Journal of Translational Medicine

REVIEW

Open Access

Microenvironmental determinants of cancer progression during obesity: emerging evidence and novel perspectives

Rossella Salemi[1], Valentina Sergi[2], Maria Sofia Basile[1], Sara Bravaccini[1], Lucia Frittitta[2], Adriana Carol Eleonora Graziano[1], Agnese Filippello[1*], Roberta Malaguarnera[1†] and Ernestina Marianna De Francesco[1†]

Abstract Obesity is a global pandemic representing a significant public health threat, with a rising number of affected individuals and numerous associated co-morbidities, including cancer. In obese cancer patients, higher mortality rates are usually observed compared to normal weight/lean individuals. The imbalanced metabolic asset of obese patients fosters tumor growth and its progression by impacting not only on cancer cells, but also affecting their cross-talk with the tumor microenvironment, which represents a relevant and multifaceted player in disease progression. Herein, we deliver a detailed overview of certain peculiar players implicated in the reprogramming of the tumor microenvironment during obesity toward disease evolution. We highlight the key metabolic, molecular and cellular players that co-opt cancer cells and their microenvironment to foster disease progression. We emphasize the role of certain hormones and growth factors-dependent pathways (Insulin/IGF signaling system and VEGF/VEGFR axis) together with inflammatory pathways (RAGE signaling system) in triggering microenvironmental-dependent evolution of neoplastic disease during obesity. Finally, we underline current pitfalls and envisage innovative tools and future directions for better investigating tumor progression in obesity.

Introduction

Obesity is a metabolic disorder arising from a chronic imbalance between energy intake and expenditure, leading to excessive fat accumulation and pathological adipose tissue expansion. This metabolic condition is currently considered as a disease [1]. In fact, in 1997 the World Health Organization, following consultation with the International Obesity Task Force, released a ground-breaking document clearly stating that obesity is a chronic disease that requires the establishment of prevention and management programs at both individual and community level [2]. Subsequently, the National Institutes of Health (in 1998) and the American Obesity Society (in 2008) confirmed that obesity is a disease [3]. In 2013, the American Medical Association House of Delegates recognized obesity as a disease that requires treatment and prevention strategies [4]. In addition, in 2017, World Obesity released a similar position statement, elaborated by a group of expert advisers in the field [5].

Due to its ever-increasing incidence worldwide, obesity is currently considered as a "global pandemic" and a major risk factor for non-communicable diseases, including cardiovascular diseases (CVDs) and cancer [6]. In the latter context, obesity is a modifiable factor associated

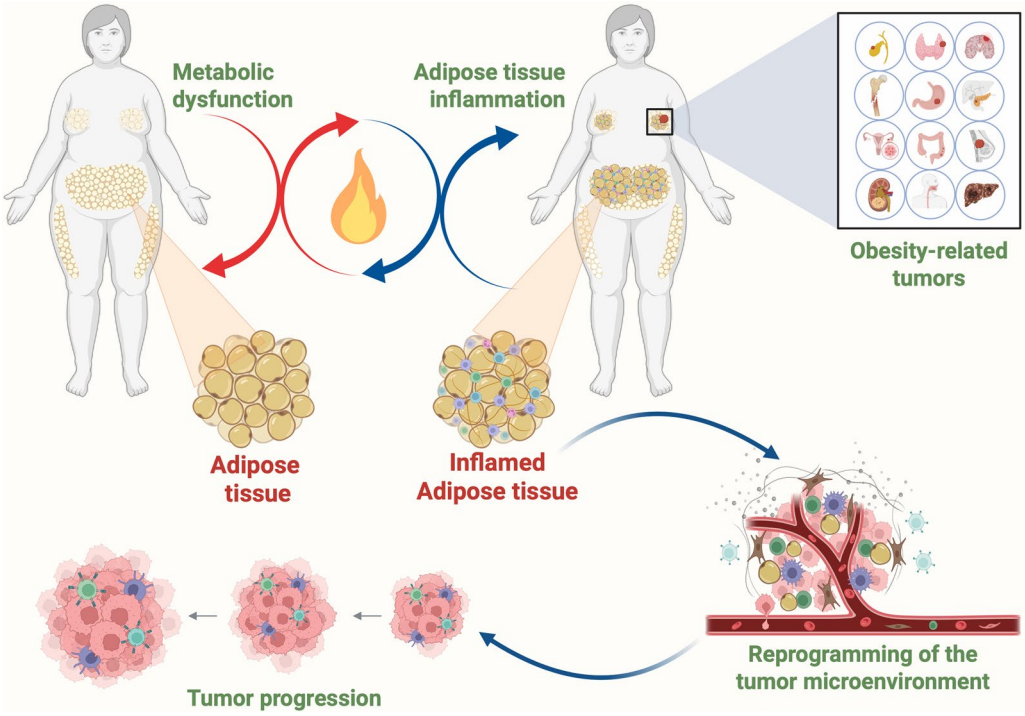
†Roberta Malaguarnera and Ernestina Marianna De Francesco have contributed equally to this work.

*Correspondence:
Agnese Filippello
agnese.filippello@unikore.it

Full list of author information is available at the end of the article

Keywords Obesity, Tumor microenvironment, Insulin/IGF system, RAGE

Graphical abstract



with increased cancer incidence and higher mortality rates. Obesity affects tumor development and progression through multiple mechanisms, such as the activation of impaired metabolic responses, the stimulation of chronic low-grade inflammation, and the aberrant activation of hormones and growth factors-dependent stimulatory pathways (Table 1).

In fact, an increased tumor risk in overweight/obese patients compared to normal weight subjects is found in colorectal, ovarian, endometrial, cervix, esophageal, pancreatic cancer, as well as in meningioma, multiple myeloma, leukemia and tumors of the stomach, liver, kidney, gallbladder and thyroid [9, 31]. A similar trend is observed for breast cancer in post-menopausal women, whereas an inverse association between cancer risk and body mass index (BMI) is detected in pre-menopausal breast cancer and in prostate cancer patients [31, 32]. Despite further investigation is needed, current literature emphasizes obesity's significant role in promoting a large subset of tumor types, accounting for nearly 40% of newly diagnosed cases [33]. Worthy, obesity impacts not only on cancer risk, but also on cancer-related mortality [34]. For instance, in obese breast cancer patients an increased risk of metastasis propagation was evidenced in a phase 3 clinical study [35]. Conversely, a lower risk of death is detected in obese patients suffering melanoma, kidney and lung cancer, indicating that tissue-dependent factors may influence cancer biology and disease evolution [36]. This phenomenon, known as "obesity paradox", refers to the controversial hypothesis proposing that overweight/obese individuals could have improved outcomes and survival rates in different co-morbidities, including cancer, when compared to normal/underweight patients [37]. In cancer patients, the "obesity paradox" could be mainly attributed to methodological limitations, such as reverse causation, selection bias, confounding, and the use of BMI as a measure of adiposity [38]. In survival studies performed on obese cancer patients, reverse causation due to both weight loss or cachexia could be the main factors underlying the "obesity paradox" [38]. On the other hand, overweight and obesity could favorably impact treatment outcomes, as excess adipose tissue can alter the pharmacokinetics of anticancer therapies and offer nutritional reserves that help patients to better tolerate surgical and oncologic interventions [39]. Furthermore, there is emerging evidence of an enhanced response to immunotherapies in obese/overweight patients compared with normal weight individuals, further supporting the "obesity paradox" [40]. However, the apparent increased efficacy of immune checkpoint

Table 1 Summary table outlining key obesity-related mechanisms and their impact on specific cancer types

Obesity-related mechanisms	Key features	Associated cancer types	Effect on cancer	References
Chronic low-grade inflammation	High levels of TNF-α, IL-6, IL-1β foster a pro-tumor microenvironment	Colorectal, Breast, Liver, Pancreatic	Improves proliferation, angiogenesis, and metastasis	[7, 8]
Insulin resistance / Hyperinsulinemia	Enhanced insulin and IGF-1 signaling stimulate the PI3K/Akt/mTOR cascade	Endometrial, Colorectal, Breast, Prostate	Enhances cellular proliferation and suppresses apoptosis	[9, 10]
Adipokine imbalance	Increased leptin (which promotes tumor growth) and decreased adiponectin (which inhibits tumor development)	Breast, Ovarian, Colorectal	Promotes angiogenesis, proliferation, and immune evasion	[11, 12]
Altered sex hormone metabolism	Excess adipose tissue increases estrogen by activating aromatase	Breast (postmenopausal), Endometrial	Estrogen receptor activation drives tumor growth	[13, 14]
Gut microbiota dysbiosis	Alterations in gut microbiota linked to obesity elevate LPS levels and trigger inflammation	Colorectal, Liver	Enhances inflammation and metabolic endotoxemia	[15, 16]
Immune dysregulation	Increased M1 macrophages, Treg/Th17 imbalance, impaired NK cell function	Multiple cancers	Impairs immune surveillance, promotes tumor escape	[17, 18]
Lipid metabolism reprogramming	Elevated fatty acid availability supports membrane biosynthesis and energy production	Prostate, Breast, Liver	Enables tumor cell growth and survival	[19, 20]
Hypoxia in expanded adipose tissue	Adipocyte hypertrophy limits oxygen diffusion, leading to HIF-1α stabilization and upregulation of VEGF/VEGFR signaling; also promotes increased expression of EGFR and its ligands (e.g., amphiregulin, TGF-α)	Breast, Pancreatic, Liver, Lung, Endometrial	Stimulates angiogenesis, vascular permeability, EMT processes, and the metastatic potential	[21–28]
AGE/RAGE signaling	Accumulation of advanced glycation end products (AGEs) activates RAGE receptor, promoting oxidative stress and chronic inflammation	Colorectal, Pancreatic, Breast	Enhances NF-κB signaling, ROS production, and tumor-promoting inflammation	[29, 30]

inhibitors in obese cancer patients could be, also in this case, influenced by reverse causality [40]. Despite further investigations are needed to better understand the mechanisms implicated in the "obesity paradox", current literature strongly underlines the importance of avoiding misinterpretation in order to prevent the mistaken conclusion that obesity is beneficial and/or protective in cancer patients [41].

In this intricate scenario, it should be mentioned that sex-related differences may be accountable for obesity-related disparities in cancer progression. In fact, death rates from all cancers are 62% higher for obese women and 52% higher for obese men compared to the normal weight counterpart [42].

Further supporting the stimulating role of obesity in cancer, obese patients exhibit larger and higher-graded tumors, and present with lymph nodes involvement that justifies a higher metastatic propensity compared with normal weight patients [43, 44].

Of note, in animal models of breast cancer, the diet-induced obese phenotype was associated with the acquisition of several malignant features including hypoxic tumor masses, intense angiogenic responses, neutrophil infiltration and epithelial to mesenchymal transition (EMT) [45]. Interestingly, the transplantation of tumor cells isolated from obese mice within normal weight mice accelerated tumor growth and boosted metastases formation [45]. Together with enhanced metastatic dissemination, obese cancer patients fail to respond to anticancer therapies more frequently compared with normal weight patients. This could be due to multiple factors [44].

First of all, certain chemotherapies like cisplatin and paclitaxel have altered clearance rates in patients with obesity, affecting drug concentration levels [46]. Beyond pharmacokinetics, obesity negatively affects the success of chemotherapy through the release of adipokines and inflammatory mediators [47, 48].

Moreover, in obesity an increase in saturated fatty acids within cell membranes reduces the bilayer fluidity, thus interfering with anticancer drug passive diffusion and endocytosis. Likewise, obesity-dependent alterations of the cell membrane may increase drug efflux through the activation of the ATP-binding cassette (ABC) multidrug efflux transporters [49, 50]. Worthy, the membrane abundance of saturated fatty acyls compared to polyunsaturated lipids render cancer cells less prompt to drug-dependent lipid peroxidation, with an ultimate reduction of chemotherapy efficacy [49].

