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The impact of the tumor microenvironment in the dual burden of obesity-cancer link

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ABSTRACT

Obesity induces systemic perturbations of tissue homeostasis, leading to dyslipidemia, insulin resistance and chronic state of inflammation. Evidence from clinical and preclinical studies links excess of adiposity with increased cancer incidence and suggests that chronic inflammation may contribute to increased cancer risk in obese patients. Over the last decades of obesity research, multifaced and complicated effects of abnormal or excessive expansion of Adipose Tissue have been uncovered. In particular, it is widely described how obesity can exacerbate the tumorigenesis for instance by fueling soluble signals and adipokines and by enhancing tissue inflammation and altering the hormonal balance. Less is known about the paracrine effects of the cancer-associated adipocytes on the tumor cells and still poorly explored is the reciprocal communication between cancer cells and the adipose component of the tumor microenvironment (TME). In this review, we will address the mechanisms by which the peritumoral Adipose Tissue can influence the dynamics of tumoral cells. We will discuss how obesity-induced changes in the tumor microenvironment may enhance tumor growth and aggressive characteristics leading to increased invasiveness and metastatic progression of cancer that leads to a worsen cancer survival in obese subjects. We conclude that targeting the peritumoral adipose component of the TME would be a therapeutic option to prevent cancer development.

1. Introduction

1.1. The tumour microenvironment and cancer formation and progression

Cancer is a very complex system of many non-cancerous cells in which genetic alterations are necessary, but not sufficient for cancer to develop. In the early stages of tumour growth, a dynamic and reciprocal relationship is established between cancer cells and components of the tumour microenvironment (TME) to support cancer cell survival, local invasion and metastasis [1]. The TME is a highly dynamic network of cell types, containing cancer cells that are surrounded by diverse non-malignant cell types, all anchored in an altered and vascularized extracellular matrix. In detail, the TME contains a wide variety of immune cells and stromal cells, such as cancer-associated fibroblasts (CAFs), endothelial cells (ECs), cancer-associated adipocytes (CAAs) and other cell types. The TME uses a pro-angiogenic program to counter a hypoxic and acidic microenvironment by balancing oxygen and nutrients and removing metabolic waste [2]. Thus, the TME and its secreted molecules are critical for cancer genesis and development and also influence tumour cell survival and are involved in the resistance to anti-tumour therapy [3] (Fig. 1). A high degree of interest has been focused on cancer-associated fibroblasts (CAFs) and tumour-associated macrophages, both of which are tumour-promoting cell types [4,5]. CAFs are key components of the TME, they cross-talk with cancer cells and the dynamic interaction between CAFs and the tumor bulk intensifies the release of extracellular components such as growth factors, cytokines and extracellular matrix. For example, secretion of TGF-β, a growth factor that promotes epithelial-mesenchymal transition (EMT) and angiogenesis [6,7], is one mechanism by which CAFs control metastasis. In turn, EMT is a pivotal step in metastasis in which epithelial cells lose cell polarity and adhesion and acquire a migratory and invasive phenotype [8,9]. Moreover, CAFs exhibit altered metabolic pathways, including enhanced glycolysis and lactate production, which can fuel adjacent cancer cells through the "reverse Warburg effect" [10,11]. Furthermore, CAFs have been shown to influence the metabolic state of cancer cells, facilitating their adaptation to hypoxic conditions

