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Adipose Tissue as an Endocrine Organ: Implications for Diabetes-Associated Cancers

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ABSTRACT

Once viewed as a passive energy reservoir, adipose tissue is now widely recognized as a dynamic endocrine organ with significant implications in systemic metabolism, inflammation, and tumorigenesis. In the context of type 2 diabetes mellitus (T2DM), chronic alterations in adipose tissue function, including hypertrophy, hypoxia, immune infiltration, and dysregulated adipokine secretion which contribute to a pro-inflammatory and insulin-resistant state that fuels the development of various cancers. This review explores the endocrine functions of adipose tissue, detailing its secretome of adipokines, cytokines, and growth factors and their interactions with insulin signaling pathways. The pathological remodeling of adipose tissue in obesity and T2DM sets the stage for carcinogenesis by promoting chronic inflammation, oxidative stress, and enhanced mitogenic signaling. We highlight the mechanistic links between adipose-derived factors such as leptin, adiponectin, resistin, TNF-α, IL-6, and their impact on key cancer-associated processes, including cell proliferation, apoptosis evasion, angiogenesis, and metastasis. Special attention is given to cancers with increased incidence in T2DM patients, including breast, colorectal, pancreatic, and liver cancers. Understanding adipose tissue's endocrine function not only deepens our insight into diabetes-associated carcinogenesis but also unveils novel therapeutic targets for cancer prevention and treatment in metabolically compromised individuals.

Keywords: Adipokines; Type 2 Diabetes Mellitus; Cancer; Chronic Inflammation; Endocrine Function

INTRODUCTION

The global rise in obesity and type 2 diabetes mellitus (T2DM) has emerged as a significant public health concern, driven by sedentary lifestyles, increased caloric intake, and urbanization[1–3]. According to the World Health Organization (WHO), over 1.9 billion adults were overweight in 2022, with more than 650 million classified as obese[4, 5]. Similarly, the prevalence of T2DM continues to climb, affecting over 537 million adults worldwide. These two metabolic disorders are not only epidemiologically linked but also share overlapping pathophysiological mechanisms, including insulin resistance, chronic low-grade inflammation, dyslipidemia, and altered adipokine signaling[2, 6]. Importantly, both obesity and T2DM significantly elevate the risk of developing several cancer types, such as colorectal, breast, endometrial, pancreatic, and liver cancers[7–9].

One of the emerging paradigms in understanding this relationship is the role of adipose tissue as an active endocrine organ. Historically viewed as a passive reservoir for fat storage, adipose tissue is now recognized for its dynamic role in energy homeostasis, glucose metabolism, and immunological regulation[10]. It achieves these functions through the secretion of a wide array of biologically active molecules collectively known as adipokines, which include cytokines, chemokines, hormones, and growth factors. These adipose-derived factors exert autocrine, paracrine, and endocrine effects, influencing various metabolic and inflammatory processes throughout the body[11, 12]. In the context of obesity, adipose tissue undergoes significant remodeling characterized by adipocyte hypertrophy, hypoxia, infiltration by pro-inflammatory immune cells, and extracellular matrix alterations[13]. These changes skew the adipose secretome toward a more pro-inflammatory and tumor-promoting profile. For instance, elevated levels of leptin and pro-inflammatory cytokines like TNF-α and IL-6 are commonly observed in obesity, whereas the protective adipokine adiponectin is markedly reduced. This dysregulated adipokine milieu contributes to systemic insulin resistance, oxidative stress, and immune dysfunction, all of which are implicated in tumor initiation, promotion, and progression[14, 15].

Furthermore, insulin resistance a hallmark of both obesity and T2DM leads to compensatory hyperinsulinemia, which, together with increased levels of insulin-like growth factor-1 (IGF-1), can activate mitogenic and anti-apoptotic pathways that favor carcinogenesis [16]. The convergence of these endocrine, metabolic, and inflammatory abnormalities creates a microenvironment conducive to oncogenesis[17]. In this regard, understanding the endocrine nature of adipose tissue provides critical insights into the mechanisms linking metabolic dysfunction with cancer. It also offers potential therapeutic targets, such as modulating adipokine signaling, improving insulin sensitivity, or reducing inflammation[18]. Moreover, the distinct behavior of different adipose depots, such as visceral versus subcutaneous fat, further refines our understanding of risk stratification and disease progression in obesity-related cancers.

