is a direct/specific crosstalk between adipose tissue and carcinomas, likely with different mechanisms and different directions depending on the organ system; b) white adipose tissue (WAT) is more important than other adipose pools in this pattern of cellular communication; and c) visceral adipose tissue (VAT) plays a central role as it is metabolically more active than subcutaneous adipose tissue (SAT). In addition, peritumoral adipose tissue that is directly present in the organ may provide an imminently present microenvironment that fosters carcinogenic progression. Whether the mediators and intensity of crosstalk between adipose tissue and cancer is affected by the tissue distance is an important but currently unanswered question.

Despite the intriguing results of studies presented within this systematic review, we still miss the complete picture that elucidates the mechanisms underlying the adipose-tumor crosstalk. In addition to the limitation of small sample sizes in most studies, other aspects that are relevant in inflammatory processes were often not reported or assessed. Inflammation can be modified by several environmental factors, such as age, smoking, medication use and diet. Even though adding another layer of complexity, such variability in the investigated study populations should be considered. Furthermore, as detailed above, distinct adipose tissue compartments have different metabolic capabilities. These potentially generate adipose tissue-specific forces that affect the tumor, locally or systemically. However, only a limited number of studies assessed or has the means to assess the distribution of adipose tissue compartments in individuals. Rather than relying on body mass index, the amount of adipose tissue in a patient and its distribution would be much more informative to investigate the effect of adipose tissues on carcinogenesis to identify means of specific intervention.

Consequently, there is a clear need for larger and more comprehensive investigations of the adipose tissue as a central player in explaining the obesity-cancer link. Overall, data of the human clinical studies, as well as *in vitro* and *in vivo* studies, suggest that efforts to eavesdrop and ultimately interfere with this cancer-enhancing crosstalk between adipose tissue and carcinomas may lead to new targets and strategies for decreasing the burden of obesity-related cancers.

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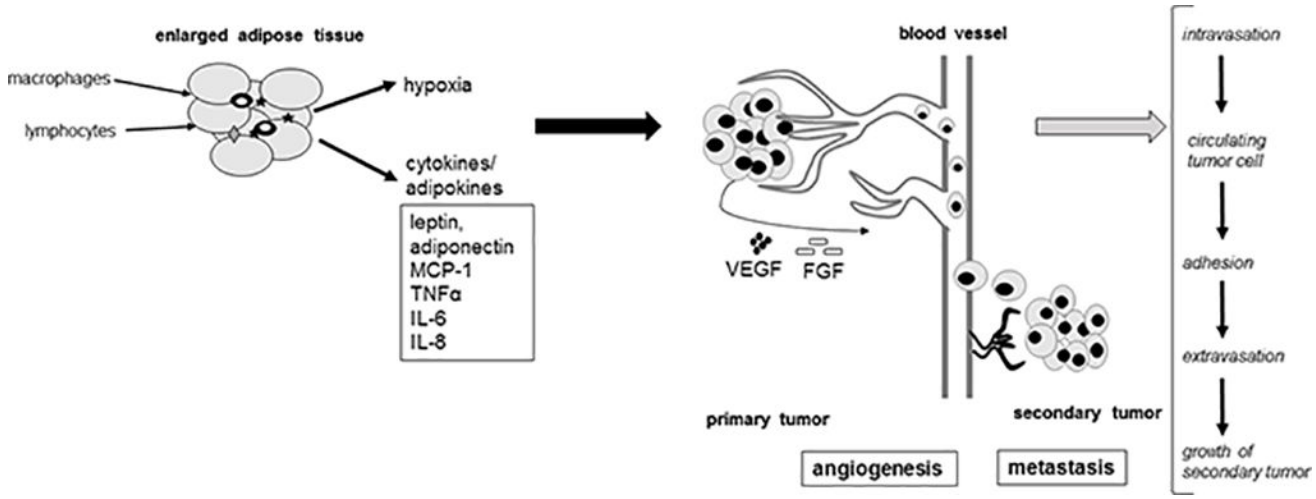

Figure 1.

Adipocyte-secreted cytokines (e.g., leptin, adiponectin, MCP-1, TNFα, IL-6, IL-8) and adipocyte-induced conditions (e.g. hypoxia) and their impact on the main hallmarks of cancer development: proliferation, angiogenesis, metastasis.

