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Review

The Role of Metabolic Inflammation and Insulin Resistance in Obesity-Associated Carcinogenesis–A Narrative Review

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Simple Summary

Cancer does not develop in isolation but is heavily influenced by the environment around tumor cells. Instead of always protecting the body, long-term low-grade inflammation can support tumor growth and spread. Obesity is one of the primary conditions that creates this harmful environment. Excess body fat mass promotes persistent inflammation, disrupts normal metabolism, and alters hormones and growth signals. These alterations intensify conditions that enhance the survival, proliferation, and invasive capacity of malignant cells. In this review, we analyze the complex interactions among obesity, chronic inflammation, and insulin resistance in driving tumor initiation and progression. We further delineate the main molecular pathways underlying these processes and highlight developing therapeutic strategies planned to disrupt them. A deeper understanding of these interconnections may facilitate the development of recent interventions aimed at mitigating the oncogenic impact of obesity and improving future cancer treatment outcomes.

Abstract

The inflammatory milieu surrounding tumors plays a pivotal yet paradoxical role in promoting carcinogenesis. Rather than simply acting as a host defense mechanism, chronic low-grade inflammation actively nurtures tumor development and supports hallmarks such as sustained proliferative signaling, apoptosis resistance, angiogenesis, and metastasis. Obesity, characterized by a chronic inflammatory state, exacerbates this tumor-promoting environment through metabolic imbalances like insulin resistance, hyperglycemia, and dyslipidemia. These conditions stimulate oncogenic signaling pathways and reshape the tumor microenvironment. Obesity-associated cytokines, altered adipokines, and insulin-related growth signals synergistically enhance processes such as epithelial-to-mesenchymal transition (EMT) and matrix remodeling. This review explores the mechanistic interplay between obesity-induced inflammation and insulin resistance in cancer progression, discusses the molecular pathways involved, and highlights emerging therapeutic approaches targeting these intersecting tumor promotion axes.

Keywords: obesity; chronic inflammation; insulin resistance; tumor microenvironment; carcinogenesis; adipokines; epithelial-to-mesenchymal transition; NF-κB; hyperinsulinemia; metabolic dysregulation

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1. Introduction

Obesity has emerged as a global health crisis, contributing significantly to the rising burden of cancer worldwide. Beyond its well-known association with metabolic and cardiovascular diseases, obesity is now recognized as a complex pathophysiological state that promotes tumorigenesis through both inflammatory and metabolic mechanisms [1,2]. The combination of chronic low-grade inflammation and insulin resistance in obese individuals prepares the ground for driving malignant evolution, tumor progression, and resistance to therapy.

Seminal studies have laid the groundwork for understanding how systemic inflammation contributes to cancer hallmarks such as sustained proliferation, resistance to cell death, angiogenesis, and metastasis [3,4]. The landmark article by Hanahan and Weinberg (2000) defined these hallmarks as central traits acquired during cancer development, and follow-up research has increasingly emphasized the pro-tumorigenic role of inflammation in shaping the tumor microenvironment (TME) [5,6].

Obesity amplifies these inflammatory signals. Adipose tissue in obese individuals becomes a hub of immune activity, secreting cytokines and adipokines that trigger oncogenic signaling pathways. The nuclear factor-kappa B (NF-κB), signal transducer and activator of transcription (STAT) 3, and phosphatidylinositol-3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/Akt/mTOR) pathways are key mediators linking adiposity to carcinogenesis, while metabolic disturbances such as hyperinsulinemia, hyperglycemia, and dyslipidemia further exacerbate the risk [2,7,8].

Large epidemiological cohorts and mechanistic studies have substantiated these insights. For example, a 2016 study published in the *New England Journal of Medicine* confirmed that excess body weight is associated with elevated risks of at least 13 types of cancer, reinforcing obesity as a modifiable cancer risk factor [9].

Recent advances also highlight the importance of immune and stromal remodeling in the TME of obese patients with cancer. Ringel et al. (2022) showed that obesity shapes the immune landscape of tumors, impairing anti-tumor immunity and promoting cancer cell escape mechanisms [10].

This review synthesizes classic and contemporary literature to explore how obesity-induced inflammation and insulin resistance function as central drivers of cancer. It further discusses the molecular pathways involved, summarizes epidemiological trends and outlines therapeutic interventions that may help mitigate this growing public health challenge.

2. Cancer Risk in Obesity: Epidemiological Evidence

A compelling body of epidemiological research has established obesity as a major risk factor for a diverse array of cancers [9]. This association is not merely correlative—it reflects the biological consequences of obesity-related inflammation and metabolic dysfunction, which promote tumorigenesis through both systemic and tissue-specific mechanisms [1].

Studies have shown that higher body mass index (BMI) is significantly associated with increased incidence and poorer outcomes in cancers of the breast (postmenopausal), colorectal region, endometrium, pancreas, kidney, liver, and esophagus [11]. Notably, the magnitude of cancer risk tends to rise with both the degree and duration of obesity, underscoring the cumulative effect of chronic metabolic and inflammatory stress [12].