In sum, the obesity and T2DM epidemic has highlighted the need for a deeper exploration of adipose tissue biology beyond traditional metabolic perspectives. By viewing adipose tissue as a dynamic endocrine organ, researchers and clinicians can better appreciate its role in systemic health and disease, particularly in the pathogenesis of cancer. This review explores the multifaceted endocrine functions of adipose tissue, the consequences of its dysfunction in obesity and T2DM, and the implications for cancer risk and progression.

2. Adipose Tissue as an Endocrine Organ

Adipose tissue, once regarded merely as a passive energy depot, is now well-established as a metabolically active endocrine organ that plays a central role in regulating systemic physiology[10, 11, 14, 15]. It is composed of a heterogeneous mix of cells, including mature adipocytes, preadipocytes, fibroblasts, vascular endothelial cells, and a diverse population of immune cells. These components collectively contribute to the endocrine functionality of adipose tissue through the synthesis and release of a wide array of bioactive molecules known as adipokines[19–21].

More than 600 adipokines have been identified, ranging from classic hormones like leptin and adiponectin to cytokines (e.g., TNF-α, IL-6), chemokines (e.g., monocyte chemoattractant protein-1 [MCP-1]), growth factors (e.g., VEGF), and enzymes involved in lipid and glucose metabolism[22]. These molecules participate in various physiological processes, including appetite regulation, glucose and lipid metabolism, insulin sensitivity, immune modulation, angiogenesis, and reproductive function[22].

The endocrine activity of adipose tissue is depot-specific. Visceral adipose tissue (VAT), which surrounds internal organs, is metabolically more active and pro-inflammatory than subcutaneous adipose tissue (SAT)[23]. VAT has a stronger association with insulin resistance, cardiovascular disease, and cancer, owing to its proximity to the portal circulation and its secretion of higher levels of inflammatory mediators. In contrast, SAT is generally considered metabolically protective, contributing to better insulin sensitivity and lower systemic inflammation. In a lean and healthy state, adipose tissue maintains metabolic homeostasis by releasing anti-inflammatory and insulin-sensitizing adipokines such as adiponectin, omentin, and apelin[24, 25]. These molecules help regulate lipid oxidation, glucose uptake, and anti-inflammatory signaling pathways. However, in the context of obesity and T2DM, adipose tissue undergoes pathological remodeling. Key features of this remodeling include[26–28]:

Adipocyte Hypertrophy: As fat storage increases, adipocytes enlarge, leading to mechanical and metabolic stress.

Hypoxia: Enlarged adipocytes can outstrip their oxygen supply, leading to local hypoxia and subsequent expression of hypoxia-inducible factors (HIFs), which further promote inflammation and angiogenesis.

Immune Cell Infiltration: Obesity leads to increased infiltration of pro-inflammatory immune cells, especially M1-type macrophages, neutrophils, and T cells, which secrete cytokines like TNF-α and IL-6.

Fibrosis: Chronic inflammation and ECM deposition cause tissue fibrosis, impairing adipocyte function and exacerbating insulin resistance.