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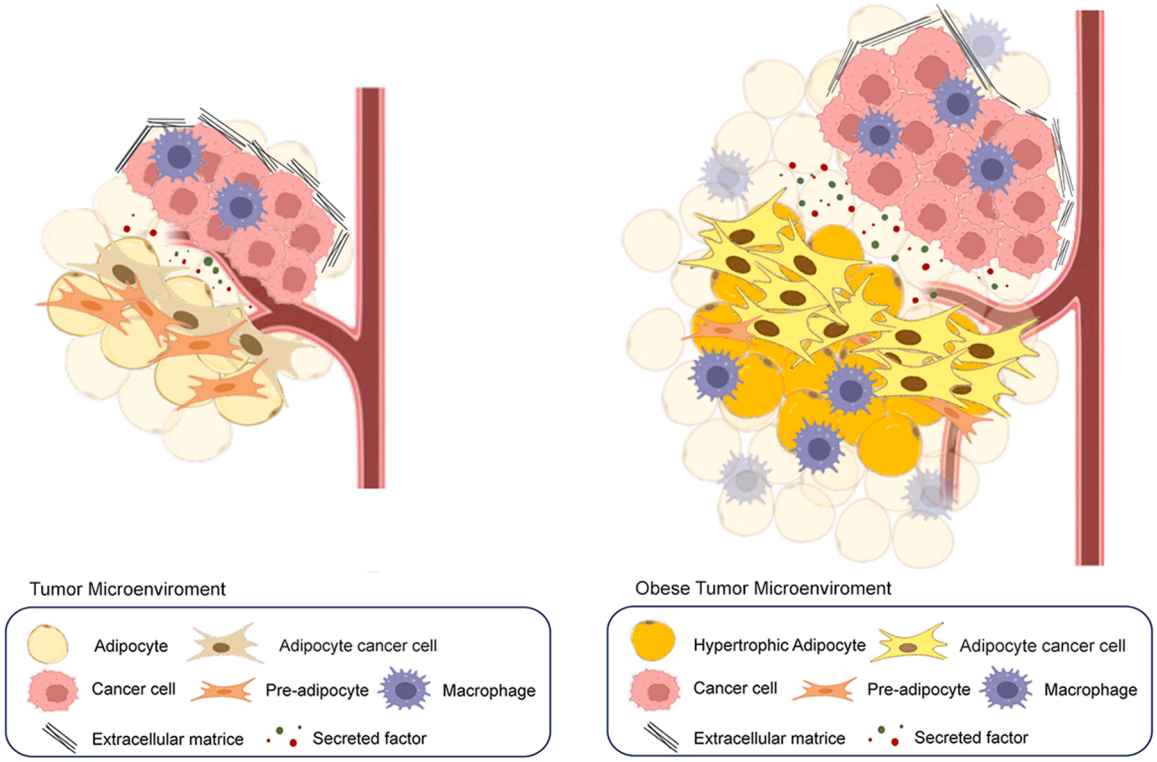

Fig. 1. The tumour microenvironment in non-obese versus obese adipose tissue. The interaction between adipocytes and cancer cells within the tumor microenvironment varies significantly between non-obese and obese conditions, influencing tumor progression, immune response, and the overall pathophysiology of cancer. In obesity, increased adiposity and altered metabolic states contribute to a pro-inflammatory and pro-tumorigenic environment, potentially enhancing cancer cell survival, proliferation, and metastasis compared to non-obese conditions. This dynamic interplay highlights the critical role of adipocytes in modulating cancer behavior and underscores the importance of understanding obesity-related tumor biology for developing targeted therapeutic strategies.

and enhancing their invasive potential [11–13].

Recent studies suggest that CAFs consist of multiple subtypes that change during tumour progression and are spatially regulated [14]. The localization of different CAF subtypes can influence their interactions with tumor cells and immune components, and it was found that CAF subtypes are associated with malignancy and play different functional roles. Among the CAF subtypes exert a crucial role matrix CAFs (mCAFs) and immunomodulatory CAFs (iCAFs); mCAFs sythesize extracellular matrix and may limit T-cell invasion in low-grade tumours by enveloping tumour nests while iCAFs express high levels of cytokines and chemokines to help recruit and activate immune cells [15]. For instance, CAFs located in the peritumoral stroma may have different effects on tumor cell behavior compared to those situated within the tumor core [16,17]. This spatial heterogeneity is supported by advanced imaging techniques and single-cell RNA sequencing, which have revealed distinct gene expression profiles associated with specific CAF locations [18,19]. Understanding these spatial dynamics is vital for developing targeted therapies that can disrupt the supportive roles of CAFs in tumor progression.

1.2. Cancer-associated adipocytes (CAAs) and tumorigenesis

In cancer, Adipose Tissue (AT) invasion reflects tumour aggressiveness and is associated with poor prognosis [20]. The Cancer Associated Adipocytes (CAAs) represent the major population of adipose cells in the TME. The origin of CAAs in tumours remains controversial and may vary according to tumour stage and cancer type. CAAs derive from both, non-tumoral adipocytes invading the tumor (especially in overweight and in obese conditions) and fibroblast-derived adipocytes that in a mutual dialogue with tumoral cells undergo oncogenic transformation [21].