In women, obesity-related insulin resistance and hormonal imbalances—particularly involving estrogen and insulin-like growth factors (IGFs)—are central to the development of gynecological cancers, including breast, endometrial, and ovarian malignancies [13]. Recent research has linked metabolic dysfunction-associated steatotic liver disease (MASLD), a common obesity-related condition, to an elevated risk of breast cancer, particularly due to insulin resistance and lipid accumulation in hepatic tissues [14]. Recent research has

linked MASLD, a common obesity-related condition, to an elevated risk of breast cancer, particularly due to insulin resistance and lipid accumulation in hepatic tissues [15].

A study by Dhar and Bhattacharjee (2024) further highlighted the genetic landscape of polycystic ovarian syndrome (PCOS), which is frequently comorbid with obesity. They identified insulin resistance and chronic low-grade inflammation as key drivers in the pathogenesis of endometrial and ovarian cancers, particularly in obese individuals [16].

The link between obesity and cancer is also evident in male populations. Adiposity has been associated with higher rates of colorectal, liver, and renal cancers [17–19], largely due to systemic inflammation and hormonal dysregulation affecting androgens and adipokines [3].

Importantly, these epidemiological trends are supported by mechanistic studies demonstrating how obesity-related metabolic changes drive cellular transformation, DNA damage, and immune evasion [1]. Together, these findings reinforce the importance of preventive strategies and early interventions in reducing obesity-associated cancer burden at the population level [2].

3. Tumor-Associated Inflammation: Friend and Foe

Inflammation, traditionally considered a defensive biological response, plays a paradoxical role in the context of cancer. Instead of solely protecting the host, chronic low-grade inflammation—common in obesity—establishes a permissive environment for tumor development and progression. This duality is reflected in inflammatory mediators' capacity to initiate oncogenic processes and support tumor survival and expansion [20]. Table 1 summarizes the main Immune and stromal cells, cytokines/adipokines, and signaling pathways linking obesity-associated chronic inflammation with cancer progression.

Table 1. Immune and stromal cells, cytokines/adipokines, and signaling pathways linking obesity-associated chronic inflammation with cancer progression. Abbreviations: White adipose tissue (WAT); extracellular matrix (ECM); tumor-associated macrophages (TAMs); vascular endothelial growth factor (VEGF); matrix metalloproteinases (MMPs); interleukin (IL); tumor necrosis factor-alpha (TNF-α); transforming growth factor-beta (TGF-β); nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB); signal transducer and activator of transcription 3 (STAT3); Janus kinase (JAK); phosphatidylinositol-3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/Akt/mTOR); insulin-like growth factor-1 (IGF-1); hypoxia-inducible factor-1 alpha (HIF-1α); epithelial-to-mesenchymal transition (EMT); metabolic dysfunction-associated steatotic liver disease (MASLD); Toll-like receptor 4 (TLR4); and mitogen-activated protein kinase (MAPK). CCL2/CCR2—Chemokine (C-C motif) ligand 2/Chemokine (C-C motif) receptor 2. CCL5/CCR5—Chemokine (C-C motif) ligand 5/Chemokine (C-C motif) receptor 5. CXCL12/CXCR4—Chemokine (C-X-C motif) ligand 12/Chemokine (C-X-C motif) receptor 4. ↑: increase; ↓: decrease.

Cell Type/Source	Key Mediators (Cytokines, Adipokines, Enzymes)	Main Pathways Activated	Functional Impact on Tumor
Adipocytes (hypertrophic WAT)	↑ Leptin, ↓ Adiponectin, Free fatty acids	STAT3, PI3K/Akt/mTOR, TLR4–NF-κB	Proliferation, angiogenesis, reduced apoptosis, systemic insulin resistance
Tumor-Associated Macrophages (TAMs, M1 polarization)	TNF-α, IL-6, VEGF, MMPs	NF-κB, STAT3, HIF-1α	ECM remodeling, angiogenesis, immunosuppression, metastasis
Neutrophils	Pro-angiogenic chemokines, MMP-9	NF-κB, MAPK	ECM degradation, angiogenesis, metastatic invasion
T Lymphocytes (Th1/Th17 skewing)	IL-17, IFN-γ, TNF-α	NF-κB, JAK/STAT	Chronic inflammation, enhanced tumor-promoting immune milieu
Adipose Tissue Fibroblasts/Stromal cells	TGF-β, ECM proteins	EMT pathways (Snail, Twist, ZEB), SMAD	Induction of epithelial-to-mesenchymal transition (EMT), invasion