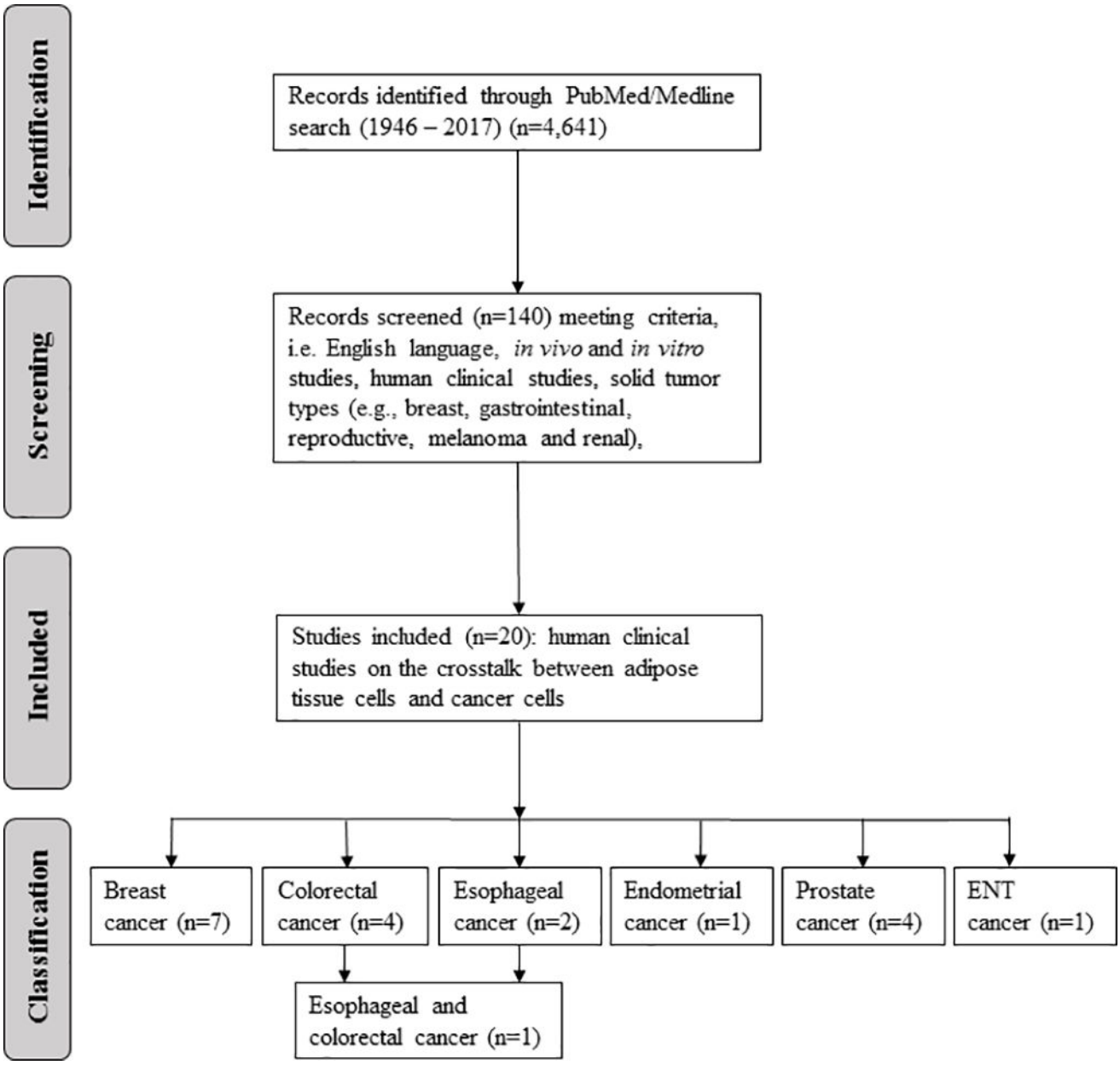

Figure 2.
Preferred Reporting Items for Systematic Reviews and Meta Analyses Protocols (PRISMA) flow diagram (63).