CAAs undergo significant morphological and functional changes during cancer progression. In the presence of cancer cells, CAAs undergo delipidation and acquire a fibroblast-like phenotype. This phenotypic change is accompanied by loss of expression of adipocyte terminal differentiation markers, such as adiponectin and leptin, and increased secretion of pro-inflammatory cytokines, such as IL-6 and PAI-1 [22], contributing to cancer cachexia [23]. CAA delipidation and the associated increased secretion of inflammatory cytokines and proteases promotes a shift in tumour cell phenotype towards increased angiogenesis, invasiveness and progression [23].

Thus, the CAAs-cancer cell cross-talk leads to phenotypical and functional changes in both cell types, further enhancing the adhesion, migration, and invasion of tumor cells. This dedifferentiation or "activation" of adipocytes is driven by tumor-derived factors [24]. CAAs can provide energy substrates, such as lactate and free fatty acids, to fuel the increased metabolic demands of cancer cells, a phenomenon known as the "cancer-AT metabolic symbiosis" [25,26]. This metabolic cooperation between CAAs and cancer cells further enhances tumor progression. As a result, lipolysis begins and adipocytes release more free fatty acids (FFAs), which is not compatible with the lipid homeostasis of the whole organism and leads to subsequent immune changes [27]. Adipocytes around tumour cells provide a readily accessible reservoir of lipids and are likely to reflect the high energy needs of cancer cells. Cancer cells use free fatty acids as fuel. They also reprogram adipocytes into CAAs to support tumour growth. Indeed, CAAs are responsible mainly for metabolic storage. Lipids are deposited here as triacylglycerols (TAGs) and released in the form of FFAs when needed. Although the cause of the increased number of fibroblast-like cells in CAAs is unclear, the adipocyte-rich microenvironment plays an important role in a subset of tumours; indeed, adipocyte-tumour cell cross-talk is an important process within the microenvironment that can promote aggressive tumour behavior. Moreover, the cross-talk between cancer cells and the neighboring AT is bidirectional. Therefore, adipocytes not only affect cancer

cells, but also undergo changes that are regulated by cancer cells [28]. However, the complex relationship between peritumoral AT and cancer cells is still incompletely understood. Therefore, understanding the cross-talk between CAAs and tumour cells and how obesity exacerbates the capacity of CAAs to promote tumorigenesis is essential for the prevention of tumour progression.

1.3. Leptin as a pro-tumorigenic adipokine

In addition to its role in energy storage, AT also plays an important endocrine role through the release of growth factors and adipokines that contribute to the pathogenesis of obesity. In particular, visceral adiposity is an important determinant of obesity-related pathologies [29,30]. Indeed, numerous scientific papers published over the last decade have highlighted the immunological role of adipocytes and their role in inflammatory responses through the secretion of adipokines. Typically, AT produces anti-inflammatory mediators, but with increasing cell hypertrophy, AT produces a range of pro-inflammatory cytokines and hormones, such as tumour necrosis factor-α (TNF-α), interleukin-6 (IL-6), plasminogen activator inhibitor-1 (PAI-1), transforming growth factor-β (TGF-β), leptin, adiponectin, resistin and monocyte chemoattractant protein-1 (MCP-1) [31]. Compared to subcutaneous adipose tissue (SAT), visceral adipose tissue (VAT) has a higher rate of lipolysis, macrophage infiltration and secretion of IL-6, MCP-1 and other inflammatory markers [32]. Among adipokines, leptin is a key hormone produced by adipocytes that supports tumour progression directly by affecting cancer cell proliferation and indirectly by activating macrophages. Interestingly, leptin levels increase dramatically in obesity and this adipokine is thought to play a key role at the interface between obesity and cancer. Individuals with obesity exhibit high levels of circulating leptin compared with normal-weight individuals, and these levels are strongly correlated with adiposity [33]. High leptin levels are also correlated with a high cancer grade, advanced tumor stage and invasive cancer subtypes, such as in Breast Cancer and Colorectal Cancer [34]. Normally, leptin, through binding to its receptor, is known to regulate several physiological processes [35–37], including energy metabolism, appetite control and food intake, immunity and reproductive processes, but several studies have found that circulating leptin levels and leptin receptors are overexpressed in several types of cancer, resulting in a poor prognostic value. Downstream effects of leptin signal through activation of specific pathways in cancer cells, such as JAK/STAT 3 and PI3K/Akt pathways, may promote cancer development [38,39]. Leptin plays a variety of functions in carcinogenesis, exerting proliferative activity in a variety of cancer cell types, including breast [40], prostate [41] and ovarian [42] cancer cells, but the tumourigenic effect of leptin also results from suppression of the apoptotic process; indeed, leptin upregulates the expression of anti-apoptotic genes such as Bcl-xl and Bcl-2 [43]. In addition, several studies have shown that leptin increases the expression of metalloproteinases that play a primary role in the degradation of the extracellular matrix, thereby facilitating the migration and spread of cancer cells. Given the substantial evidence that leptin promotes cell invasion and migration in many types of cancer cells, it may be important to consider novel therapeutic strategies to interfere with its actions and thereby inhibit the development and progression of obesity-related cancers.