Table 1. *Cont.*

Cell Type/Source	Key Mediators (Cytokines, Adipokines, Enzymes)	Main Pathways Activated	Functional Impact on Tumor
Hepatocytes/Liver microenvironment	IL-6, C-reactive protein	JAK/STAT, NF-κB	Systemic inflammation, MASLD-associated tumorigenesis
Circulating factors in obesity	Hyperinsulinemia, IGF-1, Hyperglycemia, Dyslipidemia	PI3K/Akt/mTOR, MAPK, HIF-1α stabilization	Enhanced tumor metabolism (Warburg effect), DNA damage, survival advantage
Adipocytes, stromal and immune cells in obese TME	CCL2/CCR2, CCL5/CCR5, CXCL12/CXCR4	NF-κB, JAK/STAT, MAPK	Recruitment of monocytes/TAMs, immunosuppressive polarization, EMT, metastatic dissemination, angiogenesis, matrix remodeling, immune evasion

Inflammatory cytokines, including interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), are elevated in obese individuals and accumulate within the TME. These molecules activate transcription factors like NF-κB and STAT3, which regulate genes involved in cell proliferation, angiogenesis, and inhibition of apoptosis [1,2,20]. This signaling cascade supports early neoplastic transformations and sustains tumor growth by evading immune surveillance.

Although IL-6 most prominently activates STAT3, co-activation of STAT5 has been described in specific tumor contexts and may cooperate with STAT3 to sustain proliferation, survival, and metastatic behavior. We therefore note that IL-6/JAK signaling can engage STAT5, with downstream crosstalk to PI3K/Akt and NF-κB [21].

Obesity state creates a chronic inflammatory environment enriched in IL-6 derived from adipocytes, stromal cells, and myeloid populations. IL-6 interacts with the IL-6R/gp130 receptor complex, triggering JAK1/2 activation and phosphorylation of STAT3/STAT5, which dimerize and translocate to the nucleus [22–24]. Thereby, STAT3/5 drives transcriptional programs that favor tumor progression, including Cyclin D1 (cell-cycle entry), Bcl-XL (suppression of intrinsic/extrinsic caspase cascades), and VEGF (angiogenesis) [24].

Simultaneously, signaling adaptors such as SHP2 and Grb2 activate the MAPK/ERK pathway [25], while PI3K/Akt signaling amplifies survival and metabolism. Although SOCS3 typically detains JAK/STAT signaling, chronic IL-6 exposure in obesity reduces this control [26]. Although SOCS3 is induced as a classical brake on JAK/STAT signaling, persistent IL-6 exposure in obesity blunts this restraint. Furthermore, interactions with NF-κB and HIF-1α further amplify these signals, promoting EMT, angiogenesis, and metastasis [27]. Together, the IL-6/IL-6R/gp130 axis functions as a central integrator of metabolic inflammation and oncogenic signaling in obesity-associated carcinogenesis [23,24].

Moreover, chronic inflammation promotes the secretion of matrix metalloproteinases (MMPs), enzymes that degrade the extracellular matrix (ECM), facilitating both angiogenesis and metastatic invasion [28]. Inflammatory cells such as tumor-associated macrophages (TAMs) and neutrophils contribute to this remodeling, producing vascular endothelial growth factor (VEGF) and pro-angiogenic chemokines [7,29]. These changes ensure a steady blood supply to the tumor and promote its dissemination to distant tissues.

A crucial consequence of the inflammatory milieu is the induction of epithelial-to-mesenchymal transition (EMT)—a cellular reprogramming event that endows cancer cells with migratory and invasive capabilities. TNF-α, TGF-β, and other cytokines synergistically activate EMT through Snail, Twist, and ZEB transcription factors, transforming epithelial tumor cells into mesenchymal-like phenotypes that resist therapy and evade detection [6,30,31].

Beyond cytokines, chemokine–receptor axes play a critical role in linking obesity-related inflammation to tumor progression. In particular, CCL2/CCR2 (monocyte/TAM recruitment), CCL5/CCR5 (immunosuppressive polarization, invasion), and CXCL12/CXCR4 (EMT, metastatic dissemination) activate NF-κB, JAK/STAT, and MAPK nodes to amplify angiogenesis, matrix remodeling, and immune evasion [32–34].

Thus, in obesity-driven carcinogenesis, inflammation serves as a central enabler of tumor hallmarks, transforming the TME from a battlefield into a sanctuary for cancer cells.

4. Obesity as a Chronic Inflammatory State

Obesity is not merely a disorder of excess energy storage—it is increasingly recognized as a state of persistent, low-grade systemic inflammation. This condition arises from the pathological expansion and dysfunction of white adipose tissue (WAT), which transforms from a relatively inert depot into an active endocrine and immune organ that fuels carcinogenic processes [9,33,35] (Figure 1).