This dysfunctional adipose tissue environment is marked by a shift in the adipokine profile. Leptin levels increase in obesity, yet target tissues develop leptin resistance[29–32]. Leptin has been shown to promote cancer cell proliferation, angiogenesis, and metastasis. On the other hand, adiponectin, which is an adipokine with anti-inflammatory, anti-atherogenic, and anti-cancer properties, is reduced in obese individuals and those with T2DM[11, 30]. The inverse relationship between adiponectin and cancer risk underscores its protective role. Moreover, pro-inflammatory cytokines such as TNF-α and IL-6 contribute to systemic insulin resistance by interfering with insulin receptor signaling pathways[33, 34]. These cytokines also enhance tumorigenesis through activation of transcription factors like NF-κB and STAT3, promoting cell survival, proliferation, and angiogenesis. Adipose tissue also interacts with the immune system in a bidirectional manner[35]. In obesity, adipose-resident immune cells become activated, creating a chronic inflammatory state that further disrupts metabolic regulation and supports cancer-related processes. Additionally, adipose-derived exosomes and microRNAs (miRNAs) have been implicated in intercellular communication, modulating gene expression in distant organs, and influencing tumor microenvironments[35].

The endocrine functions of adipose tissue are central to the regulation of systemic metabolism and immunity. In obesity and T2DM, the pathological transformation of adipose tissue contributes not only to metabolic

derangements but also to an environment conducive to cancer initiation and progression. Understanding these complex interactions opens up new avenues for therapeutic interventions aimed at restoring adipose tissue function and mitigating its pro-tumorigenic effects.

3. Adipokines and Their Role in Tumorigenesis

3.1 Leptin: Leptin is a hormone predominantly produced by adipocytes and is markedly elevated in obese individuals.[29, 30, 32]. While it primarily functions to regulate appetite and energy balance through its action on the hypothalamus, leptin also plays a significant role in tumorigenesis. In the context of cancer, leptin promotes tumor cell proliferation, survival, and angiogenesis through activation of multiple signaling cascades, notably the Janus kinase/signal transducer and activator of transcription (JAK/STAT), phosphoinositide 3-kinase/protein kinase B (PI3K/Akt), and mitogen-activated protein kinase (MAPK) pathways[36–38]. These signaling routes collectively enhance cellular growth and inhibit apoptosis in various cancer types, including breast, colon, and prostate cancers. Additionally, leptin can upregulate aromatase expression, the enzyme responsible for converting androgens to estrogens[39]. This is particularly significant in estrogen receptor-positive (ER+) breast cancers, where local estrogen production within adipose tissue fuels tumor progression[40–43]. Leptin also contributes to chronic inflammation within the tumor microenvironment, facilitating immune evasion and tumor-promoting immune responses. Elevated leptin levels have been associated with poor prognosis and resistance to therapy in certain cancers. Therefore, understanding the molecular underpinnings of leptin signaling may provide insight into novel therapeutic targets for obesity-associated malignancies.

3.2 Adiponectin: Adiponectin is another key adipokine secreted by adipose tissue, with functions largely opposite to those of leptin[11, 30, 34]. Unlike leptin, adiponectin levels are typically reduced in individuals with obesity and type 2 diabetes mellitus (T2DM). This decline contributes to the pro-inflammatory and tumor-promoting milieu associated with metabolic disorders. Adiponectin exerts anti-inflammatory, anti-proliferative, and insulin-sensitizing effects through a variety of mechanisms[44]. It inhibits key pro-oncogenic signaling pathways, such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and signal transducer and activator of transcription 3 (STAT3), thereby suppressing inflammatory cytokine production and tumor cell survival. Adiponectin also enhances AMP-activated protein kinase (AMPK) signaling, leading to improved metabolic homeostasis and inhibition of the mammalian target of rapamycin (mTOR) pathway—a critical axis for cancer cell growth and survival[44]. Additionally, adiponectin promotes apoptosis and inhibits angiogenesis in tumor tissues. Its protective role is evident in several cancers, including breast, endometrial, colorectal, and liver cancers, where higher adiponectin levels correlate with reduced risk and improved prognosis[45]. The inverse relationship between adiponectin and cancer risk underscores the significance of restoring adiponectin levels or mimicking its function as a potential therapeutic approach in obesity-associated cancer prevention and treatment.