2. The protumorigenic role of the caas in the renal cancer carcinoma

CAAs play a crucial role in different types of cancer, as the renal cancer (RCC). For instance, the presence of cancer-associated adipocytes in clear cell renal cell carcinoma (ccRCC) has been shown to enhance tumor aggressiveness and contribute to resistance to common therapeutic agents used in renal cancer treatment [44]. This suggests that the microenvironment shaped by AT can significantly impact the efficacy of cancer therapies. Moreover, the browning of perirenal AT has been linked to the expression of EMT markers in renal cells, indicating a potential mechanism by which AT may exacerbate tumor progression [45]. The transition of white AT into a more metabolically active brown-like state appears to promote a pro-tumorigenic environment, further complicating the treatment landscape for renal cancer [45].

The inflammatory state induced by CAAs is a critical factor in renal cancer progression. AT, particularly in the context of obesity, is characterized by an increased infiltration of immune cells, including macrophages and neutrophils, which secrete pro-inflammatory cytokines such as TNF-α and IL-6. These cytokines have been implicated in promoting tumor growth and metastasis [46,47]. The interaction between adipocytes and macrophages within the tumor microenvironment can lead to a chronic inflammatory state that supports cancer cell survival and proliferation [47]. Additionally, the metabolic dysregulation associated with obesity, characterized by insulin resistance and increased oxidative stress, has been shown to exacerbate kidney damage and promote the development of renal cancer [48]. The accumulation of visceral AT, particularly around the kidneys, is associated with adverse renal outcomes, including chronic kidney disease (CKD) [49]. Additionally, obesity plays a crucial role in tumor promotion by enhancing stromal remodeling through the upregulation of the metalloproteinase ADAM12 in the RCC [28]. Moreover, the expression of CYP1B1, a Cytochrome P450 enzyme, involved in the oxidative metabolism, in fat metabolism and energy homeostasis, is enhanced in obesity, thus elevating the propension of RCC toward malignancy [28]. These observations underscore the importance of targeting AT as a potential therapeutic strategy in renal cancer. Recent studies have highlighted the metabolic reprogramming that occurs in CAAs, which can further influence renal cancer progression. CAAs exhibit altered lipid metabolism and energy expenditure, contributing to a hypermetabolic state that supports tumor growth [50]. The secretion of extracellular vesicles (EVs) from adipocytes has also been identified as a mechanism of intercellular communication that can support tumor progression by transferring oncogenic signals to cancer cells [51].

The dysregulation of adipokines such as adiponectin and leptin in the context of obesity has been shown to correlate with poor prognosis in renal cancer patients. Low levels of adiponectin, an anti-inflammatory adipokine, are associated with increased tumor invasiveness, while elevated leptin levels can promote cell proliferation and survival [52]. This suggests that restoring the balance of adipokines may represent a viable therapeutic approach to mitigate the adverse effects of CAAs on renal cancer.