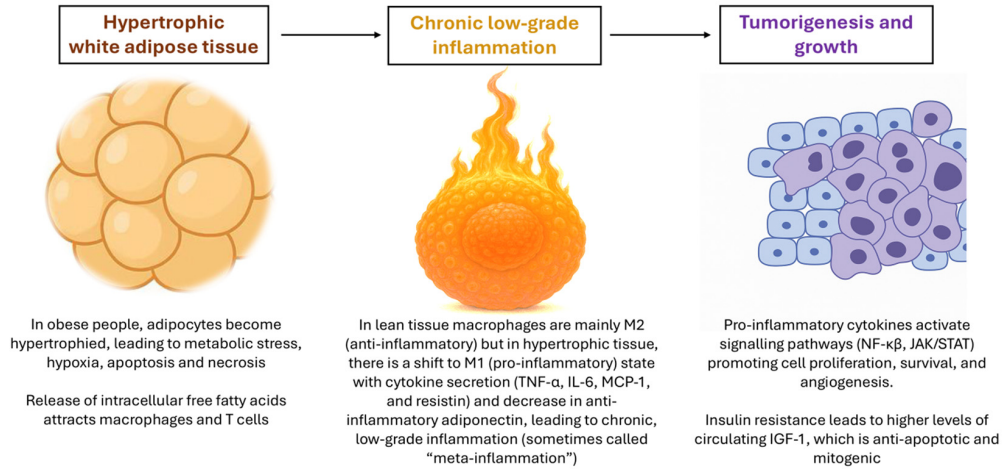

Figure 1. Link Between Obesity-Induced Adipose Tissue Dysfunction and Cancer Development. This figure illustrates the mechanistic pathway linking hypertrophic white adipose tissue in obesity to tumorigenesis. In obese individuals, adipocytes become enlarged, resulting in metabolic stress, hypoxia, and cell death, which triggers immune cell recruitment. This initiates chronic low-grade inflammation due to a shift in macrophage polarization from the anti-inflammatory M2 phenotype to the pro-inflammatory M1 phenotype, with elevated secretion of cytokines (TNF-α, IL-6, MCP-1, and resistin) and reduced adiponectin levels. These pro-inflammatory mediators activate key oncogenic signaling pathways (e.g., NF-κB, JAK/STAT), enhancing cell proliferation, angiogenesis, and survival. Concurrently, insulin resistance increases IGF-1 levels, further promoting mitogenesis and resistance to apoptosis.

As adipose tissue enlarges, it becomes hypoxic and fibrotic, leading to the recruitment of immune cells, especially M1 macrophages polarization, T lymphocytes, and neutrophils, into the adipose milieu. Adopting a pro-inflammatory profile, these immune cells release cytokines—including TNF-α, IL-1β, and IL-6—that fuel a self-sustaining inflammatory loop and drive systemic insulin resistance [1,2,36,37].

Adipocytes contribute to this inflammatory storm by altering their secretion of adipokines—bioactive peptides that regulate metabolism and immune function. In obesity, the balance of adipokines turns significantly: leptin levels rise, supporting pro-inflammatory and pro-angiogenic activities, while adiponectin levels fall, removing an important anti-inflammatory and insulin-sensitizing brake [2]. This dysregulation exacerbates metabolic disturbances and creates a microenvironment favorable to tumor growth.

Moreover, crosstalk between adipocytes and macrophages intensifies inflammation throughout paracrine signaling [37]. Free fatty acids released by hypertrophic adipocytes activate Toll-like receptors (TLRs) on immune cells, further enhancing the release of inflammatory cytokines, promoting inflammation and subsequent cellular insulin resistance [38]. This sustained inflammatory interaction primes distant tissues—such as the liver [39,40], colon [41,42], and breast [43,44]—for malignant transformation, linking obesity directly to increased cancer risk [45,46].

The systemic reach of this inflammatory state affects not only insulin sensitivity and glucose homeostasis but also immune surveillance, cell cycle regulation, and DNA repair—thereby functioning as a cancer-enabling mechanism at the metabolic-immunological interface [47,48].

5. Insulin Resistance and Metabolic Dysregulation

A key feature of obesity-driven metabolic abnormalities is insulin resistance, characterized by impaired cellular responsiveness to insulin's regulatory actions on glucose and lipid metabolism. This chronic dysfunction impairs glycemic control and profoundly influences cancer progression, as well as the advancement through growth-promoting and anti-apoptotic pathways [49,50].

Insulin resistance in obese individuals often leads to compensatory hyperinsulinemia, whereby pancreatic β-cells increase insulin output to maintain blood glucose homeostasis [50,51]. This persistent elevation of insulin levels has oncogenic implications. Insulin directly stimulates mitogenic pathways such as PI3K/Akt and MAPK, which facilitate cell proliferation, angiogenesis, and survival in precancerous and malignant cells [52]. In parallel, elevated insulin-like growth factor-1 (IGF-1) amplifies these signals by binding to its receptor (IGF-1R), which is overexpressed in several tumor types [53,54].

In addition to insulin and IGF-1, metabolic dysregulation encompasses hyperglycemia and dyslipidemia, both of which contribute to cancer-promoting effects [55]. High glucose levels create a pro-oxidant environment, enhancing DNA damage and supporting anaerobic glycolysis (the Warburg effect)—a hallmark of cancer metabolism [4,6]. Meanwhile, elevated triglycerides and free fatty acids provide fuel for rapidly dividing cancer cells and activate lipid-sensitive transcription factors, which modulate gene expression in favor of tumorigenesis [56]. Saturated fatty acids, liberated through obesity-associated lipolysis, promote macrophage activation via engagement of Toll-like receptor 4 (TLR4), leading to the stimulation of NF-κB signaling pathways. This activation subsequently drives the transcription of pro-inflammatory genes, such as COX-2, IL-6, IL-1β, and TNFα [57].