Similar to standard chemotherapy, obesity jeopardizes the success of targeted therapies. For instance, a meta-analysis indicates that HER2-positive breast cancer patients receiving target therapies in neoadjuvant regimen were less likely to achieve pathologic complete response if overweight/obese [51]. Furthermore, visceral fat area (VFA) predicted poorer response to bevacizumab as a first-line treatment in metastatic colorectal cancer patients [52].

Despite these challenges, some studies suggest the previously mentioned "obesity paradox," where obese patients may experience better responses to certain immunotherapies compared to their normal-weight counterparts. This is the case for immunotherapeutic strategies, where the obese landscape may trigger PD-1 mediated T cell exhaustion and immune aging [53]. In this metabolically impaired environment, tumor progression is facilitated but, on the other hand, the efficacy of PD-1/PD-L1 blockade appears to be higher, as evidenced in both animal models and clinical samples [53]. Adding to this, immune checkpoint inhibitors have shown increased efficacy in obese patients affected by triple-negative breast cancer [54, 55]. On the other hand, these observations must take into account data coming from mice models of obesity, both genetically and diet-induced, showing that the systemic response to immunotherapy within the inflammatory-enhanced environment may lead to potentially lethal toxic responses, particularly in aged mice [56].

In this intricate scenario, survival pathways activated by hormones and growth factors elicit a stimulatory role in the obese environment, thus dampening the efficacy of anticancer strategies.

Overall, understanding the metabolic derangements that occur during obesity may help clarifying the multifaceted aspects that orchestrate disease progression. Uncovering the intricate connections between inflammatory mediators and hormones/growth factors-related pathways may contribute to the identification of more beneficial anticancer strategies, particularly in obese patients.

Obesity shapes the tumor microenvironment

The tumor microenvironment (TME) is a complex component of the tumor mass, consisting of both cellular (adipocytes, fibroblasts, and immune cells) and non-cellular elements (blood and lymphatic vessels, cytokines, and the Extracellular Matrix—ECM) [57]. The TME coordinates a number of reciprocal and bidirectional interactions between cancer cells and their *milieu* to foster disease progression [58]. This occurs through the secretion of autocrine and paracrine molecular mediators and through the modification of the cellular and physical properties of the host tissue [58].

During obesity, most components of the TME undergo significant reprogramming due to both systemic and local factors. Solid research efforts have attempted to uncover how the re-shaping of the TME during obesity affects cancer progression, identifying the cellular and molecular players involved. Such players include stromal cells and stromal derived-factors, certain hormones and growth factors-dependent pathways, together with angiogenic and inflammatory signaling axes (Table 1).

Stromal cells and stromal derived-factors

Adipose tissue is distributed in the body in anatomically distinct depots, each with specialized metabolic roles. The two major types of adipose tissue are brown adipose tissue (BAT) and white adipose tissue (WAT). BAT, found predominantly in the interscapular region in infants and in supraclavicular and perirenal areas in adults, is specialized for non-shivering thermogenesis and energy expenditure. In contrast, WAT primarily serves as an energy storage depot, and is further divided into subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT), each with distinct functional properties [59, 60]. VAT, located around internal organs such as the liver and intestine, is particularly metabolically active and has been strongly associated with adverse metabolic outcomes, including insulin resistance and cardiovascular disease. In contrast, SAT, found beneath the skin, is generally considered more metabolically benign [59]. In the context of obesity, WAT—especially in its visceral location—undergoes pathological remodeling. Adipocytes enlarge (hypertrophy) and may eventually die, prompting immune cell infiltration and the establishment of a chronic, low-grade inflammatory state. The inflamed microenvironment includes not only adipocytes, but also immune cells, fibroblasts, and endothelial cells, all of which interact in a dynamic and dysregulated manner. Key inflammatory mediators such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), interleukin-1β (IL-1β) and interferon-gamma (IFN-γ) are upregulated, contributing to systemic insulin resistance, tissue fibrosis, and vascular dysfunction [61, 62].

These observations suggest that the anatomical location of adipose tissue critically determines its function, with BAT favoring energy dissipation, SAT offering relatively protective energy storage, and VAT playing a central role in metabolic disease when dysregulated.

Beyond its role in metabolic dysfunction, emerging evidence highlights that adipose tissue, particularly dysfunctional WAT, serves as a key player in cancer development and progression. The chronic inflammatory and metabolically altered state of obese adipose tissue creates a permissive TME, where adipocytes not only interact with cancer cells but actively contribute to their survival, proliferation, and metastasis [63].

This supportive environment is not homogeneous; rather, it reflects a dynamic remodeling of adipose tissue in obesity, marked by the emergence of distinct adipocyte subtypes with tumor-promoting functions.

For instance, the analysis of mouse and human WAT at the single cell level has determined that several cancer-associated adipocyte subtypes coexist in the TME, with different abilities to elicit tumor-promoting actions, thereby affecting prognosis [64].

As relevant stimulatory players, adipocytes boost the TME by (i) actively feeding tumor cells through lipid transfer; (ii) secreting inflammatory mediators; (iii) contributing to metabolic and cellular plasticity.

Balaban and co-workers demonstrated that the transferring of adipocytes-derived free fatty acids (FFAs) to breast cancer cells provides energy for their proliferation and migration [65]. Not surprisingly, FFA serum levels are higher in cancer vs non-cancer patients [66]. It is worth mentioning that FFAs function as bioactive signaling molecules mediating intercellular and intracellular communication. These signaling roles are integral to a wide range of cancer-related processes, including inflammation, immune regulation, metabolism, and cell proliferation [67, 68]. Among FFAs, polyunsaturated fatty acids (PUFAs), notably arachidonic acid, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA), serve as precursors for lipid mediators such as prostaglandins, leukotrienes, resolvins, and protectins, which exert potent autocrine and paracrine effects on inflammation, immune function, and tissue homeostasis [69, 70]. Additionally, in cancer FFAs influence gene expression by serving as endogenous ligands for nuclear receptors such as peroxisome proliferator-activated receptors (PPARs) as well as toll-like receptors (TLRs), thereby modulating transcriptional programs central to neoplastic evolution [71, 72]. Interestingly, alterations in the composition of FFAs within membrane lipids, affects receptor distribution and signaling pathways, as well as malignant transformation [73–75].

Adding to the enormous amount of literature demonstrating the tumor-promoting role of FFAs, a recently published study has elegantly shown that removing these metabolic mediators may be a useful tool to suppress tumor growth [76]. In particular, the authors performed a CRISPRa-mediated "browning" of human adipocytes by up-regulating the genes (uncoupling protein 1 (UCP-1), peroxisome proliferator-activated receptor-gamma coactivator (PGC)-1alpha (PGC-1α), or PR domain containing 16 (PRDM16). This strategy endowed adipocytes with higher capability to uptake FFAs, which were no longer available for the energy demands of cancer cells. In fact, the in vivo implantation of engineered adipocytes, which outcompeted tumors for nutrients, was able to repress tumor growth and progression [76]. This strategy of adipose manipulation transplant supports the wise remodeling of adipocytes as a cancer therapeutic approach that warrants future investigations.

Further exploring the opportunity to manipulate the cross-talk between adipocytes and cancer cells in anticancer efforts, Ruiz-Vela and collaborators demonstrated that the stimulation of diverse human cancer cell lines with unsaturated fatty acids prompts certain phenotypic changes suggestive of adipogenic transdifferentiation [77]. In fact, in hepatic, ovarian, breast and melanoma cancer cells exposed to palmitoleic, oleic and lineoleic acids a dramatic up-regulation of the adipogenic regulator PPARG was detected [77]. Furthermore, stimulated cells were subjected to an adipocyte-like phenotypic switch, as evidenced by the massive biogenesis of lipid droplets [77].

What's more, the transdifferentiation of breast cancer cells into post-mitotic and functional adipocytes represents a further mechanism for halting tumor progression [78].

In fact, breast tumor cells undergoing EMT were terminally differentiated into adipocytes using the PPARγ agonist rosiglitazone in combination with the MEK inhibitor trametinib [79]. Such plasticity mechanism was exclusively shared by breast cancer cells with mesenchymal features, and not by their purely epithelial counterpart. These observations suggest that EMT may represent an efficient route through which tumor cells are transformed into adipocytes, thereby repressing primary tumor invasion and metastasis formation [78].

Additionally, in well-differentiated liposarcoma (WDLPS) and dedifferentiated liposarcoma (DDLPS) cells, the treatment with well-known adipogenic stimulators is sufficient to mount a transcriptional and translational response that sustained both maintenance of stemness and adipogenic differentiation. These molecular responses were associated with the inhibition of tumor growth in vitro and in vivo [80].

Beyond their ability to feed tumor cells and to regulate microenvironmental plasticity, adipocytes also secrete several cytokines that promote cancer cell survival. In fact, in prostate cancer, adipocytes-derived C–C motif chemokine ligand 7 (CCL7) is recruited to C–C motif chemokine receptor 3 (CCR3)-expressing tumor cells, driving their migration to survival niches present in the periprostatic fat [81]. This suggests that paracrine factors from adipocytes may contribute to cancer cell dormancy in sites commonly associated with tumor recurrence such as the periprostatic adipose tissue [81]. Additionally, obesity increases levels of many other cytokines and adipokines such as leptin, adiponectin, IL-6, TNF-α, and resistin that contribute to several cancer promoting events [82, 83]. For instance, high adiponectin levels (implicated in the regulation of insulin sensitivity, glucose levels, and lipid accumulation) is associated with lower body weight and reduced cancer risk, while its decline in obesity correlates with increased cancer susceptibility [84–86].

Conversely, leptin (implicated in the regulation of lipolysis and food intake) is elevated in obesity and associated with cancer cell proliferation and metastasis, especially when its receptor (Ob-R, leptin receptor) is overexpressed [87]. In this regard, in breast cancer cells,

leptin -by binding to Ob-R- enhances pro-tumorigenic responses mainly through the aberrant activation of the MAPK/ERK and PI3K/AKT signaling pathways [88].

Within the adipose stroma, adipose tissue-derived mesenchymal stromal/stem cells (ASCs/MSCs), which belong to mesenchymal stromal/stem cells (MSCs), significantly shape the TME during obesity [89]. The dynamic interaction between ASCs, immune cells, and cancer cells fosters disease progression through direct communications and chemotactic signals that recruit ASCs and MSCs to the tumor site [89–92]. Furthermore, during obesity, ASCs gain de-differentiation properties, generating cancer-associated fibroblasts (CAFs), which play a pivotal role in cancer progression and prognosis [93–95]. Accordingly, factors secreted by tumor cells, combined with direct interactions between cancer cells and ASCs/MSCs, select for a pro-tumorigenic population of MSCs, which can differentiate into CAFs and cancer-associated adipocytes (CAAs) [96].

Despite the precise mechanisms driving the de-differentiation of CA (Cancer-Associated)-MSCs are not fully understood yet, various evidence suggests that the TME is the main trigger for such process.

Together with stromal-derived factors and molecular mediators, inflammation, vascularity and fibrosis contribute to the acquisition of malignant cancer features during obesity. These events parallel adipocytes gradual enlargement toward hyperplasia and hypertrophy, leading to the compression of the vascular structure and the establishment of hypoxia. A key marker of adipose tissue fibrosis is the increased deposition of type VI collagen (Col 6), which exacerbates metabolic dysfunction and limits adipose tissue plasticity [97]. Col 6 contribution to adipose fibrosis is further amplified by endotrophin, a product derived from the carboxy-terminal cleavage of Col6 alpha 3; notably, endotrophin prompts the expansion of the fibrotic response and enhances tumor growth and metastasis in breast and lung cancer [98, 99].