The complex interactions between CAAs and renal cancer cells present both challenges and opportunities for therapeutic intervention. Understanding the role of the tumor microenvironment in renal cancer can inform the development of targeted therapies aimed at disrupting the pro-tumorigenic effects of AT. For instance, strategies that target the inflammatory pathways activated by CAAs may enhance the efficacy of existing treatments and improve patient outcomes [53]. Furthermore, the potential for utilizing AT-derived stem cells in regenerative medicine and cancer therapy is an emerging area of research. The unique properties of perirenal AT, including its high content of brown adipocytes, may offer novel avenues for therapeutic development [54]. By harnessing the regenerative potential of AT, it may be possible to counteract the detrimental effects of CAAs on renal cancer progression.

3. Breast cancer and the mammary adipose tissue

The relationship between mammary AT (MAT) and breast cancer has garnered significant attention in recent years, particularly due to the increasing prevalence of obesity and its association with cancer risk.

Mammary AT constitutes a substantial portion of the breast, comprising approximately 90 % of its volume [55]. This tissue is not merely a passive storage depot for lipids; rather, it plays an active role in regulating various physiological processes, including hormone

metabolism and immune responses. Adipocytes in the mammary gland secrete a variety of bioactive molecules such as adipokines, which can influence both local and systemic metabolic processes [56,57]. For instance, leptin has been implicated in promoting breast cancer cell proliferation and survival, particularly in the context of obesity [58,59]. Elevated levels of leptin in obese patients may contribute to a pro-tumorigenic environment by enhancing angiogenesis and inflammation within the mammary tissue [60].

Obesity is associated with chronic low-grade inflammation, which can alter the composition of the mammary AT microenvironment. Studies have shown that obesity leads to an increase in macrophage infiltration and a shift towards a pro-inflammatory phenotype within the mammary fat pad [61,62]. This inflammatory milieu is characterized by elevated levels of cytokines such as TNF-alpha and IL-6, which have been shown to promote breast cancer progression [60,61]. Furthermore, the fibrotic remodeling of AT in obese individuals can create a dense and rigid microenvironment that may facilitate tumor growth and metastasis [63,64]. The interplay between obesity-induced inflammation and the fibrotic changes in mammary AT is critical for understanding how these factors contribute to breast cancer risk.

The hormonal environment within the mammary gland is another crucial factor influencing the relationship between AT and breast cancer. AT is a significant source of estrogen due to the aromatization of androgens, particularly in postmenopausal women. Elevated estrogen levels can stimulate the proliferation of estrogen receptor-positive breast cancer cells, thereby increasing the risk of tumor development [60]. Moreover, the interaction between AT and estrogen signaling pathways can further exacerbate the risk of breast cancer in obese individuals [60,65]. Furthermore, thyroid hormone (TH) is increasingly recognized for its role in cancer progression [66]. Nappi et al. demonstrated that TH activation in the MCF7 cell line enhances tumor growth and invasiveness by inducing phenotypic and genotypic changes in Mammary AT-derived Mesenchymal Stromal/Stem Cells via a paracrine effect [67].

The extracellular matrix (ECM) within the mammary gland also plays a pivotal role in the interaction between AT and breast cancer cells. The ECM provides structural support and biochemical signals that influence cell behavior. In the context of obesity, alterations in ECM composition can lead to increased stiffness and altered signaling pathways that promote tumorigenesis [68]. For example, increased collagen deposition in the mammary stroma has been associated with enhanced tumor cell invasion and metastasis [61,62]. Additionally, the expression of ECM proteins can be modulated by adipokines, further complicating the relationship between AT and cancer progression [63]. The interplay between mammary AT and systemic factors, such as insulin and growth factors, is also critical in understanding breast cancer risk. Huang et al. highlight the role of insulin-like growth factors (IGFs) in promoting tumor growth in an estrogen-dependent manner, indicating that mammary AT can influence systemic hormonal environments that favor cancer progression. In addition to the direct effects of AT on breast cancer cells, the metabolic alterations associated with obesity can also influence cancer progression. Obesity is characterized by insulin resistance and hyperinsulinemia, which can promote tumor growth through the activation of insulin signaling pathways [69]. Insulin and IGFs can enhance cell proliferation and inhibit apoptosis, creating a favorable environment for cancer development [69]. The interplay between insulin signaling, adipokines, and the inflammatory response in the mammary microenvironment underscores the complexity of the relationship between obesity and breast cancer. The interactions between immune cells and adipocytes within the mammary tissue further complicate the tumor microenvironment. Doyle et al. demonstrated how macrophages, which are often elevated in breast tissue during remodeling phases such as pregnancy, can enhance the angiogenic and proliferative potential of breast cancers when interacting with adipose stromal cells [70]. This suggests that the immune landscape within the mammary AT is integral to understanding breast cancer biology.