Dysregulated metabolism also affects immune cell function, impairing anti-tumor immunity and reinforcing a chronic inflammatory state [58]. Inflammatory adipokines, such as resistin and visfatin, further disrupt tissue insulin signaling, completing a feedback loop that links metabolic dysfunction with oncogenic transformation [59].

Notably, this metabolic-inflammatory interface varies by sex, organ system, and hormonal context. For instance, in women, metabolic dysfunction-associated steatotic liver disease (MASLD) has been implicated in elevated risk for breast and gynecological cancers, partly due to altered estrogen metabolism and insulin resistance [60].

6. Molecular Pathways Linking Obesity and Cancer

A network of intracellular signaling bridges the interface between chronic inflammation and metabolic dysregulation in obesity cascades, collectively driving tumor initiation, promotion, and progression [12]. These molecular pathways are activated in response to cytokines, free fatty acids, and hyperinsulinemia, and they regulate diverse processes such as cell survival, proliferation, angiogenesis, and immune modulation [61] (Figure 2).

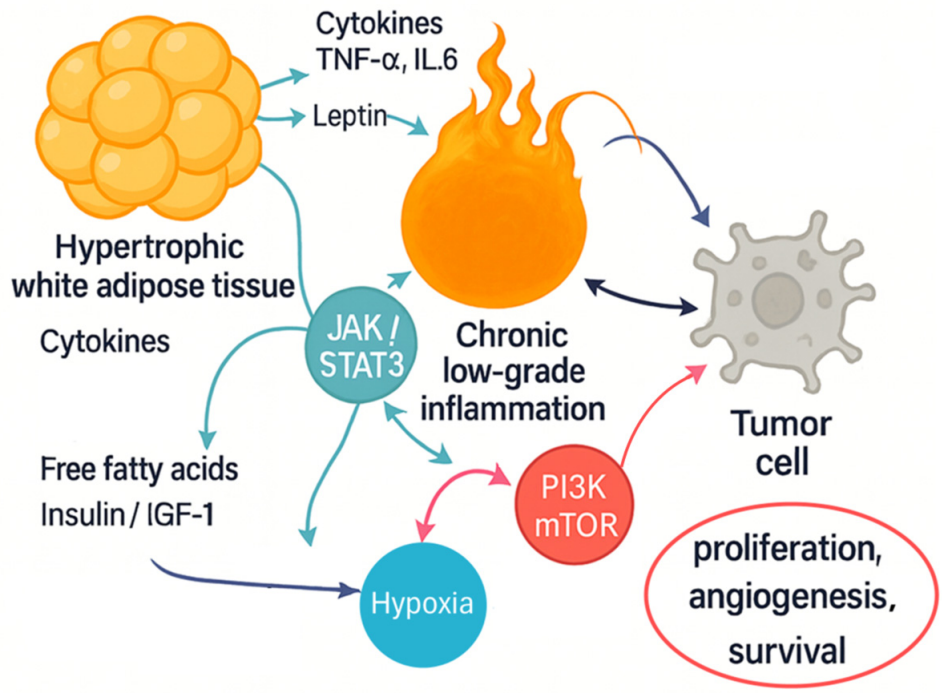

Figure 2. Intracellular signaling networks link chronic inflammation and metabolic dysregulation in obesity, triggering pathways—stimulated by cytokines, free fatty acids, and hyperinsulinemia—that promote tumor development by regulating cell survival, proliferation, angiogenesis, and immune responses: Nuclear factor-kappa B (NF-κB) pathway NF-κB is a transcription factor that responds to inflammatory stimuli like TNF-α and IL-6 and. promotes the expression of genes involved in cell proliferation, inhibition of apoptosis, and angiogenesis. In obese individuals, NF-κB is constitutively activated due to chronic low-grade inflammation, thus maintaining a pro-tumorigenic microenvironment. Janus kinase / signal transducer and activator of transcription (JAK/STAT) pathway (STAT3) Activated by IL-6 and leptin, STAT3 upregulates oncogenes such as Cyclin D1, Bcl-XL, and VEGF, supporting tumor growth and angiogenesis [46]. Leptin, which is elevated in obesity, is especially potent in activating STAT3, linking adiposity to tumor promotion through leptin-STAT signaling. Phosphoinositide 3-kinase (PI3K) / Akt / mTOR pathway Primarily stimulated by insulin and IGF-1, this pathway integrates metabolic cues into cellular growth and survival. In many cancers, it is hyperactivated due to either insulin resistance or receptor overexpression, contributing to uncontrolled proliferation and resistance to cell death. Hypoxia-inducible factor-1 alpha (HIF-1α) Stabilized under hypoxic conditions common in hypertrophic adipose tissue, HIF-1α further enhances angiogenesis and glycolysis—both necessary for tumor expansion. HIF-1α also cooperates with NF-κB and PI3K/Akt to modify the tumor stroma and promote immune evasion. Arrow conventions: Straight arrows (→) denote activation or stimulation of signaling pathways and biological processes. Curved or bidirectional arrows (↔) represent feedback regulation or crosstalk between pathways. Abbreviations: vascular endothelial growth factor (VEGF); interleukin-6 (IL-6); interleukin-6 receptor (IL-6R); tumor necrosis factor-alpha (TNF-α); factor kappa-light-chain-enhancer of activated B cells (NF-κB); signal transducer and activator of transcription 3 (STAT3); Janus kinase (JAK); phosphatidylinositol-3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/Akt/mTOR); insulin-like growth factor-1 (IGF-1); insulin-like growth factor-1 receptor (IGF-1R); hypoxia-inducible factor-1 alpha (HIF-1α); and mitogen-activated protein kinase (MAPK).