The VEGF/VEGFR axis

In the context of obesity, the changes in adipose tissue structure involve not only adipogenesis but also angiogenesis. As previously mentioned, the increase in the number and size of adipocytes during obesity induces a mild hypoxic state, which drives the adipose tissue to promote angiogenesis in order to overcome hypoxic stress [100]. Interestingly, obese patients exhibit overexpression of the active form of the transcription factor hypoxia-inducible factor 1 alpha (HIF-1α), similar to tumor tissues [101, 102].

The up-regulation of HIF-1α is pivotal for the transcription of HIF-1 target genes, which permit cell adaptation to hypoxic stress via activation of angiogenic programs [103]. Among the transcriptional targets of HIF-1, the vascular endothelial growth factor-A (VEGF-A) and angiopoietin-like 4 (ANGPTL4) play a key role in tumor angiogenesis [104].

VEGF-A, secreted primarily by tumor cells, interacts with the vascular endothelial growth factor receptor 2 (VEGFR2) thus promoting endothelial cell proliferation, survival, and migration. These biological events support the formation of new blood vessels that supply nutrients and oxygen to the growing tumor mass [105]. Of note, adipocytes also produce VEGF and other angiogenic factors necessary for proper vascularization, toward the expansion of both the adipose tissue expansion and the tumor mass [106]. In this context, a positive correlation has been highlighted between the degree of microvascular invasion , an angiogenic activity marker linked to poor prognosis, and BMI in hepatocellular carcinoma patients. This indicates that in obese patients the activation of angiogenic programs may accelerate disease progression [107].

Furthermore, angiogenic factors secreted by adipose cells from obese patients activate the expression of genes involved in inflammation and lipid metabolism, including ANGPTL4, instigating a vicious cycle that fosters cancer progression [108]. Worthy, ANGPTL4 has been associated with increased proliferation and invasion of cancer cells [108]. These observations highlight the role of the adipose tissue secretome in promoting cancer cell adaptation to hypoxic stress by metabolic, angiogenic and inflammatory factors. Altogether, these mediators contribute to the aggressive phenotypes observed in obese cancer patients [108].

Hormone and growth factors: the Insulin/IGF system

The cross-talk between tumor cells and adipocytes during obesity involves complex microenvironmental interactions facilitated by cytokines, adipokines, hormones, and growth factors (Fig. 1) [109].

As it concerns hormones, a paradigmatic example is the local production of 17-β estradiol (E2) from androgens in the adipose tissue mediated by the enzyme aromatase [110]. This leads to E2-dependent activation of the estrogen receptor (ER) in cancer cells, stimulating various estrogen-sensitive tumors like breast cancer [111].

Interestingly, pro-inflammatory cytokines such as IL-6 may increase aromatase expression in obese mammary adipose tissue, further amplifying estrogen-dependent signaling pathways [112]. Adding to this, certain metabolites, like 25-hydroxycholesterol, can activate transduction cascades that promote disease progression by activating ER-dependent responses in cancer cells [113]. What's more, hypercholesterolemia, commonly observed in obesity, triggers the activation of estrogen-related

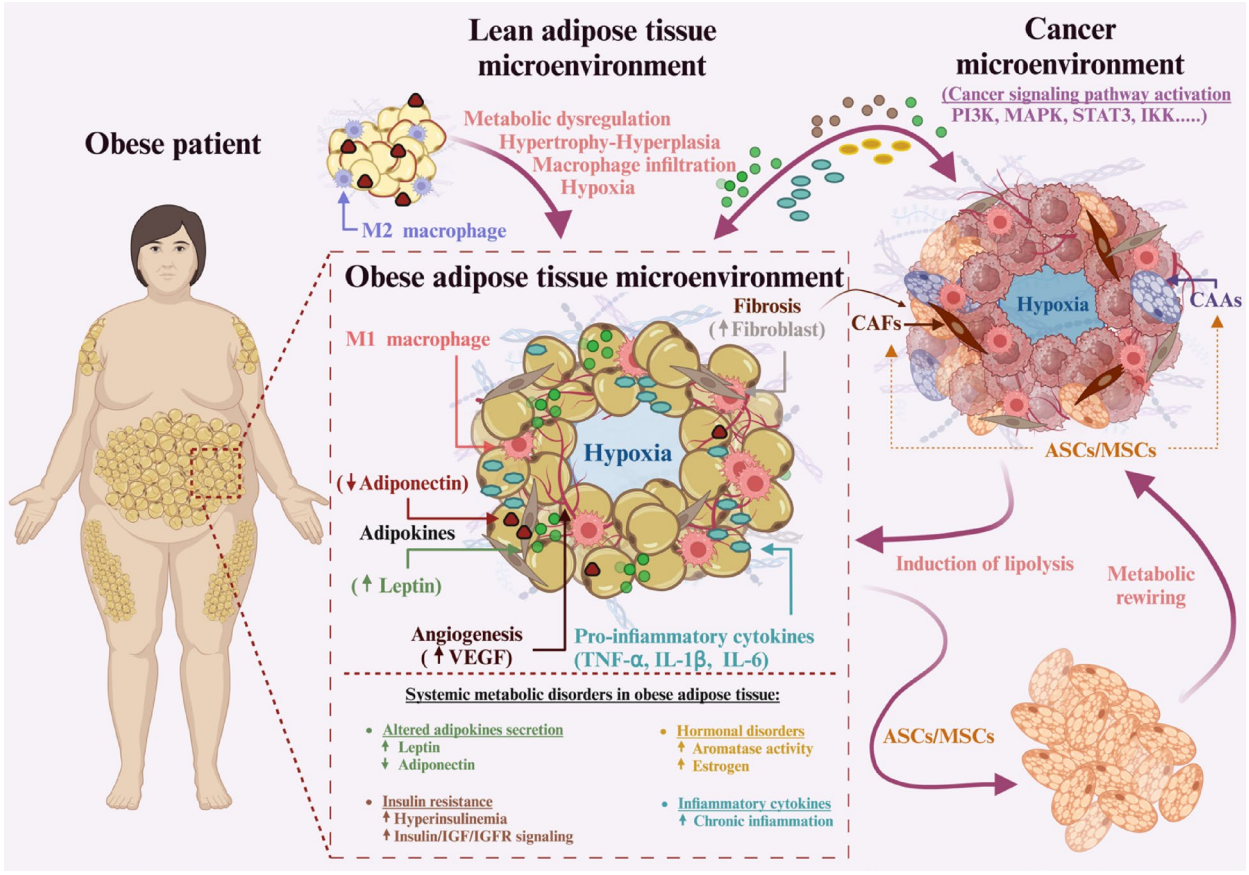


Fig. 1 Adipocyte/cancer cell cross-talk in the obese state. Obesity increases the risk of developing cancer by promoting multiple meta-inflammatory alterations. First, an increase in body weight enlarges adipocyte size, leading to inadequate vascularization and hypoxia, combined with fibrosis and chronic inflammation. This is associated with an increase in M1 macrophages that produce various pro-inflammatory cytokines toward insulin-resistance. Second, adipocyte hypertrophy in obesity is associated with changes in adipokine secretion, reinforcing the pro-inflammatory phenotype. Third, abnormally expanded adipocytes may release hormones and growth factors that contribute to the activation of cancer-related pathways, such as the Vascular Endothelial Growth Factor (VEGF) axis, the insulin/IGF/IGFR signaling (Insulin-like Growth Factor/Insulin-like Growth Factor Receptor), and estrogen pathway. Fourth, obesity-associated metabolic disorders, initiated in the tissue and propagated systemically through autocrine and paracrine effects, increase the risk of developing cancer by promoting the activation of stimulatory signaling pathways: phosphatidylinositol 3- kinase (PI3K); mitogen-activated protein kinase (MAPK); IkB kinase (IKK); signal transducer and activator of transcription 3 (STAT3); Interleukin-1β (IL-1β); interleukin-6 (IL-6); tumor necrosis factor-α (TNF-α). Fifth, a functional cooperation between cancer cells as well as adipose tissue-derived mesenchymal stromal/stem cells (ASCs/MSCs), cancer-associated adipocytes (CAA) and cancer-associated fibroblasts (CAFs) drive obesity-dependent cancer progression. Figure created with BioRender.com

receptor α toward both ER-positive and ER-negative breast cancer cell proliferation [114].

While estrogen signaling primarily contributes to neoplastic progression in estrogen-sensitive tissues, the Insulin/Insulin-like Growth Factor (IIGF) axis is hyperactivated across various cancer types, particularly in overweight and obese patients (Fig. 1) [115, 116]. Noteworthy, a cross-talk between estrogen signaling and IIGF axis has been largely demonstrated [117–120].

In fact, higher levels of the three ligands IGF-I, IGF-II and insulin, along with hyperactivation of their receptors (Insulin Receptor- IR, and insulin-like growth factor 1 receptor -IGFIR), are linked to increased cancer risk [115].

Extending these findings, compensatory hyperinsulinemia, consequent to insulin resistance commonly observed in obese patients, is a strong candidate for the increased cancer risk associated with metabolic disorders [121]. Mechanisms connecting hyperinsulinemia to cancer include: 1) increased synthesis and bioavailability of IGFs leading to IGF-IR overactivation; 2) overexpression and stimulation of IR, particularly isoform A (IR-A), which mediates the non-metabolic but mitogenic effects of insulin in tumor cells. This isoform has a higher affinity for IGF-II, which in turn, stimulates a peculiar gene profile and signaling response; 3) activation of IR-mediated downstream pathways such as MAPK and PI3K/AKT/mTOR cascades, playing a role in cancer stem cell biology stem/progenitors cells differentiation [122, 123].

Additionally, in obesity the dysregulation of insulin and IGFs activity is tightly linked with the instigation of