3.3 Resistin, TNF-α, and IL-6: Resistin, tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6) are pro-inflammatory adipokines that are commonly upregulated in obesity and contribute significantly to insulin resistance and chronic low-grade inflammation[46, 47]. These adipokines are increasingly recognized for their roles in cancer development and progression. Resistin enhances cancer cell proliferation and metastasis by activating Toll-like receptor 4 (TLR4)-mediated NF-κB signaling[47]. TNF-α, a master regulator of inflammation, promotes tumorigenesis by facilitating epithelial-to-mesenchymal transition (EMT), enhancing invasive properties of tumor cells, and promoting angiogenesis[8]. Moreover, TNF-α induces the production of reactive oxygen species (ROS) and DNA damage, contributing to genetic instability. IL-6, another critical inflammatory cytokine, activates the STAT3 pathway, which supports tumor cell survival, proliferation, and immune evasion. IL-6 is also involved in promoting cancer stemness and resistance to chemotherapy in various tumors, including colorectal, prostate, and breast cancers[8]. These adipokines synergistically create a pro-tumorigenic microenvironment characterized by persistent inflammation, immune dysregulation, and enhanced metastatic potential[8]. The chronic elevation of resistin, TNF-α, and IL-6 in obese individuals not only contributes to metabolic dysfunction but also establishes conditions conducive to cancer initiation and progression, making them potential biomarkers and therapeutic targets in obesity-related malignancies.

4. Interconnection Between T2DM, Adipose Dysfunction, and Cancer

Type 2 diabetes mellitus (T2DM) is a complex metabolic disorder marked by insulin resistance, compensatory hyperinsulinemia, and chronic low-grade inflammation[2, 6, 33]. These interconnected abnormalities significantly contribute to the endocrine dysfunction of adipose tissue, which plays a critical role beyond energy storage by secreting a wide array of bioactive molecules known as adipokines that influence systemic metabolism and inflammation[48–51]. In the context of T2DM, persistent hyperinsulinemia arises due to the reduced sensitivity of peripheral tissues to insulin, leading the pancreas to secrete more insulin in an attempt to maintain glucose homeostasis. However, elevated insulin levels have oncogenic implications[52, 53]. A key pathway linking T2DM to cancer development is the insulin/insulin-like growth factor (IGF) axis. This pathway is a well-established mitogenic and anti-apoptotic signaling cascade[54]. Hyperinsulinemia reduces the expression

of IGF-binding proteins, particularly IGFBP-1 and IGFBP-2, thereby increasing the levels of bioavailable IGF-1. IGF-1, through binding to its receptor (IGF-1R), activates several intracellular signaling pathways—such as the Ras/Raf/MEK/ERK and PI3K/Akt/mTOR pathways—which promote cellular proliferation, inhibit apoptosis, and support angiogenesis, all of which are hallmarks of cancer[55].

Moreover, adipose tissue in T2DM becomes a source of chronic inflammation due to the infiltration of immune cells and the increased secretion of pro-inflammatory cytokines like TNF-α, IL-6, and MCP-1[55]. This inflammatory milieu synergizes with the activated insulin/IGF signaling to create a tumor-promoting microenvironment. The combination of metabolic dysregulation, pro-inflammatory adipokine secretion, and enhanced mitogenic signaling fosters conditions favorable for neoplastic transformation and tumor progression. Thus, the metabolic and inflammatory disturbances characteristic of T2DM intricately link to increased cancer risk and underscore the importance of metabolic control in cancer prevention and management.