Among the central players is the NF-κB pathway. NF-κB is a transcription factor that responds to inflammatory stimuli like TNF-α and IL-6 and promotes the expression of genes involved in cell proliferation, inhibition of apoptosis, and angiogenesis. In obese individuals, NF-κB is constitutively activated due to chronic low-grade inflammation, thus maintaining a pro-tumorigenic microenvironment [1,62]. Apoptotic pathways, whether initiated through death receptors (Fas/TNF-R leading to caspase-8 activation) or mitochon-

drial signals (cytochrome c release triggering caspase-9), ultimately activate executioner caspases-3 and -7. Inflammatory signals associated with obesity drive the activation of NF-κB, STAT3, and PI3K-Akt pathways, which in turn upregulate anti-apoptotic factors like Bcl-XL. This adaptive response dampens caspase activity and contributes to the development of apoptosis resistance within the tumor microenvironment, a key hallmark of cancer progression under chronic inflammation [33,34].

Another critical signaling route is the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway, particularly STAT3. Activated by IL-6 and leptin, STAT3 upregulates oncogenes such as Cyclin D1, Bcl-XL, and VEGF, supporting tumor growth and angiogenesis [63]. Leptin, which is elevated in obesity, is especially potent in activating STAT3, linking adiposity to tumor promotion through leptin-STAT signaling [63,64] (Figure 2).

The PI3K/Akt/mTOR pathway, primarily stimulated by insulin and IGF-1, integrates metabolic cues into cellular growth and survival. In many cancers, this pathway is hyperactivated due to either insulin resistance or receptor overexpression, contributing to uncontrolled proliferation and resistance to cell death [65,66].

Hypoxia-inducible factor-1 alpha (HIF-1α), stabilized under hypoxic conditions common in hypertrophic adipose tissue, further enhances angiogenesis and glycolysis—both necessary for tumor expansion. HIF-1α also cooperates with NF-κB and PI3K/Akt to modify the tumor stroma and promote immune evasion [67,68].

These pathways do not act in isolation. They converge and interact, reinforcing each other's outputs and creating a self-sustaining oncogenic loop in obese individuals. Obesity creates a paradoxical biological environment in cancer. On one hand, its metabolic and inflammatory pathways converge and interact, reinforcing each other's outputs and creating a self-sustaining oncogenic loop [69]. This molecular synergy explains why obesity not only increases cancer incidence but also correlates with aggressive disease phenotypes and poorer prognoses. On the other hand, observational studies have reported an "obesity paradox," where overweight or mildly obese cancer patients sometimes exhibit improved survival. This apparent contradiction is influenced by methodological limitations. First, reverse causality occurs when weight loss caused by undiagnosed cancer precedes diagnosis, potentially distorting the association between body weight and survival. Second, collider stratification bias arises when analyses condition on disease status (such as having cancer), which can introduce spurious associations between obesity and survival. Lastly, the use of BMI as a proxy for adiposity is inherently limited, as BMI does not distinguish between fat mass, lean muscle, and fat distribution—all of which may differentially influence cancer outcomes [70,71]. In obese patients, white adipose tissue may contribute to a chronic inflammatory microenvironment, thereby promoting tumor progression, as previously described. Conversely, in certain cancer types, the conversion of white adipose tissue into brown adipose tissue—a process known as "browning"—has been associated with weight loss. Although this phenomenon might be considered beneficial in the context of obesity, it has been linked to poorer prognosis in specific oncologic populations due to the accompanying metabolic alterations. These include the secretion of pro-inflammatory and catabolic mediators involved in cancer cachexia and body mass loss, such as Lipid Mobilizing Factor (LMF), Proteolysis Inducing Factor (PIF), and Parathyroid Hormone-related Protein (PTHrP) [72,73].