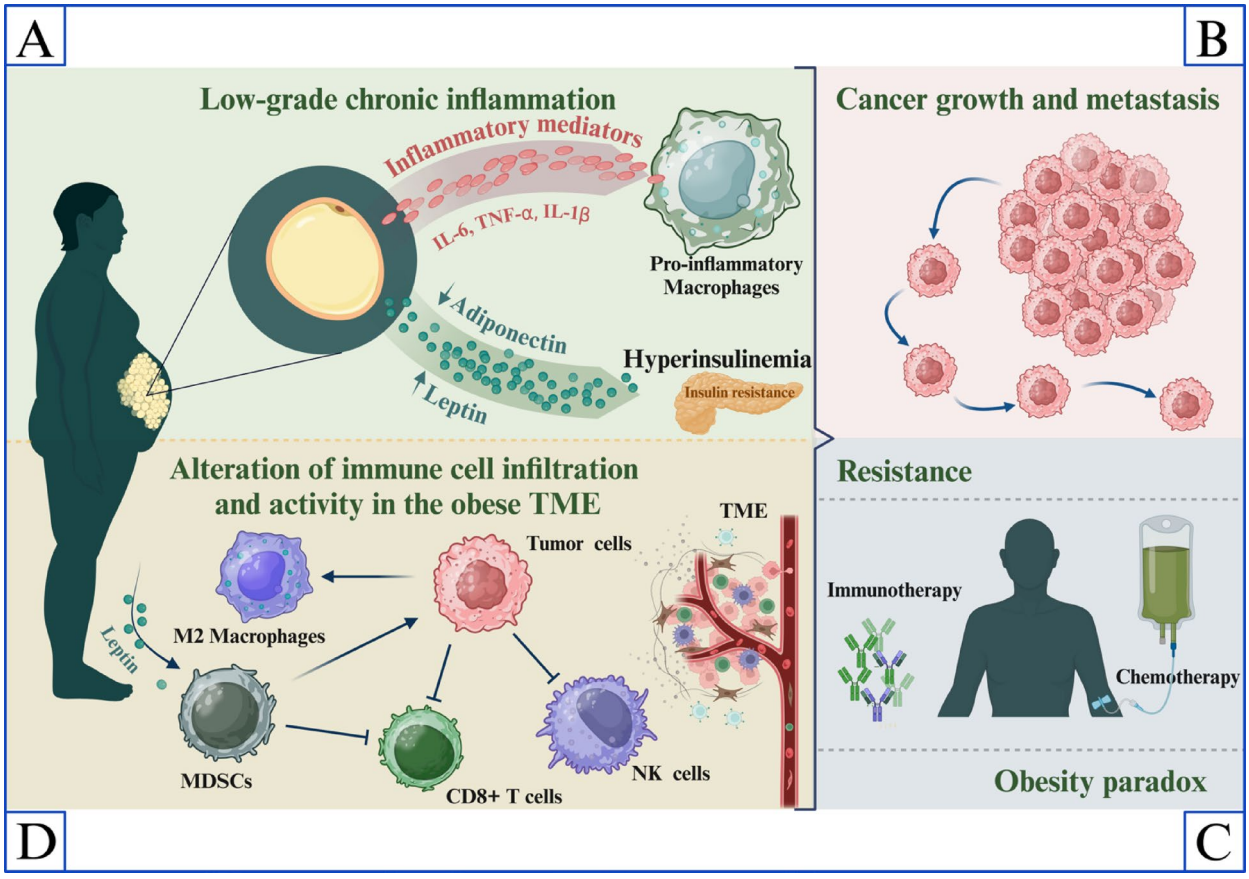


Fig. 2 Schematic representation of the main inflammation-dependent alterations of cancer immunity and associated effects. **A**–**B** Adipose tissue inflammation supported by pro-inflammatory macrophages leads to the release of inflammatory mediators, such as interleukin-6 (IL-6), Tumor Necrosis Factor-α (TNF-α), Interleukin-1β (IL-1β), toward insulin resistance and compensatory hyperinsulinemia, implicated in cancer progression. **B**–**D** The obese TME is primarily infiltrated by suppressive cell populations, including M2 macrophages and myeloid-derived suppressor cells (MDSCs). Leptin promotes the build-up of MDSCs in the tumor microenvironment (TME), thus inhibiting the activation of cytotoxic CD8 + T cells. Obesity also results in the loss of the antitumor functions of natural killer (NK) cells, ultimately facilitating tumor burden. Although obesity can induce resistance to certain anticancer therapies, it can also elicit a positive impact on the outcomes of some of them ("obesity paradox"). Figure created with BioRender.com

chronic low-grade inflammation, thus contributing to the development and progression of cancer [109, 124–126].

In this context, obesity leads to an increase in M1 pro-inflammatory macrophages, resulting in adipose tissue inflammation and insulin resistance [109, 127]. In fact, FFAs released from hypertrophic adipocytes and cytokines such as IL-6, TNF-α, and C-reactive protein may directly block insulin signaling by hampering its signal transduction through IR [128–131]. This action involves the activation of inflammatory signaling pathways (JNK, IKK/NF-κB, JAK/STAT) [132]. The JNK pathway, activated by TNF-α and leukotriene B4 from immune cells, impairs IRS-1 signaling, reducing PI3K and AKT phosphorylation, which induces insulin resistance in adipose tissue, liver, and muscle. Pro-inflammatory cytokines also activate IKK kinases, facilitating NF-κB translocation into the nucleus and promoting inflammatory gene expression that contributes to insulin resistance. In addition, IL-6 activates the JAK/STAT pathway inducing suppressor of cytokine signaling 3 (SOCS-3) expression that leads to the direct degradation of insulin receptor substrate 1 (IRS-1) by proteasome, ultimately impairing insulin signaling [133].

The subsequent establishment of insulin resistance paves the way to the increased release of insulin from pancreas, which in turn determines hyperinsulinemia, associated with cancer progression [121] (Fig. 2A).

The meta-inflammatory AGE/RAGE pathway

Among the obese individuals, certain subjects harbor metabolic imbalances typically associated with obesity, whereas others show a preserved metabolic function [134]. This observation challenges the linear relationship between BMI and adverse clinical outcomes, as metabolically healthy obese (MHO) individuals are at a lower risk of developing obesity-related morbidities compared to their metabolically unhealthy counterparts (MUO- metabolically unhealthy obese) [135].

Supporting this observation, only MUO subjects experience metabolic disorders that lead to altered glucose metabolism and insulin resistance, toward the establishment of the metabolic syndrome.

In MUO patients, glucose metabolism imbalances and insulin resistance are mainly initiated by the inflammatory state instigated within the hypertrophic adipose tissue. Therefore, inflammation is regarded as a key orchestrator of the metabolic aberrations typically observed in obesity [136].

The receptor for advanced glycation end products (RAGE) has been pointed out as an important mediator of chronic-low grade inflammation firstly initiated within the adipose tissue and then propagated systemically. Identified as a receptor for the advanced glycation end products (AGEs) generated during hyperglycemia, RAGE has been shown to mediate AGE-dependent responses that contribute to the complications of obesity and type 2 diabetes T2D through the transcriptional activation of inflammatory programs [137–140].

Beyond AGEs, several other ligands have been shown to bind to and activate RAGE, including S100 family proteins, the alarmin HMG-B1, (High Mobility Group-Box 1), Mac-1, and beta sheet fibrils [139, 141]. Of note, RAGE and its ligands accumulate in the adipose tissue during obesity, contributing to weight gain, inflammation and insulin resistance [137, 138].

In addition, RAGE expression is elevated in many cancer tissues where it supports sustained growth signals and the insensitivity to growth suppressors, immune evasion, neoangiogenesis, inflammation, the reprogramming of tumor metabolism, and the promotion of tissue invasion and metastasis [142–147]. On the basis of these observations, RAGE has been considered as a pivotal mediator in the *liaison* between inflammation and cancer [148].

Surprisingly, the cross-talk between RAGE and the IIGF axis in the establishment of metabolic-dependent inflammation has been indicated as an important player in cancer progression [142]. For instance, in breast cancer cells, IGF-1 upregulates S100A7 which binds to RAGE on endothelial cells thus triggering angiogenesis [144]. Additionally, a pharmacological inhibitor of RAGE, has been shown to blunt insulin-induced oncogenic signaling in vitro and in vivo [149]. Hence, targeting RAGE may offer a promising anticancer strategy, particularly in hyperinsulinemic conditions commonly associated with obesity.

Obesity impacts tumor immune infiltration

Obesity exacerbates cancer outcomes in part due to its immunosuppressive effects [150]. Several evidence shows that adipose tissue dysfunction and excessive fat accumulation in adipocytes contribute to the development of a microenvironment in which pro-inflammatory cytokines and dysregulated adipokines (leptin and adiponectin) impact the anti-tumor immune responses [151]. Macrophages play a fundamental role in both inflammation and insulin resistance in metabolic disorders and also exert a significant regulatory influence in cancer progression [152]. Unlike the traditional M1 macrophages activated during acute infections, macrophages in obese adipose tissue are "metabolically active" and exhibit a pro-inflammatory profile in response to obesity [153, 154]. These specialized cells produce numerous pro-inflammatory cytokines, such as TNF-α and IL-1β contributing to chronic inflammation and lipid metabolism regulation (Fig. 2A) [154].

Both obesity-dependent inflammation and immune cell dysfunctions foster cancer growth and metastasis by hampering anti-tumor immune responses [155] (Fig. 2B). Different from the adipose tissue, the obese TME is primarily infiltrated by suppressive cell populations, including M2 macrophages, T-regulatory cells, and myeloid-derived suppressor cells (MDSCs), whose accumulation is driven by immunosuppressive factors derived from cancer cells [155, 156]. In this regard, the obesity-related adipokine leptin promotes MDSCs accumulation in the TME, repressing cytotoxic T cell activation and increasing tumor burden [157] (Fig. 2D).

Similarly, obesity facilitates the exhaustion of CD8 + T cells and the expression of elevated levels of the immune checkpoints PD-1, Lag3 and Tim3 [158].

Of note, tumor-associated CD8 + T cells undergo a metabolic reprogramming that depends on certain energetic features and plasticity of the TME [158]. For example, in lipid-rich TME such as breast cancer, CD8 + T cells stimulated by the leptin/signal transducer and activator of transcription 3 (STAT3) pathway utilize fatty acid oxidation over glycolysis, leading to diminished anti-tumor responses [158]. Conversely, in low-lipid TME like colorectal tumors, obesity causes fatty acid starvation in CD8 + T cells due to their preferential utilization by tumor cells [158]. Obesity also reduces glutamine levels in the TME, disrupting amino acid metabolism and causing CD8 + T cell dysfunction [158].

Therefore, obesity may weaken anti-tumor immunity by multiple metabolic-related mechanisms that are selected in a tissue-specific manner.

Worthy, obesity alters lipid metabolism in tumor-infiltrating natural killer (NK) cells, leading to metabolic paralysis through the mTOR-PPAR pathway, which diminishes NK cell anti-tumor functions [158].

Despite advances in understanding how metabolic factors modulate immune responses in cancer, the complex role of obesity on immune cell activity within the TME remains inadequately characterized [155, 158]. A comprehensive understanding of how obesity impacts on patients' response to anticancer therapies is still lacking,

and some controversial aspects have been reported [150, 159].

Regarding chemotherapy, obesity has been shown to hinder its efficacy through mechanisms like chronic low-grade inflammation associated with NF-κB, and cycloxygenase 2 activation [160]. Preclinical studies indicate that obesity negatively impacts immunotherapy outcomes [161]. For instance, in murine breast cancer model, the diet-induced obese phenotype triggered higher intratumoral CXCL1, enhancing CXCR2-mediated accumulation of Fas Ligand$^+$ granulocytic MDSCs, which increases CD8 + T cell apoptosis, thus fostering immunotherapy resistance [162]. On the other hand, according to the previously described phenomenon known as the "obesity paradox", obesity may positively influence the outcomes of certain anticancer therapies [161] (Fig. 2C). While immune dysfunctions associated with obesity compromise immune surveillance and tumor editing, they may also enhance the immunogenicity of tumors and their sensitivity to immune checkpoint inhibitors [163]. Likewise, a systematic review and meta-analysis demonstrates an improved Overall Survival and Progression-Free Survival in patients with high BMI after receiving immune checkpoint inhibitors treatment compared with low BMI patients [164]. Furthermore, obesity has been linked to increased expression of immune checkpoints on T cells, which correlates with enhanced sensitivity to immune checkpoint inhibitors across various cancers [165].

Conclusion and future perspectives

Several mechanisms have been found to enable and facilitate cancer development and progression during obesity. Additional research efforts need to be dedicated to clarify the multifaceted aspects of cancer cells biology, as well as the mounting role of the TME in disease progression, particularly in the context of obesity. Not surprisingly, despite cancer presents as a different molecular, metabolic and biological entity in obese vs normal weight patients, the clinical approach foreseen in these two subpopulations is currently the same. This leads to poor clinical benefit and potential dispersion of healthcare resources, thus encouraging to collect further preclinical and clinical evidence that may drive decision-making processes in precision medicine strategies.

Growing epidemiological and experimental data suggest that lifestyle interventions like nutrition and diet may lower cancer risk and potentially enhance the success of anticancer therapies [166–168].