5. Site-Specific Cancers Associated with Adipose-Endocrine Dysfunction

5.1 Breast Cancer: In postmenopausal women, obesity and type 2 diabetes mellitus (T2DM) are significant risk factors for breast cancer development[56]. Adipose tissue becomes a primary source of estrogen after menopause, and elevated levels of leptin, commonly observed in obesity, further stimulate aromatase expression, thereby increasing local estrogen synthesis in breast tissue[57, 58]. Concurrently, insulin resistance and compensatory hyperinsulinemia suppress insulin-like growth factor-binding proteins (IGFBPs), leading to elevated free IGF-1 levels[59]. This promotes mitogenic and anti-apoptotic signaling through pathways such as PI3K/Akt and MAPK/ERK, enhancing cellular proliferation and survival in mammary epithelium. Leptin can also directly activate the JAK/STAT3 and Notch signaling pathways, contributing to tumor initiation, angiogenesis, and metastasis[60]. In contrast, adiponectin being an anti-inflammatory and insulin-sensitizing adipokine, is typically reduced in obese, diabetic individuals. Adiponectin exerts anti-proliferative effects on breast cancer cells by activating AMPK and inhibiting mTOR signaling[60]. The combined effect of high leptin and low adiponectin levels creates a pro-tumorigenic microenvironment. Moreover, chronic low-grade inflammation, characterized by increased cytokines such as TNF-α and IL-6, contributes to DNA damage and further fuels tumorigenesis. Altogether, the interplay of hormonal dysregulation, metabolic disturbances, and adipose tissue-derived factors underpins the enhanced risk and aggressiveness of breast cancer in women with obesity and T2DM.

5.2 Colorectal Cancer: Colorectal cancer (CRC) risk is notably increased in individuals with visceral obesity and T2DM, largely due to inflammatory and metabolic disruptions in the colonic microenvironment[61]. Visceral adiposity is associated with the release of pro-inflammatory cytokines, particularly interleukin-6 (IL-6), TNF-α, and IL-1β, which activate STAT3 and NF-κB signaling in colonic epithelial cells, promoting unchecked proliferation and inhibiting apoptosis. Chronic exposure to these cytokines also enhances oxidative stress and DNA damage, setting the stage for oncogenic mutations[61]. Additionally, insulin resistance and hyperinsulinemia contribute to elevated IGF-1 levels, which further stimulate colonic epithelial growth through the PI3K/Akt and MAPK pathways. Another key factor is obesity-associated gut microbiota dysbiosis. Alterations in microbial composition can increase the production of carcinogenic metabolites (e.g., secondary bile acids) and reduce beneficial short-chain fatty acids, such as butyrate, which normally inhibit inflammation and support mucosal integrity. The result is a compromised intestinal barrier, enhanced local inflammation, and increased exposure of colonic cells to harmful substances. Moreover, increased adipose tissue within the mesentery and pericolonic regions may facilitate paracrine crosstalk with tumor cells, supporting angiogenesis and invasion[62]. Together, these mechanisms illustrate how adipose tissue dysfunction in obesity and T2DM drives colorectal carcinogenesis.

5.3 Pancreatic Cancer: Pancreatic cancer, particularly pancreatic ductal adenocarcinoma (PDAC), is strongly associated with obesity and T2DM, conditions that foster a tumor-supportive environment through both systemic and local mechanisms[63]. Hyperinsulinemia, a hallmark of insulin resistance, increases the bioavailability of IGF-1, which promotes cell proliferation and inhibits apoptosis via PI3K/Akt and Ras/MAPK signaling cascades. Additionally, adipose-derived pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), along with adipokines like resistin, induce epithelial-to-mesenchymal transition (EMT), enhancing the invasive and metastatic potential of pancreatic cancer cells[63]. These inflammatory mediators also activate stellate cells, contributing to the dense fibrotic stroma (desmoplasia) characteristic of PDAC, which not only shields tumor cells from chemotherapy but also sustains their growth through paracrine signaling[64]. Furthermore, altered lipid metabolism in obesity leads to increased fatty acid availability, which fuels oxidative phosphorylation and metabolic reprogramming in cancer cells, enhancing their survival and adaptability under hypoxic conditions. T2DM-associated hyperglycemia also exacerbates oxidative stress and genomic instability[64]. Collectively, the inflammatory milieu, metabolic alterations, and hormonal imbalances in obesity and T2DM synergize to accelerate PDAC development, progression, and resistance to therapy, making metabolic intervention a potentially valuable adjunct in pancreatic cancer management.