Furthermore, some tumors in obese individuals may exhibit less aggressive biology or better treatment responses, while excess adipose tissue might serve as an energy reserve during anticancer therapy, including malignancies characterized by elevated metabolic requirements and increased energy expenditure, such as head and neck cancers and esophageal carcinoma [74,75]. Previous data indicate that, in esophageal cancer, elevated body mass

index (BMI) and increased visceral adiposity are associated with a higher risk of esophageal adenocarcinoma. However, an inverse association has been observed between BMI, abdominal fat, and the risk of esophageal squamous cell carcinoma. Moreover, specific components of metabolic syndrome—such as diabetes mellitus—may confer a survival advantage in patients with esophageal squamous cell carcinoma, though this effect is not observed in adenocarcinoma [76]. These findings suggest that the metabolic phenotype of adipose tissue may exhibit distinct biomarker profiles depending on the tumor's histological subtype [77]. Thus, obesity's role in cancer is both deleterious and, under specific circumstances, deceptively protective—a paradox demanding cautious interpretation and methodological rigor.

7. Inflammation-Induced EMT, Angiogenesis, and Metastasis

The transition from localized tumor growth to metastatic dissemination is heavily influenced by chronic inflammation—particularly in the context of obesity. Inflammatory signals not only support tumor proliferation but also orchestrate the molecular events underlying epithelial-to-mesenchymal transition (EMT), angiogenesis, and extracellular matrix (ECM) remodeling—all essential for cancer invasion and metastasis [31,78].

EMT is a process wherein epithelial cells lose their cell–cell adhesion and apical-basal polarity and acquire mesenchymal traits, including motility and invasiveness. Inflammatory cytokines such as TNF-α, IL-6, and TGF-β act as key EMT inducers in the tumor microenvironment [3]. These molecules activate transcription factors such as Snail, Twist, and ZEB1, which downregulate epithelial markers (e.g., E-cadherin) and upregulate mesenchymal markers (e.g., vimentin, N-cadherin) [31,78]. In obesity, adipose-derived cytokines enhance these EMT signals, creating a systemic predisposition to tumor aggressiveness [5,79].

The angiogenic switch, a hallmark of cancer progression, is likewise driven by obesity-induced inflammation. Vascular endothelial growth factor (VEGF), generated by adipocytes and tumor-associated macrophages, plays a central position in stimulating neovascularization, ensuring a sustained nutrient supply for expanding tumors [7,29]. The pro-inflammatory state also induces HIF-1α, which amplifies VEGF transcription and promotes endothelial proliferation even under normoxic conditions [67,68].

Additionally, the ECM—usually a structural barrier to metastasis—is degraded by matrix metalloproteinases (MMPs), particularly MMP-2 and MMP-9, which are upregulated in obese, inflamed tissues [28]. This ECM remodeling facilitates tumor cell escape from the primary site and invasion into the surrounding stroma and vasculature [2,31].

These interconnected processes—EMT, angiogenesis, and ECM degradation—are not only enhanced in obesity but also correlate with poor cancer outcomes, including therapy resistance and early metastasis. Hence, targeting these inflammation-driven mechanisms is a promising therapeutic avenue for obesity-related malignancies [2].

8. Interventions and Future Directions

Given the well-established links between obesity, chronic inflammation, insulin resistance, and cancer, therapeutic strategies are increasingly focused on targeting the metabolic–inflammatory axis to reduce cancer risk and improve outcomes in obese patients. These interventions span lifestyle, pharmacological, and molecular domains, with promising implications for both prevention and therapy [80,81].

8.1. Diet and Nutrition

Modifiable risk factors play a key role in reducing the incidence and prevalence of both obesity and cancer. Current guidelines and studies emphasize that dietary improvements,

reduced alcohol consumption, and regular physical activity are fundamental pillars of a healthy lifestyle and critical strategies for the prevention of obesity and non-communicable chronic diseases (NCDs) [82,83]. In addition to its role in cancer and obesity prevention, nutrition is essential during cancer treatment, as maintaining a healthy body weight has been associated with improved tolerance to antineoplastic therapies. Among cancer survivors, adherence to a healthy dietary pattern and the prevention of excessive weight gain have been linked to better long-term survival outcomes [84].

The Mediterranean diet has shown promise in reversing obesity trends. It is characterized by the consumption of minimally processed and plant-based foods with high fiber content (vegetables, fruits, legumes), healthy fats that support cardiovascular health (nuts, olive oil), whole grains, and lean proteins—especially fish and seafood—as well as moderate intake of dairy (with emphasis on yogurt), and limited consumption of red meat and sweets. This dietary pattern has been associated with a reduced risk of several cancer types, including colorectal, gastric, head and neck, breast, and renal cell carcinoma. In contrast, the Western diet—rich in ultra-processed foods and sugar-sweetened beverages—is more strongly associated with obesity and NCDs [85–87].