In this context, nutraceuticals and supplemental micronutrients have been recently proposed as promising potential adjunct tools in prevention and treatment of cancers for their antioxidant and anti-inflammatory actions.

For instance, oleuropein, luteolin, lycopene, and anthocyanins interfere with some TME players that prompt cancer progression, such as the IIGF axis, RAGE and PPARγ pathways, exerting anti-inflammatory and antitumor effects [169–173]. Despite preliminary preclinical data suggest the usefulness of functional food and nutraceutics, their use as supplements for cancer prevention or during chemotherapy remains a controversial issue without a definitive consensus [174].

Well-designed clinical studies with long-term follow ups could shed light into this intricate topic, together with more solid preclinical evidence.

As it concerns the preclinical models, a robust research pipeline aimed at advancing knowledge in the field of cancer prevention and treatment in obesity must consider the use of proper advanced experimental systems. The ideal model should allow the simultaneous investigation of the systemic and local environmental aspects of the neoplastic disease, mimicking the multiple aberrations of the obese microenvironment. To this aim, several rodent models have been proposed: (a) genetic models obtained by mutation of a single gene (such as mutations of leptin or Ob-R) that give raise to a monogenic form of obesity; (b) polygenic obesity-prone rodent models (such as the Osborne-Mendel model); (c) diet-induced obesity (DIO) models [175, 176]. DIO models are more physiologically relevant considering that in humans the establishment of obesity mostly recognizes both genetic and environmental cues. However, BMI criteria are defined differently in rodents compared to humans; thus, specific dietary regimens, including duration of the diet, fat content and energy densities to reach the overweight/obese state have been defined in a mice strain frequently used for modelling DIO [177].

It should be mentioned that a competent immune system in rodents is necessary for the development of obesity induced by diet. On the other hand, the establishment of advanced animal models of cancer (for instance patient-derived tumor models) requires the effective suppression of the immune system in the rodent host for proper tumor take. Adding to this, mice models often fail to recapitulate the features of the human TME.

To overcome this challenge, manipulated 3D platforms (organoids and organ-on-a-chip models) for culturing freshly resected patient-derived samples across different metabolic environments provide a valuable alternative to rodent studies, facilitating the exploration of homotypic and heterotypic cell–cell interactions within the TME while accounting for metabolic imbalances [178–181].

Additional efforts should be also put in place to better assess the potential of transdifferentiation therapies, particularly in precision medicine strategies for obese breast cancer patients. In fact, inducing the adipogenic transdifferentiation of human tumor cells may represent

a promising add-on to conventional strategies, pending a deeper understanding of the molecular mechanisms that drive cancer cells conversion into adipocytes.

Overall, the use of advanced investigating tools will allow a more comprehensive understanding of the intricate cell–cell interactions and paracrine cross-talk between cancer cells and their host tissue during obesity. This approach will help identifying novel therapeutic targets and designing more effective treatments in precision-medicine strategies for cancer patients with obesity.

Abbreviations

ABC	ATP-binding cassette
AGEs	Advanced glycation end products
ANGPTL4	Angiopoietin-like 4
ASCs	Adipose-derived stem cells
BAT	Brown adipose tissue
BMI	Body mass index
CAAs	Cancer-associated adipocytes
CAFs	Cancer associated fibroblasts
CCL7	C–C motif chemokine ligand 7
CCR3	C-C motif chemokine receptor 3
COL 6	Type VI collagen
CVD	Cardiovascular disease
DHA	Docosahexaenoic acid
DIO	Diet-induced obesity
E2	17-β Estradiol
ECM	Extracellular matrix
EMT	Epithelial to mesenchymal transition
EPA	Eicosapentaenoic acid
ER	Estrogen receptor
FFAs	Free Fatty Acids
HIF-1α	Hypoxia inducible factor 1 subunit alpha
HMG-B1	High mobility group-box 1
IFN-γ	Interferon gamma
IGF	Insulin-like growth factor
IIGF	Insulin/Insulin-like Growth Factor
IGF-IR	Insulin-like growth factor 1 receptor
IL-1β	Interleukin-1β
IL-6	Interleukin-6
IR	Insulin receptor
IR-A	Isoform A
IRS-1	Insulin receptor substrate 1
MAPK	Mitogen-activated protein kinase
MDSCs	Myeloid-derived suppressor cells
MHO	Metabolically healthy obese
MSCs	Mesenchymal stromal/stem cells
MUO	Metabolically unhealthy obese
NK	Natural killer
Ob-R	Leptin receptor
PPAR	Peroxisome proliferator-activated receptor
PUFAs	Polyunsaturated fatty acids
RAGE	Receptor for advanced glycation end products
SAT	Subcutaneous adipose tissue
STAT3	Signal transducer and activator of transcription 3
SOCS-3	Suppressor of cytokine signaling 3
TME	Tumor microenvironment
TNF-α	Tumor necrosis factor-α
VAT	Visceral adipose tissue
VEGF-A	Vascular endothelial growth factor-A
VEGFR2	Vascular endothelial growth factor receptor 2
VFA	Visceral fat area
WAT	White adipose tissue

Acknowledgements
Figures were created with Biorender.com.

Author contributions
RS, VS: Conceptualization, Writing—original draft, Writing—review & editing. MSB, SB, AF: Conceptualization, Writing—review & editing. LF, ACGE: Writing—review & editing. RM, EDF: Conceptualization, Funding acquisition, Writing—review & editing.

Funding
1) Cascade funding associated to ANTHEM (AdvaNced Technologies for Human-centrEd Medicine), Spoke 4, an initiative of the National Plan for NRRP Complementary Investments (PNC, established with the decree-law 6 May 2021, n. 59, converted by law n. 101 of 2021) in the call for the funding of research initiatives for technologies and innovative trajectories in the health and care sectors (Directorial Decree n. 931 of 06-06-2022) - project n. PNC0000003- E.M.D.F and R.M. This work reflects only the authors' views and opinions, neither the Ministry for University and Research nor the European Commission can be considered responsible for them. 2) Fondazione AIRC under Start-Up 2018—ID. 21651—E.M.D.F. 3) MUR—PRIN 2022 PNRR (Next Generation EU, componente M4C2, investimento 1.1.), grant number P2022MALRP-EDF and grant n. P202272FJC —A.C.E.G. and R.M. This work reflects only the authors' views and opinions, neither the Ministry for University and Research nor the European Commission can be considered responsible for them. 4) Ministry for Health: "Medicina rigenerativa, predittiva e personalizzata" -Traiettoria 3 -Piano Sviluppo e Coesione Salute (FSC 2014–2020); "LIFEMAP: dalla patologia pediatrica alle malattie cardiovascolari e neoplastiche nell'adulto: mappatura genomica per la medicina e prevenzione personalizzata. ID. T3-AN-14—A.C.E.G. and R.M. 5) MUR-PNRR - Initiative of the National Plan for NRRP Complementary Investments in the call for the funding of research initiatives for technologies and innovative trajectories in the health and care sectors- "DARE - Digital Lifelong Prevention"-project n. PNC0000002—R.S. and R.M. This work reflects only the authors' views and opinions, neither the Ministry for University and Research nor the European Commission can be considered responsible for them. 6) MUR-PNRR-Initiative 4.1- supports the PhD course of V.S.

Data availability
Not applicable.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interest
The authors declare that they have no competing interests.

Author details
[1]Department of Medicine and Surgery, "Kore" University of Enna, 94100 Enna, Italy
[2]Endocrinology Unit, Department of Clinical and Experimental Medicine, Garibaldi - Nesima Hospital, University of Catania, 95122 Catania, Italy

Received: 1 July 2025 / Accepted: 4 August 2025
Published online: 24 September 2025

References

1. De Lorenzo A, Gratteri S, Gualtieri P, Cammarano A, Bertucci P, Di Renzo L. Why primary obesity is a disease? J Transl Med. 2019;17(1):169.
2. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. World Health Organ Tech Rep Ser. 2000;894:i–xii, 1–253.
3. Rosen H. Is obesity a disease or a behavior abnormality? Did the AMA get it right? Mo Med. 2014;111(2):104–8.
4. Schumacher LM, Ard J, Sarwer DB. Promise and unrealized potential: 10 years of the American Medical Association classifying obesity as a disease. Front Public Health. 2023;11:1205880.