Table 1

Human clinical/ epidemiologic studies

Author (year, journal)	Study population/ tissue type	Focus	Results
Human			
Breast cancer			
Mullooly et al (2017, Breast Cancer Res)	Postmenopausal women (n=83) benign breast tissue	• crown-like structures and sex-steroid hormones in breast adipose tissue	• Crown-like structures were observed in 36% of the tissue samples and increased in obese patients (p=0.03) • Crown-like structures were not related to hormone levels or tumor characteristics, but was associated with hormone ratios
Koru-Sengul et al (2016, Brest Cancer Res Treat)	women (n=150) caucasian (CA), non-black latinas (NBLA), blacks (BL); each breast tissue	• association between the number of tumor-associated macrophages (TAM) and/or crown-like structures with patient survival • differences among ethnicities (caucasian, non-black latinas, blacs)	• significantly different density of TAMs among ethnicities, with black patients having the highest, followed by non-black latinas, and caucasian presenting the lowest density. • the majority of TAMs presented an immunosuppressive, with black patients showing the highest density
Jung et al (2015, Tumour Biol.)	women (n=939) n=642 fibrous stroma type (100% fibrous stroma) n= 297 adipose stroma (>50% adipose tissue in tumor) breast tissue	• relationship between stroma type and tumor phenotype classification • effect of stroma type on gene expression of tumor cell	• luminal A subtype was more prevalent in adipose stroma breast cancer type. ($p<0.001$) • tumor cell expression of podoplanin and FAPα was higher in adipose stroma type, while higher expression of prolyl 4-hydroxylase and PDGFRα in fibrous stroma type.
Iyengar et al (2015, Clin Cancer Res.)	women (n=227) cohort 1: cross-sectional prospective study (n=100) who undergo mastectomy for breast cancer risk reduction (n=10) or treatment (n=90) cohort 2: retrospective study (n=127) who developed metastatic cancer	• breast WAT inflammation • circulating inflammatory factors	• breast white adipose tissue inflammation was detected in 52 of 100 patients (52%) of cohort 1 and 52 of 127 patients (41%) of cohort 2

Author (year, journal)	Study population/ tissue type	Focus	Results
	breast WAT		
Iyengar et al (2015, Cancer Prev Res (Phila))	women (n=237) breast WAT	• association of breast WAT inflammation with BMI and menopause	• WAT inflammation was significantly associated with menopausal status ($p<0.001$) and BMI ($p<0.001$)
Savolainen-Peltonen et al (2014, J Clin Endocrinol metab.)	postmenopausal women (n=14) with ER-positive breast tumor women undergoing breast reduction mammoplasty (n=14) breast subcutaneous adipose tissue	• estrone, estradiol, and estradiol fatty acyl ester concentrations in breast adipose tissue • mRNA expression levels of estrogen-converting enzymes in breast adipose tissue	• estradiol concentration in breast subcutaneous adipose tissue was lower in women with cancer compared to controls ($p=0.002$), whereas the serum concentrations did not differ • mRNA expression for 17β-hydroxysteroid dehydrogenase type 12 was lower in cancer patients ($p=0.018$)
Morris et al (2011, Cancer Prev Res(Phila))	obese (BMI ≥ 30 kg/m^2) women (n=30) breast adipose tissue	• aromatase activity • adipocyte size • serum inflammation marker	• the severity of breast inflammation, defined as the CLS (crown-like structures)-B index, correlated with both body mass index ($P < 0.001$) and adipocyte size ($P = 0.01$) • Increased NF-kB binding activity and elevated aromatase expression and activity were found in the inflamed breast tissue of overweight and obese women
Colorectal cancer			
Liesenfeld et al (2015, Am J Clin Nutr.)	women or men (n=59) VAT and SAT	• VAT and SAT: 1065 metabolites • serum: 1810 metabolites • anthropometric measurements	• VAT displayed elevated markers of inflammatory lipid metabolism, free arachidonic acid, phospholipases (PLA2G10), and prostaglandin synthesis-related enzymes (PTGD/ PTGS2S) • plasmalogen concentrations were lower in VAT than in SAT, which was supported by lower gene expression of FAR1, the rate-limiting enzyme for ether-lipid synthesis in VAT • serum sphingomyelin concentrations were inversely correlated ($P = 0.0001$) with SAT adipose triglycerides • logistic regression identified lipids in patients' adipose tissues,

Author (year, journal)	Study population/ tissue type	Focus	Results
			which were associated with tumor stage
Amor et al (2015, Int J Colorectal Dis.)	Women or men (n=36) Visceral peritumoral and non-tumoral adipose tissue	• differences between obese and lean patients' adipose tissue secretion	• peritumoral adipose tissue secreted higher amounts of nitrites and nitrates than non-tumoral • peritumoral adipose tissue secretion was increased in obese cancer patients
Notarnicola et al (2012, Lipids.)	women or men (n=32) adipose tissue (10 cm distance from tumor location)	• enzymes (LPL and FAS) activity and gene expression	• significant reduction in both LPL and FAS gene expression and activity levels in adipose tissue adjacent to tumor lesion compared to those detected in paired tissue distant from the cancer.
Catalan et al (2011, J Nutr Biochem.)	women or men with colorectal cancer (n=11) healthy women or men (n=18) VAT	• mRNA levels of proinflammatory adipokines (lipocalin-2, chitinase-3 like-1 and osteopontin,IGF1,IGFBP3) and angiogenic-related factors (HIF-1, VAGF, and MMP2 and MMP9) in VAT	• increased mRNA expression levels of lipocalin-2 (p=0.014), osteopontin (p=0.027), TNFα (p=0.016) and chitinase-3 like-1 (p=0.006) in patients with colorectal cancer • significantly higher levels of HIF-1, VAGF and MMP2 (p<0.001) in patients with colorectal cancer • expression of IGF-1, IGFBP3 and MMP9 followed same, but not significant (p>0.001)
Esophageal cancer			
Trevellin et al (2015, Oncotarget.)	women or men (n=60) peritumoral and distal adipose tissue of esophageal cancer patients	• peritumoral adipose tissue: adipocyte and adipokine expression • BMI and obesity-related parameters (e.g. Leptin mRNA levels)	• increased adipocyte size was directly associated with leptin expression, angiogenesis (CD31) and lymph angiogenesis (podoplanin); however, these parameters were associated with nodal metastasis only in peritumoral but not distal adipose tissue of patients
Lysaght et al (2011, Br J Surg.)	women or men (n=35) omental adipose tissue	• T cell activation status and cytokine production in omental adipose tissue	• omental CD4+ and CD8+ T cells displayed significantly enhanced expression of the T cell activation markers CD69 (p<0.001) and CD107a (CD8+ T cells: p<0.01), and significantly decreased CD62L expression (p<0.05), compared with blood • interferon γ was the most abundant cytokine