Intermittent fasting (IF) has been associated with reductions in adiposity and systemic inflammation, improved insulin sensitivity, and metabolic reprogramming of the tumor microenvironment. Preclinical and translational reports—particularly in breast cancer—suggest attenuation of proliferation, EMT, and pro-inflammatory signaling under IF regimens [88]. IF has emerged as a promising approach in cancer research, particularly concerning its impact on obesity-induced triple-negative breast cancer (TNBC). A study by Son et al. (2024) provides substantial evidence that IF can significantly attenuate the progression of TNBC. The researchers found that IF disrupts the cell cycle and epithelial–mesenchymal transition (EMT), alters the immune contexture, and reduces pro-inflammatory signatures, all of which contribute to its cancer-fighting properties [88].

Similarly, Zhao et al. (2021) discuss the dual role of intermittent fasting in tumor dynamics. They highlight various mechanisms by which IF may act as both a protective and harmful influence on tumor development. This nuanced view suggests that while IF has potential benefits in slowing tumor progression and enhancing metabolic health, its effects can vary depending on the specific cancer context and individual metabolic state [89].

Together, these studies underscore the complex relationship between intermittent fasting, metabolic health, and cancer, particularly in the realm of TNBC, where IF may offer a therapeutic pathway to mitigate cancer progression and improve treatment outcomes [88,89].

8.2. Physical Activity

Physical activity plays an essential role in the management of obesity by promoting a reduction in body fat, particularly visceral or abdominal adiposity. This contributes to the improvement of the inflammatory profile through decreased estrogen levels and enhanced insulin sensitivity. Evidence indicates that regular physical exercise also serves as a preventive factor for cancer, with notable associations observed in breast, colorectal, endometrial, esophageal adenocarcinoma, gastric, renal, bladder, and lung cancers [83].

These protective effects are primarily attributed to reductions in oxidative stress and DNA damage and suppression of inflammatory signaling pathways involved in the development of NCDs and carcinogenesis [82,90].

Current recommendations advocate for at least 150 min per week of moderate-intensity physical activity or 75 min per week of vigorous-intensity exercise. In cancer patients, physical activity has been associated with improved chemotherapy uptake by enhancing

tissue perfusion and normalizing tumor microenvironment vasculature. Furthermore, it has been linked to increased overall survival and a reduced risk of developing a second primary tumor [91,92].

8.3. Anti-Inflammatory Agents

Chronic low-grade inflammation contributes significantly to the oncogenic potential of obesity, making anti-inflammatory approaches an attractive option. Agents such as aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), and metformin have been shown to reduce the incidence of several cancers by inhibiting pro-inflammatory pathways like NF-κB and COX-2 and improving insulin sensitivity [8,81]. Additionally, vitamin D supplementation has demonstrated modulatory effects on inflammatory signaling and leptin-mediated carcinogenesis in obesity [93].

8.4. Metabolic Modulation Therapies

Glucagon-like peptide-1 (GLP-1) receptor agonists, originally developed for type 2 diabetes, have gained attention for their dual roles in weight reduction and insulin sensitivity restoration [94]. Recent studies suggest they may also inhibit tumor progression by dampening inflammatory cytokines and normalizing metabolic homeostasis, particularly in gynecological cancers [95]. Regarding semaglutide, mechanistic plausibility exists—via weight loss, improved insulinemia/insulin sensitivity, and reduced inflammatory tone—that GLP-1RAs could reduce pro-tumorigenic signaling in obesity [96]. However, clinical evidence on tumor growth reduction or cancer risk modulation remains limited and mixed, and long-term oncologic outcomes are still under active investigation. We therefore maintain a balanced stance: GLP-1RAs are valuable metabolic tools with potential anticancer benefits mediated indirectly through metabolic and inflammatory improvements, but definitive cancer endpoints will require prospective data [97].

Although GLP-1 receptor agonist therapies have demonstrated promising results in the management of obesity, their associated adverse effects—such as nausea, fatigue, and loss of muscle and bone mass—underscore that pharmacological intervention alone is not a definitive solution. These findings highlight the critical role of lifestyle modification, particularly nutritional support aimed at mitigating side effects and preserving lean body mass and bone density, as well as regular physical activity to promote long-term maintenance of weight and fat loss [98].

Furthermore, bariatric surgery remains the most effective intervention for reversing severe obesity and insulin resistance [99]. Longitudinal data show that significant weight loss after surgery reduces levels of inflammatory cytokines and correlates with lower cancer incidence and mortality, especially in women [100].

8.5. Emerging Molecular Targets

As our understanding deepens, novel therapeutic targets are emerging. Inhibitors of STAT3, HIF-1α, and PI3K/Akt/mTOR signaling are under investigation for their roles in disrupting obesity-driven tumor pathways. Immunometabolism, a field that studies the interface of immune signaling and metabolic function, is opening new avenues for cancer immunotherapy specifically tailored to obese patients [2,65].

Despite these advances, a major challenge remains in tailoring interventions to individual patients. Future research must address the heterogeneity in metabolic profiles, genetic predispositions, and cancer types, while also considering sex-specific hormonal environments and the role of gut microbiota [101].

A multidisciplinary approach—integrating oncology, endocrinology, immunology, and nutrition—will be essential in crafting personalized strategies to mitigate the cancer risk imposed by obesity and metabolic disease.

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