5. Bray GA, Kim KK, Wilding JPH, World Obesity F. Obesity: a chronic relapsing progressive disease process. A position statement of the World Obesity Federation. Obes Rev. 2017;18(7):715–23.
6. Bluher M. Obesity: global epidemiology and pathogenesis. Nat Rev Endocrinol. 2019;15(5):288–98.
7. Hotamisligil GS. Inflammation and metabolic disorders. Nature. 2006;444(7121):860–7.
8. Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. Cell. 2010;140(6):883–99.
9. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. Lancet. 2008;371(9612):569–78.
10. Gallagher EJ, LeRoith D. Epidemiology and molecular mechanisms tying obesity, diabetes, and the metabolic syndrome with cancer. Diabetes Care. 2013;36(Suppl 2):S233–9.
11. Renehan AG, Zwahlen M, Egger M. Adiposity and cancer risk: new mechanistic insights from epidemiology. Nat Rev Cancer. 2015;15(8):484–98.
12. Park J, Euhus DM, Scherer PE. Paracrine and endocrine effects of adipose tissue on cancer development and progression. Endocr Rev. 2011;32(4):550–70.
13. Cleary MP, Grossmann ME. Minireview: obesity and breast cancer: the estrogen connection. Endocrinology. 2009;150(6):2537–42.
14. Key TJ, Verkasalo PK, Banks E. Epidemiology of breast cancer. Lancet Oncol. 2001;2(3):133–40.
15. Tilg H, Adolph TE, Gerner RR, Moschen AR. The intestinal microbiota in colorectal cancer. Cancer Cell. 2018;33(6):954–64.
16. Schwabe RF, Jobin C. The microbiome and cancer. Nat Rev Cancer. 2013;13(11):800–12.
17. Ostrand-Rosenberg S, Sinha P. Myeloid-derived suppressor cells: linking inflammation and cancer. J Immunol. 2009;182(8):4499–506.
18. Ruffell B, Coussens LM. Macrophages and therapeutic resistance in cancer. Cancer Cell. 2015;27(4):462–72.
19. Rohrig F, Schulze A. The multifaceted roles of fatty acid synthesis in cancer. Nat Rev Cancer. 2016;16(11):732–49.
20. Santos CR, Schulze A. Lipid metabolism in cancer. FEBS J. 2012;279(15):2610–23.
21. Ye J. Emerging role of adipose tissue hypoxia in obesity and insulin resistance. Int J Obes (Lond). 2009;33(1):54–66.
22. Semenza GL. Hypoxia-inducible factors in physiology and medicine. Cell. 2012;148(3):399–408.
23. Carmeliet P. VEGF as a key mediator of angiogenesis in cancer. Oncology. 2005;69(Suppl 3):4–10.
24. Cao Y. Angiogenesis modulates adipogenesis and obesity. J Clin Invest. 2007;117(9):2362–8.
25. Yarden Y, Pines G. The ERBB network: at last, cancer therapy meets systems biology. Nat Rev Cancer. 2012;12(8):553–63.
26. Seo BR, Bhardwaj P, Choi S, Gonzalez J, Andresen Eguiluz RC, Wang K, et al. Obesity-dependent changes in interstitial ECM mechanics promote breast tumorigenesis. Sci Transl Med. 2015;7(301): 301ra130.
27. Aird R, Wills J, Roby KF, Benezech C, Stimson RH, Wabitsch M, et al. Hypoxia-driven metabolic reprogramming of adipocytes fuels cancer cell proliferation. Front Endocrinol (Lausanne). 2022;13: 989523.
28. O'Reilly SM, Leonard MO, Kieran N, Comerford KM, Cummins E, Pouliot M, et al. Hypoxia induces epithelial amphiregulin gene expression in a CREB-dependent manner. Am J Physiol Cell Physiol. 2006;290(2):C592-600.
29. Gaens KH, Stehouwer CD, Schalkwijk CG. Advanced glycation endproducts and its receptor for advanced glycation endproducts in obesity. Curr Opin Lipidol. 2013;24(1):4–11.
30. Ramasamy R, Yan SF, Schmidt AM. The RAGE axis and endothelial dysfunction: maladaptive roles in the diabetic vasculature and beyond. Trends Cardiovasc Med. 2005;15(7):237–43.
31. Bhaskaran K, Douglas I, Forbes H, dos Santos SI, Leon DA, Smeeth L. Body-mass index and risk of 22 specific cancers: a population-based cohort study of 524 million UK adults. Lancet. 2014;384(9945):755–65.
32. Harvie M, Hooper L, Howell AH. Central obesity and breast cancer risk: a systematic review. Obes Rev. 2003;4(3):157–73.
33. Steele CB, Thomas CC, Henley SJ, Massetti GM, Galuska DA, Agurs-Collins T, et al. Vital signs: trends in incidence of cancers associated with overweight and obesity - United States, 2005–2014. MMWR Morb Mortal Wkly Rep. 2017;66(39):1052–8.
34. Wen H, Deng G, Shi X, Liu Z, Lin A, Cheng Q, et al. Body mass index, weight change, and cancer prognosis: a meta-analysis and systematic review of 73 cohort studies. ESMO Open. 2024;9(3): 102241.
35. Olsson LT, Walens A, Hamilton AM, Benefield HC, Fleming JM, Carey LA, et al. Obesity and breast cancer metastasis across genomic subtypes. Cancer Epidemiol Biomarkers Prev. 2022;31(10):1944–51.
36. Petrelli F, Cortellini A, Indini A, Tomasello G, Ghidini M, Nigro O, et al. Association of obesity with survival outcomes in patients with cancer: a systematic review and meta-analysis. JAMA Netw Open. 2021;4(3): e213520.
37. Lee B, Han HS, Yoon YS, Park Y, Kang M, Kim J. "Obesity Paradox" as a new insight from long-term survivors in pancreatic cancer patients. HPB (Oxford). 2025;27(7):922–9.
38. Lee DH, Giovannucci EL. The obesity paradox in cancer: epidemiologic insights and perspectives. Curr Nutr Rep. 2019;8(3):175–81.
39. Donini LM, Pinto A, Giusti AM, Lenzi A, Poggiogalle E. Obesity or BMI paradox? Beneath the tip of the iceberg. Front Nutr. 2020;7:53.
40. Slawinski CGV, Barriuso J, Guo H, Renehan AG. Obesity and cancer treatment outcomes: interpreting the complex evidence. Clin Oncol (R Coll Radiol). 2020;32(9):591–608.
41. O'Connell F, O'Sullivan J. Help or hindrance: the obesity paradox in cancer treatment response. Cancer Lett. 2021;522:269–80.
42. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med. 2003;348(17):1625–38.
43. Jiralerspong S, Goodwin PJ. Obesity and breast cancer prognosis: evidence, challenges, and opportunities. J Clin Oncol. 2016;34(35):4203–16.
44. Osman MA, Hennessy BT. Obesity correlation with metastases development and response to first-line metastatic chemotherapy in breast cancer. Clin Med Insights Oncol. 2015;9:105–12.
45. Bousquenaud M, Fico F, Solinas G, Ruegg C, Santamaria-Martinez A. Obesity promotes the expansion of metastasis-initiating cells in breast cancer. Breast Cancer Res. 2018;20(1):104.
46. Sparreboom A, Wolff AC, Mathijssen RH, Chatelut E, Rowinsky EK, Verweij J, et al. Evaluation of alternate size descriptors for dose calculation of anticancer drugs in the obese. J Clin Oncol. 2007;25(30):4707–13.
47. Incio J, Liu H, Suboj P, Chin SM, Chen IX, Pinter M, et al. Obesity-induced inflammation and desmoplasia promote pancreatic cancer progression and resistance to chemotherapy. Cancer Discov. 2016;6(8):852–69.
48. Bartucci M, Svensson S, Ricci-Vitiani L, Dattilo R, Biffoni M, Signore M, et al. Obesity hormone leptin induces growth and interferes with the cytotoxic effects of 5-fluorouracil in colorectal tumor stem cells. Endocr Relat Cancer. 2010;17(3):823–33.
49. Rysman E, Brusselmans K, Scheys K, Timmermans L, Derua R, Munck S, et al. De novo lipogenesis protects cancer cells from free radicals and chemotherapeutics by promoting membrane lipid saturation. Cancer Res. 2010;70(20):8117–26.
50. Kopecka J, Trouillas P, Gasparovic AC, Gazzano E, Assaraf YG, Riganti C. Phospholipids and cholesterol: inducers of cancer multidrug resistance and therapeutic targets. Drug Resist Updat. 2020;49: 100670.
51. Chen L, Wu F, Chen X, Chen Y, Deng L, Cai Q, et al. Impact of body mass index in therapeutic response for HER2 positive breast cancer treated with neoadjuvant targeted therapy: a multi-center study and meta-analysis. NPJ Breast Cancer. 2023;9(1):46.
52. Guiu B, Petit JM, Bonnetain F, Ladoire S, Guiu S, Cercueil JP, et al. Visceral fat area is an independent predictive biomarker of outcome after first-line bevacizumab-based treatment in metastatic colorectal cancer. Gut. 2010;59(3):341–7.
53. Wang Z, Aguilar EG, Luna JI, Dunai C, Khuat LT, Le CT, et al. Paradoxical effects of obesity on T cell function during tumor progression and PD-1 checkpoint blockade. Nat Med. 2019;25(1):141–51.
54. Dirix LY, Takacs I, Jerusalem G, Nikolinakos P, Arkenau HT, Forero-Torres A, et al. Avelumab, an anti-PD-L1 antibody, in patients with locally advanced or metastatic breast cancer: a phase 1b JAVELIN Solid Tumor study. Breast Cancer Res Treat. 2018;167(3):671–86.
55. Naik A, Monjazeb AM, Decock J. The obesity paradox in cancer, tumor immunology, and immunotherapy: potential therapeutic implications in triple negative breast cancer. Front Immunol. 2019;10:1940.
56. Mirsoian A, Bouchlaka MN, Sckisel GD, Chen M, Pai CC, Maverakis E, et al. Adiposity induces lethal cytokine storm after systemic administration of stimulatory immunotherapy regimens in aged mice. J Exp Med. 2014;211(12):2373–83.
57. Wei R, Liu S, Zhang S, Min L, Zhu S. Cellular and extracellular components in tumor microenvironment and their application in early diagnosis of cancers. Anal Cell Pathol (Amst). 2020;2020:6283796.