5.4 Liver Cancer: Obesity and T2DM significantly elevate the risk of hepatocellular carcinoma (HCC), primarily through the development of non-alcoholic fatty liver disease (NAFLD) and its progressive form, non-alcoholic steatohepatitis (NASH). In NAFLD, hepatic lipid accumulation induces oxidative stress and lipotoxicity, which, over time, promote inflammation, hepatocyte injury, and fibrosis [22, 28, 29, 61]. NASH is marked by chronic inflammation, hepatocellular ballooning, and infiltration of immune cells, particularly Kupffer cells and macrophages that secrete TNF-α, IL-6, and TGF-β a key mediators in the fibrogenic and carcinogenic processes[2, 5, 65]. Obesity-associated adipokine imbalance further aggravates this progression. Low levels of adiponectin fail to suppress hepatic inflammation and fibrogenesis, while elevated leptin promotes stellate cell activation and collagen deposition, contributing to cirrhosis and increasing the risk of malignant transformation. Additionally, insulin resistance and hyperinsulinemia stimulate hepatocyte proliferation and inhibit apoptosis through insulin/IGF-1 receptor signaling, facilitating oncogenic mutations. T2DM-associated hyperglycemia also induces DNA damage and epigenetic alterations. Furthermore, the dysregulated lipid metabolism in obesity enhances β-oxidation and mitochondrial dysfunction, producing reactive oxygen species (ROS) that damage cellular macromolecules[2, 66, 67]. Over time, these insults culminate in cellular transformation and HCC development. Therefore, the hepatic consequences of metabolic disease create a pro-tumorigenic environment in the liver.

6. Therapeutic Implications and Future Perspectives

Targeting adipokine signaling pathways presents a compelling therapeutic avenue for mitigating cancer risk in patients with type 2 diabetes mellitus (T2DM). The dysregulated secretion of adipokines, such as reduced adiponectin and elevated leptin, creates a pro-tumorigenic environment that contributes to cancer initiation and progression in individuals with obesity and T2DM. Therapeutic strategies aimed at correcting this imbalance hold promise. Pharmacological agents like peroxisome proliferator-activated receptor gamma (PPAR-γ) agonists, for instance, can enhance adiponectin levels, thereby exerting anti-inflammatory and anti-proliferative effects on tumor cells. Conversely, inhibiting leptin signaling through leptin receptor antagonists could block leptin's stimulatory actions on cancer cell growth and angiogenesis. Additionally, targeting inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) with specific inhibitors may further disrupt the chronic inflammatory state that underpins both insulin resistance and cancer development.

Lifestyle interventions also remain essential components of this therapeutic paradigm. Structured diet and exercise regimens help restore adipose tissue function and reduce systemic inflammation, thereby rebalancing adipokine profiles and potentially lowering cancer risk. Beyond therapy, there is growing interest in incorporating adipose-derived biomarkers into cancer risk assessment models for diabetic patients. Biomarkers reflecting adipokine levels and adipose tissue dysfunction could provide additional predictive power alongside traditional cancer screening tools, enabling earlier detection and more personalized risk stratification. This integration could prove especially valuable in identifying high-risk individuals who may benefit from targeted surveillance or preventive interventions. Looking ahead, the convergence of metabolic and oncologic research is likely to yield novel therapeutic targets within adipokine signaling networks. Future perspectives include the development of multi-targeted agents that modulate multiple adipokine-related pathways simultaneously, and the use of personalized medicine approaches to tailor interventions based on an individual's metabolic and inflammatory profile.

CONCLUSION

Adipose tissue functions as a critical endocrine organ whose dysregulation in T2DM significantly contributes to cancer risk and progression. The interplay between adipokines, insulin resistance, and chronic inflammation orchestrates a tumor-promoting microenvironment. Elucidating the molecular pathways connecting adipose dysfunction to cancer provides valuable insights into novel therapeutic interventions aimed at disrupting the obesity-diabetes-cancer axis. A holistic strategy combining metabolic control with targeted molecular therapies holds promise for reducing cancer burden in metabolically vulnerable populations.

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