Author (year, journal)	Study population/ tissue type	Focus	Results
			expressed by omental T cells
Colorectal and Esophageal cancer			
Lysaght et al (2011, Br J Surg.)	women or men (n=35) SAT and VAT of colorectal or esophageal patients	• effect of SAT or VAT conditioned media on colorectal or esophageal cancer cells • levels of pro-inflammatory and tumor proliferative properties in VAT and SAT	• significantly higher levels of VEGF and IL6, and higher proportions of CD8 T cells and NKT cells in VAT • cancer cells cultured with VAT conditioned media shoed significant increase in cell proliferation
Endometrial cancer			
Modesitt et al (2012 Int J Gynaecol Cancer)	women (n=8) with endometrial cancer (n=4) without endometrial cancer (n=4) VAT, SAT and endometrium	• gene expression in VAT and SAT	• n=19 gene sets were regulated in in VAT and SAT • n=47 gene set pathways in in VAT • n=38 gene set pathways in SAT • n=5 pathways were significantly regulated in all 3 tissues including glycolysis/ ribosome, peroxisome proliferator activator receptor signaling, pathogenic Escherichia coli infection, and natural killer-mediated cytotoxicity
Prostate cancer			
Zhang et al (2016, Cytokine)	women or men (n=30) peri-prostatic adipose tissue	• gene expression of IL-6, Leptin and Adiponectin in per-prostatic adipose tissue	• IL-6 and leptin were positively associated to the aggressiveness of prostate cancer, whether adiponectin was negatively associated
Venkatasubramanian et al (2014, Prostate)	men (n=40) peri-prostatic adipose tissue and SAT	• levels of secretes in peri-prostatic adipose tissue	• peri-prostatic adipose tissue secretions were significantly more proliferative in both prostate cancer cells and endothelial cells compared with lean or overweight men and SAT.
Ribeiro et al (2012, BMC Med)	men (n=18) peri-prostatic adipose tissue	• gene expression in human peri-prostatic adipose tissue	• in obese and overweight patient samples increased expression of proliferative, adipogenic, and immunoinflammatory genes (e.g. *LEP* and *ANGPTI*)
Finley et al (2009, J Urology)	men (n=7)	• cytokine expression in peri-prostatic adipose tissue	• IL-6 in periprostatic adipose tissue conditioned mediuim was about 375

Author (year, journal)	Study population/ tissue type	Focus	Results
	peri-prostatic adipose tissue	• inflammatory infiltrates in peri-prostatic adipose tissue	times greater compared to patients' serum • peri-prostatic adipose tissue showed a greater phosphorylation on STAT3 with high grade tumors.
Ear-nose-throat (ENT) cancer			
Iyengar et al (2016, Cancer)	women or men (n=125) tongue and neck tissue	• association between WAT inflammation and cancer-specific survival	• WAT inflammation was associated with BMI, increased tumor thickness, and vascular invasion ($p<0.05$) • WAT inflammation was associated with worse cancer-specific and overall survival in early stage cancer patients

Abbreviation: WAT, white adipose tissue; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; BMI, body mass index (kg/m^2); ERα, estrogen alpha receptor; Ob-R, leptin receptor; Lcn2, lipocalin 2, PLA2G10, phospholipase A2 G10; PTGD/PTGS2S, prostaglandin synthesis related enzymes; PDGFRα, platelet-derived growth factor receptor alpha; NF-kB, nuclear factor kappa B ; FAPα, fibroblast-activation protein alpha; LPL; lipoprotein lipase; FAS, fatty acid synthase; CLS, crown-like-structures, FERKO, fat-specific ERα knock-out mouse