58. Kartikasari AER, Huertas CS, Mitchell A, Plebanski M. Tumor-induced inflammatory cytokines and the emerging diagnostic devices for cancer detection and prognosis. Front Oncol. 2021;11: 692142.
59. Ibrahim MM. Subcutaneous and visceral adipose tissue: structural and functional differences. Obes Rev. 2010;11(1):11–8.
60. Rosen ED, Spiegelman BM. What we talk about when we talk about fat. Cell. 2014;156(1–2):20–44.
61. Fuentes L, Roszer T, Ricote M. Inflammatory mediators and insulin resistance in obesity: role of nuclear receptor signaling in macrophages. Mediators Inflamm. 2010;2010: 219583.
62. Liu R, Nikolajczyk BS. Tissue immune cells fuel obesity-associated inflammation in adipose tissue and beyond. Front Immunol. 2019;10:1587.
63. Quail DF, Dannenberg AJ. The obese adipose tissue microenvironment in cancer development and progression. Nat Rev Endocrinol. 2019;15(3):139–54.
64. Liu SQ, Chen DY, Li B, Gao ZJ, Feng HF, Yu X, et al. Single-cell analysis of white adipose tissue reveals the tumor-promoting adipocyte subtypes. J Transl Med. 2023;21(1):470.
65. Balaban S, Shearer RF, Lee LS, van Geldermalsen M, Schreuder M, Shtein HC, et al. Adipocyte lipolysis links obesity to breast cancer growth: adipocyte-derived fatty acids drive breast cancer cell proliferation and migration. Cancer Metab. 2017;5:1.
66. Zhang L, Han L, He J, Lv J, Pan R, Lv T. A high serum-free fatty acid level is associated with cancer. J Cancer Res Clin Oncol. 2020;146(3):705–10.
67. Calder PC. Marine omega-3 fatty acids and inflammatory processes: Effects, mechanisms and clinical relevance. Biochim Biophys Acta. 2015;1851(4):469–84.
68. Lopez-Vicario C, Rius B, Alcaraz-Quiles J, Garcia-Alonso V, Lopategi A, Titos E, et al. Pro-resolving mediators produced from EPA and DHA: Overview of the pathways involved and their mechanisms in metabolic syndrome and related liver diseases. Eur J Pharmacol. 2016;785:133–43.
69. Serhan CN, Chiang N, Van Dyke TE. Resolving inflammation: dual anti-inflammatory and pro-resolution lipid mediators. Nat Rev Immunol. 2008;8(5):349–61.
70. Im DS. Omega-3 fatty acids in anti-inflammation (pro-resolution) and GPCRs. Prog Lipid Res. 2012;51(3):232–7.
71. Zou Y, Watters A, Cheng N, Perry CE, Xu K, Alicea GM, et al. Polyunsaturated fatty acids from astrocytes activate PPArgamma signaling in cancer cells to promote brain metastasis. Cancer Discov. 2019;9(12):1720–35.
72. Amine H, Benomar Y, Taouis M. Palmitic acid promotes resistin-induced insulin resistance and inflammation in SH-SY5Y human neuroblastoma. Sci Rep. 2021;11(1):5427.
73. Lefterova MI, Lazar MA. New developments in adipogenesis. Trends Endocrinol Metab. 2009;20(3):107–14.
74. Maulucci G, Cohen O, Daniel B, Sansone A, Petropoulou PI, Filou S, et al. Fatty acid-related modulations of membrane fluidity in cells: detection and implications. Free Radic Res. 2016;50(sup1):S40–50.
75. Szachowicz-Petelska B, Sulkowski S, Figaszewski ZA. Altered membrane free unsaturated fatty acid composition in human colorectal cancer tissue. Mol Cell Biochem. 2007;294(1–2):237–42.
76. Nguyen HP, An K, Ito Y, Kharbikar BN, Sheng R, Paredes B, et al. Implantation of engineered adipocytes suppresses tumor progression in cancer models. Nat Biotechnol. 2025.
77. Ruiz-Vela A, Aguilar-Gallardo C, Martinez-Arroyo AM, Soriano-Navarro M, Ruiz V, Simon C. Specific unsaturated fatty acids enforce the transdifferentiation of human cancer cells toward adipocyte-like cells. Stem Cell Rev Rep. 2011;7(4):898–909.
78. Ishay-Ronen D, Diepenbruck M, Kalathur RKR, Sugiyama N, Tiede S, Ivanek R, et al. Gain fat-lose metastasis: converting invasive breast cancer cells into adipocytes inhibits cancer metastasis. Cancer Cell. 2019;35(1):17-32 e6.
79. Ishay-Ronen D, Christofori G. Targeting cancer cell metastasis by converting cancer cells into fat. Cancer Res. 2019;79(21):5471–5.
80. Kim YJ, Yu DB, Kim M, Choi YL. Adipogenesis induces growth inhibition of dedifferentiated liposarcoma. Cancer Sci. 2019;110(8):2676–83.
81. Laurent V, Guerard A, Mazerolles C, Le Gonidec S, Toulet A, Nieto L, et al. Periprostatic adipocytes act as a driving force for prostate cancer progression in obesity. Nat Commun. 2016;7:10230.
82. Hu MB, Xu H, Zhu WH, Bai PD, Hu JM, Yang T, et al. High-fat diet-induced adipokine and cytokine alterations promote the progression of prostate cancer in vivo and in vitro. Oncol Lett. 2018;15(2):1607–15.
83. D'Esposito V, Ambrosio MR, Giuliano M, Cabaro S, Miele C, Beguinot F, et al. Mammary Adipose Tissue Control of Breast Cancer Progression: Impact of Obesity and Diabetes. Front Oncol. 2020;10:1554.
84. Bocian-Jastrzebska A, Malczewska-Herman A, Kos-Kudla B. Role of leptin and adiponectin in carcinogenesis. Cancers (Basel). 2023;15(17):4250.
85. Capuozzo M, Celotto V, Landi L, Ferrara F, Sabbatino F, Perri F, et al. Beyond body size: adiponectin as a key player in obesity-driven cancers. Nutr Cancer. 2023;75(10):1848–62.
86. Tumminia A, Vinciguerra F, Parisi M, Graziano M, Sciacca L, Baratta R, et al. Adipose tissue, obesity and adiponectin: role in endocrine cancer risk. Int J Mol Sci. 2019;20(12):2863.
87. Kim JW, Kim JH, Lee YJ. The role of adipokines in tumor progression and its association with obesity. Biomedicines. 2024;12(1):97.
88. Sanchez-Jimenez F, Perez-Perez A, de la Cruz-Merino L, Sanchez-Margalet V. Obesity and breast cancer: role of leptin. Front Oncol. 2019;9:596.
89. Louwen F, Ritter A, Kreis NN, Yuan J. Insight into the development of obesity: functional alterations of adipose-derived mesenchymal stem cells. Obes Rev. 2018;19(7):888–904.
90. Ritter A, Friemel A, Kreis NN, Hoock SC, Roth S, Kielland-Kaisen U, et al. Primary cilia are dysfunctional in obese adipose-derived mesenchymal stem cells. Stem Cell Reports. 2018;10(2):583–99.
91. Lee HY, Hong IS. Double-edged sword of mesenchymal stem cells: cancer-promoting versus therapeutic potential. Cancer Sci. 2017;108(10):1939–46.
92. Krueger TEG, Thorek DLJ, Denmeade SR, Isaacs JT, Brennen WN. Concise review: mesenchymal stem cell-based drug delivery: the good, the bad, the ugly, and the promise. Stem Cells Transl Med. 2018;7(9):651–63.
93. Miyazaki Y, Oda T, Inagaki Y, Kushige H, Saito Y, Mori N, et al. Adipose-derived mesenchymal stem cells differentiate into heterogeneous cancer-associated fibroblasts in a stroma-rich xenograft model. Sci Rep. 2021;11(1):4690.
94. Zhou S, Zhao Z, Wang Z, Xu H, Li Y, Xu K, et al. Cancer-associated fibroblasts in carcinogenesis. J Transl Med. 2025;23(1):50.
95. Talia M, Cesario E, Cirillo F, Scordamaglia D, Di Dio M, Zicarelli A, et al. Cancer-associated fibroblasts (CAFs) gene signatures predict outcomes in breast and prostate tumor patients. J Transl Med. 2024;22(1):597.
96. Ritter A, Kreis NN, Hoock SC, Solbach C, Louwen F, Yuan J. Adipose tissue-derived mesenchymal stromal/stem cells, obesity and the tumor microenvironment of breast cancer. Cancers (Basel). 2022;14(16):3908.
97. Khan T, Muise ES, Iyengar P, Wang ZV, Chandalia M, Abate N, et al. Metabolic dysregulation and adipose tissue fibrosis: role of collagen VI. Mol Cell Biol. 2009;29(6):1575–91.
98. Lee YS. The mechanism for adipose endotrophin production. Diabetes. 2022;71(8):1617–9.
99. Harris BHL, Macaulay VM, Harris DA, Klenerman P, Karpe F, Lord SR, et al. Obesity: a perfect storm for carcinogenesis. Cancer Metastasis Rev. 2022;41(3):491–515.
100. Roumiguie M, Esteve D, Manceau C, Toulet A, Gilleron J, Belles C, et al. Periprostatic adipose tissue displays a chronic hypoxic state that limits its expandability. Am J Pathol. 2022;192(6):926–42.
101. AbdelMassih A, Yacoub E, Husseiny RJ, Kamel A, Hozaien R, El Shershaby M, et al. Hypoxia-inducible factor (HIF): the link between obesity and COVID-19. Obes Med. 2021;22: 100317.
102. Lee SH, Golinska M, Griffiths JR. HIF-1-independent mechanisms regulating metabolic adaptation in hypoxic cancer cells. Cells. 2021;10(9):2371.
103. Magar AG, Morya VK, Kwak MK, Oh JU, Noh KC. A molecular perspective on HIF-1alpha and angiogenic stimulator networks and their role in solid tumors: an update. Int J Mol Sci. 2024;25(6):3313.
104. Hu K, Babapoor-Farrokhran S, Rodrigues M, Deshpande M, Puchner B, Kashiwabuchi F, et al. Hypoxia-inducible factor 1 upregulation of both VEGF and ANGPTL4 is required to promote the angiogenic phenotype in uveal melanoma. Oncotarget. 2016;7(7):7816–28.
105. Kim DY, Park JA, Kim Y, Noh M, Park S, Lie E, et al. SALM4 regulates angiogenic functions in endothelial cells through VEGFR2 phosphorylation at Tyr1175. FASEB J. 2019;33(9):9842–57.
106. Michalczyk K, Niklas N, Rychlicka M, Cymbaluk-Ploska A. The influence of biologically active substances secreted by the adipose tissue on endometrial cancer. Diagnostics (Basel). 2021;11(3):494.
107. Simeon J, Thrush J, Bailey TA. Angiopoietin-like protein 4 is a chromatin-bound protein that enhances mammosphere formation in vitro and experimental triple-negative breast cancer brain and liver metastases in vivo. J Carcinog. 2021;20:8.
108. Blucher C, Iberl S, Schwagarus N, Muller S, Liebisch G, Horing M, et al. Secreted factors from adipose tissue reprogram tumor lipid metabolism and induce motility by modulating PPARalpha/ANGPTL4 and FAK. Mol Cancer Res. 2020;18(12):1849–62.

109. Kahn CR, Wang G, Lee KY. Altered adipose tissue and adipocyte function in the pathogenesis of metabolic syndrome. J Clin Invest. 2019;129(10):3990–4000.
110. Simpson ER, Clyne C, Rubin G, Boon WC, Robertson K, Britt K, et al. Aromatase–a brief overview. Annu Rev Physiol. 2002;64:93–127.
111. Barone I, Caruso A, Gelsomino L, Giordano C, Bonofiglio D, Catalano S, et al. Obesity and endocrine therapy resistance in breast cancer: Mechanistic insights and perspectives. Obes Rev. 2022;23(2): e13358.
112. Simpson ER, Brown KA. Minireview: Obesity and breast cancer: a tale of inflammation and dysregulated metabolism. Mol Endocrinol. 2013;27(5):715–25.
113. Lappano R, Recchia AG, De Francesco EM, Angelone T, Cerra MC, Picard D, et al. The cholesterol metabolite 25-hydroxycholesterol activates estrogen receptor alpha-mediated signaling in cancer cells and in cardiomyocytes. PLoS ONE. 2011;6(1): e16631.
114. Ghanbari F, Mader S, Philip A. Cholesterol as an endogenous ligand of ERRalpha promotes ERRalpha-mediated cellular proliferation and metabolic target gene expression in breast cancer cells. Cells. 2020;9(8):1765.
115. Morrione A, Belfiore A. Obesity, diabetes, and cancer: the role of the insulin/IGF axis; mechanisms and clinical implications. Biomolecules. 2022;12(5):612.
116. Vigneri R, Goldfine ID, Frittitta L. Insulin, insulin receptors, and cancer. J Endocrinol Invest. 2016;39(12):1365–76.
117. Cirillo F, Pellegrino M, Talia M, Perrotta ID, Rigiracciolo DC, Spinelli A, et al. Estrogen receptor variant ERalpha46 and insulin receptor drive in primary breast cancer cells growth effects and interleukin 11 induction prompting the motility of cancer-associated fibroblasts. Clin Transl Med. 2021;11(11): e516.
118. Vella V, De Francesco EM, Lappano R, Muoio MG, Manzella L, Maggiolini M, et al. Microenvironmental determinants of breast cancer metastasis: focus on the crucial interplay between estrogen and insulin/insulin-like growth factor signaling. Front Cell Dev Biol. 2020;8: 608412.
119. De Marco P, Cirillo F, Vivacqua A, Malaguarnera R, Belfiore A, Maggiolini M. Novel aspects concerning the functional cross-talk between the insulin/IGF-I system and estrogen signaling in cancer cells. Front Endocrinol (Lausanne). 2015;6:30.
120. De Marco P, Romeo E, Vivacqua A, Malaguarnera R, Abonante S, Romeo F, et al. GPER1 is regulated by insulin in cancer cells and cancer-associated fibroblasts. Endocr Relat Cancer. 2014;21(5):739–53.
121. Gallagher EJ, LeRoith D. Hyperinsulinaemia in cancer. Nat Rev Cancer. 2020;20(11):629–44.
122. Pandini G, Medico E, Conte E, Sciacca L, Vigneri R, Belfiore A. Differential gene expression induced by insulin and insulin-like growth factor-II through the insulin receptor isoform A. J Biol Chem. 2003;278(43):42178–89.
123. Sacco A, Morcavallo A, Pandini G, Vigneri R, Belfiore A. Differential signaling activation by insulin and insulin-like growth factors I and II upon binding to insulin receptor isoform A. Endocrinology. 2009;150(8):3594–602.
124. Szukiewicz D. Molecular mechanisms for the vicious cycle between insulin resistance and the inflammatory response in obesity. Int J Mol Sci. 2023;24(12):9818.
125. Scordamaglia D, Talia M, Cirillo F, Zicarelli A, Mondino AA, De Rosis S, et al. Interleukin-1beta mediates a tumor-supporting environment prompted by IGF1 in triple-negative breast cancer (TNBC). J Transl Med. 2025;23(1):660.
126. Scordamaglia D, Cirillo F, Talia M, Santolla MF, Rigiracciolo DC, Muglia L, et al. Metformin counteracts stimulatory effects induced by insulin in primary breast cancer cells. J Transl Med. 2022;20(1):263.
127. Orliaguet L, Ejlalmanesh T, Alzaid F. Metabolic and molecular mechanisms of macrophage polarisation and adipose tissue insulin resistance. Int J Mol Sci. 2020;21(16):5731.
128. Kalupahana NS, Moustaid-Moussa N, Claycombe KJ. Immunity as a link between obesity and insulin resistance. Mol Aspects Med. 2012;33(1):26–34.
129. Uemura H, Katsuura-Kamano S, Yamaguchi M, Bahari T, Ishizu M, Fujioka M, et al. Relationships of serum high-sensitivity C-reactive protein and body size with insulin resistance in a Japanese cohort. PLoS ONE. 2017;12(6): e0178672.
130. Dandona P, Weinstock R, Thusu K, Abdel-Rahman E, Aljada A, Wadden T. Tumor necrosis factor-alpha in sera of obese patients: fall with weight loss. J Clin Endocrinol Metab. 1998;83(8):2907–10.
131. Werida RH, El-Gharbawy NM, Mostafa TM. Circulating IL-6, clusterin and irisin in obese subjects with different grades of obesity: association with insulin resistance and sexual dimorphism. Arch Endocrinol Metab. 2021;65(2):126–36.
132. Chen J. Multiple signal pathways in obesity-associated cancer. Obes Rev. 2011;12(12):1063–70.
133. Ueki K, Kondo T, Kahn CR. Suppressor of cytokine signaling 1 (SOCS-1) and SOCS-3 cause insulin resistance through inhibition of tyrosine phosphorylation of insulin receptor substrate proteins by discrete mechanisms. Mol Cell Biol. 2004;24(12):5434–46.
134. Iacobini C, Pugliese G, Blasetti Fantauzzi C, Federici M, Menini S. Metabolically healthy versus metabolically unhealthy obesity. Metabolism. 2019;92:51–60.
135. Wildman RP, Muntner P, Reynolds K, McGinn AP, Rajpathak S, Wylie-Rosett J, et al. The obese without cardiometabolic risk factor clustering and the normal weight with cardiometabolic risk factor clustering: prevalence and correlates of 2 phenotypes among the US population (NHANES 1999–2004). Arch Intern Med. 2008;168(15):1617–24.
136. Barbarroja N, Lopez-Pedrera R, Mayas MD, Garcia-Fuentes E, Garrido-Sanchez L, Macias-Gonzalez M, et al. The obese healthy paradox: is inflammation the answer? Biochem J. 2010;430(1):141–9.
137. Feng Z, Zhu L, Wu J. RAGE signalling in obesity and diabetes: focus on the adipose tissue macrophage. Adipocyte. 2020;9(1):563–6.
138. Zeng C, Li Y, Ma J, Niu L, Tay FR. Clinical/translational aspects of advanced glycation end-products. Trends Endocrinol Metab. 2019;30(12):959–73.
139. Hudson BI, Lippman ME. Targeting RAGE signaling in inflammatory disease. Annu Rev Med. 2018;69:349–64.
140. Feng Z, Du Z, Shu X, Zhu L, Wu J, Gao Q, et al. Role of RAGE in obesity-induced adipose tissue inflammation and insulin resistance. Cell Death Discov. 2021;7(1):305.
141. Song F, Hurtado del Pozo C, Rosario R, Zou YS, Ananthakrishnan R, Xu X, et al. RAGE regulates the metabolic and inflammatory response to high-fat feeding in mice. Diabetes. 2014;63(6):1948–65.
142. Vella V, Lappano R, Bonavita E, Maggiolini M, Clarke RB, Belfiore A, et al. Insulin/IGF axis and the receptor for advanced glycation end products: role in meta-inflammation and potential in cancer therapy. Endocr Rev. 2023;44(4):693–723.
143. Palanissami G, Paul SFD. RAGE and its ligands: molecular interplay between glycation, inflammation, and hallmarks of cancer-a review. Horm Cancer. 2018;9(5):295–325.
144. Muoio MG, Talia M, Lappano R, Sims AH, Vella V, Cirillo F, et al. Activation of the S100A7/RAGE pathway by IGF-1 contributes to angiogenesis in breast cancer. Cancers (Basel). 2021;13(4):621.
145. Santolla MF, Talia M, Cirillo F, Scordamaglia D, De Rosis S, Spinelli A, et al. The AGEs/RAGE transduction signaling prompts IL-8/CXCR1/2-mediated interaction between cancer-associated fibroblasts (CAFs) and breast cancer cells. Cells. 2022;11(15):2402.
146. Talia M, Cirillo F, Spinelli A, Zicarelli A, Scordamaglia D, Muglia L, et al. The ephrin tyrosine kinase a3 (EphA3) is a novel mediator of RAGE-prompted motility of breast cancer cells. J Exp Clin Cancer Res. 2023;42(1):164.
147. Rigiracciolo DC, Nohata N, Lappano R, Cirillo F, Talia M, Adame-Garcia SR, et al. Focal Adhesion Kinase (FAK)-Hippo/YAP transduction signaling mediates the stimulatory effects exerted by S100A8/A9-RAGE system in triple-negative breast cancer (TNBC). J Exp Clin Cancer Res. 2022;41(1):193.
148. Sparvero LJ, Asafu-Adjei D, Kang R, Tang D, Amin N, Im J, et al. RAGE (receptor for advanced glycation endproducts), RAGE ligands, and their role in cancer and inflammation. J Transl Med. 2009;7:17.
149. Muoio MG, Pellegrino M, Rapicavoli V, Talia M, Scavo G, Sergi V, et al. RAGE inhibition blunts insulin-induced oncogenic signals in breast cancer. Breast Cancer Res. 2023;25(1):84.
150. Vick LV, Canter RJ, Monjazeb AM, Murphy WJ. Multifaceted effects of obesity on cancer immunotherapies: Bridging preclinical models and clinical data. Semin Cancer Biol. 2023;95:88–102.
151. Kawai T, Autieri MV, Scalia R. Adipose tissue inflammation and metabolic dysfunction in obesity. Am J Physiol Cell Physiol. 2021;320(3):C375–91.
152. Heusinkveld M, van der Burg SH. Identification and manipulation of tumor associated macrophages in human cancers. J Transl Med. 2011;9:216.
153. Taylor EB. The complex role of adipokines in obesity, inflammation, and autoimmunity. Clin Sci (Lond). 2021;135(6):731–52.
154. Yao J, Wu D, Qiu Y. Adipose tissue macrophage in obesity-associated metabolic diseases. Front Immunol. 2022;13: 977485.
155. Kulkarni A, Bowers LW. The role of immune dysfunction in obesity-associated cancer risk, progression, and metastasis. Cell Mol Life Sci. 2021;78(7):3423–42.
156. Li Y, Zhang C, Jiang A, Lin A, Liu Z, Cheng X, et al. Potential anti-tumor effects of regulatory T cells in the tumor microenvironment: a review. J Transl Med. 2024;22(1):293.
157. Heintzman DR, Fisher EL, Rathmell JC. Microenvironmental influences on T cell immunity in cancer and inflammation. Cell Mol Immunol. 2022;19(3):316–26.

158. Zhang X, Gao L, Meng H, Zhang A, Liang Y, Lu J. Obesity alters immunopathology in cancers and inflammatory diseases. Obes Rev. 2023;24(12): e13638.
159. Assumpcao JAF, Pasquarelli-do-Nascimento G, Duarte MSV, Bonamino MH, Magalhaes KG. The ambiguous role of obesity in oncology by promoting cancer but boosting antitumor immunotherapy. J Biomed Sci. 2022;29(1):12.
160. Lashinger LM, Rossi EL, Hursting SD. Obesity and resistance to cancer chemotherapy: interacting roles of inflammation and metabolic dysregulation. Clin Pharmacol Ther. 2014;96(4):458–63.
161. Farag KI, Makkouk A, Norian LA. Re-evaluating the effects of obesity on cancer immunotherapy outcomes in renal cancer: what do we really know? Front Immunol. 2021;12: 668494.
162. Gibson JT, Orlandella RM, Turbitt WJ, Behring M, Manne U, Sorge RE, et al. Obesity-associated myeloid-derived suppressor cells promote apoptosis of tumor-infiltrating CD8 T Cells and immunotherapy resistance in breast cancer. Front Immunol. 2020;11: 590794.
163. Piening A, Ebert E, Gottlieb C, Khojandi N, Kuehm LM, Hoft SG, et al. Obesity-related T cell dysfunction impairs immunosurveillance and increases cancer risk. Nat Commun. 2024;15(1):2835.
164. An Y, Wu Z, Wang N, Yang Z, Li Y, Xu B, et al. Association between body mass index and survival outcomes for cancer patients treated with immune checkpoint inhibitors: a systematic review and meta-analysis. J Transl Med. 2020;18(1):235.
165. Savva C, Copson E, Johnson PWM, Cutress RI, Beers SA. Obesity is associated with immunometabolic changes in adipose tissue that may drive treatment resistance in breast cancer: immune-metabolic reprogramming and novel therapeutic strategies. Cancers (Basel). 2023;15(9):2440.
166. Lauby-Secretan B, Scoccianti C, Loomis D, Grosse Y, Bianchini F, Straif K, et al. Body fatness and cancer-viewpoint of the IARC working group. N Engl J Med. 2016;375(8):794–8.
167. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209–49.
168. Liu YM, Wu TH, Chiu YH, Wang H, Li TL, Hsia S, et al. Positive effects of preventive nutrition supplement on anticancer radiotherapy in lung cancer bearing mice. Cancers (Basel). 2020;12(9):2445.
169. Rishmawi S, Haddad F, Dokmak G, Karaman R. A comprehensive review on the anti-cancer effects of oleuropein. Life (Basel). 2022;12(8):1140.
170. Fang J, Zhou Q, Shi XL, Jiang BH. Luteolin inhibits insulin-like growth factor 1 receptor signaling in prostate cancer cells. Carcinogenesis. 2007;28(3):713–23.
171. Ozkan G, Gunal-Koroglu D, Karadag A, Capanoglu E, Cardoso SM, Al-Omari B, et al. A mechanistic updated overview on lycopene as potential anticancer agent. Biomed Pharmacother. 2023;161: 114428.
172. Brum I, Mafra D, Moreira LSG, Teixeira KTR, Stockler-Pinto MB, Cardozo L, et al. Consumption of oils and anthocyanins may positively modulate PPAR-gamma expression in chronic noncommunicable diseases: A systematic review. Nutr Res. 2022;105:66–76.
173. Kowalczyk T, Muskala M, Merecz-Sadowska A, Sikora J, Picot L, Sitarek P. Anti-inflammatory and anticancer effects of anthocyanins in in vitro and in vivo studies. Antioxidants (Basel). 2024;13(9):1143.
174. Vernieri C, Nichetti F, Raimondi A, Pusceddu S, Platania M, Berrino F, et al. Diet and supplements in cancer prevention and treatment: Clinical evidences and future perspectives. Crit Rev Oncol Hematol. 2018;123:57–73.
175. Kleinert M, Clemmensen C, Hofmann SM, Moore MC, Renner S, Woods SC, et al. Animal models of obesity and diabetes mellitus. Nat Rev Endocrinol. 2018;14(3):140–62.
176. Giles ED, Jackman MR, MacLean PS. Modeling diet-induced obesity with obesity-prone rats: implications for studies in females. Front Nutr. 2016;3:50.
177. Nunez NP, Perkins SN, Smith NC, Berrigan D, Berendes DM, Varticovski L, et al. Obesity accelerates mouse mammary tumor growth in the absence of ovarian hormones. Nutr Cancer. 2008;60(4):534–41.
178. Hu W, Lazar MA. Modelling metabolic diseases and drug response using stem cells and organoids. Nat Rev Endocrinol. 2022;18(12):744–59.
179. Sontheimer-Phelps A, Hassell BA, Ingber DE. Modelling cancer in microfluidic human organs-on-chips. Nat Rev Cancer. 2019;19(2):65–81.
180. Biton M, Haber AL, Rogel N, Burgin G, Beyaz S, Schnell A, et al. T helper cell cytokines modulate intestinal stem cell renewal and differentiation. Cell. 2018;175(5):1307-20 e22.
181. Rogal J, Roosz J, Teufel C, Cipriano M, Xu R, Eisler W, et al. Autologous human immunocompetent white adipose tissue-on-chip. Adv Sci (Weinh). 2022;9(18): e2104451.

Publisher's note