The potential for therapeutic interventions targeting the adipose microenvironment is an emerging area of interest. Several studies suggest that modulating the inflammatory and metabolic profiles of AT could enhance the efficacy of existing breast cancer treatments. For instance, therapies aimed at reducing AT inflammation may improve responses to chemotherapy and reduce tumor burden [71,72]. This indicates that targeting the adipose microenvironment could be a promising strategy in breast cancer management.

The interplay between mammary AT and breast cancer is multifaceted, involving hormonal, inflammatory, and metabolic factors. The presence of excess AT in the mammary gland creates a unique microenvironment that can promote tumorigenesis through various mechanisms, including the secretion of adipokines, the recruitment of inflammatory cells, and the remodeling of the extracellular matrix. As obesity rates continue to rise globally, understanding the role of mammary AT in breast cancer development becomes increasingly important for developing targeted prevention and treatment strategies [73].

4. The terapeutic relevance of targeting the peritumoral adipose tissue

The peritumoral AT (PAT) has emerged as a dynamic and biologically active component of the tumor microenvironment, playing a pivotal role in cancer progression. Its influence on cancer development, metastasis and resistance to therapy underscores the need for innovative therapeutic strategies that specifically target adipose-tumor interactions [74,75]. In the context of breast cancer and renal cancer, where CAAs and their secretory profiles significantly modulate tumor behavior, targeting these interactions represents a promising avenue for enhancing treatment outcomes. In breast cancer, the proximity of mammary AT to malignant epithelial cells creates a microenvironment rich in pro-tumorigenic signals [76]. CAAs undergo a phenotypic shift characterized by lipid depletion and increased secretion of adipokines like leptin, resistin and inflammatory cytokines such as TNF-α and IL-6 [77]. Leptin, in particular, has garnered significant attention for its role in promoting tumor proliferation, angiogenesis, and metastasis through the activation of JAK/STAT3 and PI3K/AKT signaling pathways [78]. Given leptin's overexpression in obese patients, anti-leptin strategies are a critical target. Monoclonal antibodies against leptin or leptin receptor antagonists have shown preclinical efficacy by attenuating tumor growth and reducing leptin-driven inflammatory signaling [39]. Furthermore, interventions targeting metabolic pathways in CAAs offer a dual advantage of disrupting tumor-promoting lipid metabolism and reducing systemic obesity-related risks [79]. Inhibitors of fatty acid synthase (FASN) and lipogenesis-associated pathways are under investigation for their capacity to impair lipid transfer from adipocytes to tumor cells. First-generation FASN inhibitors, such as cerulenin and Orlistat, showed interesting promises in preclinical studies, by reducing tumor growth, despite side effects such as anorexia and weight loss are still a limiting factors [80]. Newer FASN inhibitors, including TVB-3166 and TVB-2640, have also demonstrated antitumoral potential in preclinical models, showing an increased tolerability in early clinical trials [81]. Additionally, targeting aromatase activity in CAAs, which is upregulated in postmenopausal women and contributes to estrogen biosynthesis, is a cornerstone of anti-hormonal therapies in estrogen receptor-positive breast cancer [82,83]. Similarly, inhibiting CD36 fatty acid transporters in CAAs may reduce intratumoral regulatory T cells and promote the infiltration of effector T cells, enhancing the efficacy of immunotherapy [84]. The dual targeting of CD36 and immune checkpoint inhibitors, such as anti-PD-1 therapy, has shown promise in improving antitumor activity and combating tumor resistance [85].

RCC, particularly ccRCC, is profoundly influenced by the perirenal AT (PRAT) [28,86]. Obesity-driven changes in PRAT enhance tumorigenicity through chronic inflammation, oxidative stress, and metabolic reprogramming [87]. Unlike breast cancer, the browning of PRAT—a process where white AT adopts thermogenic properties—has been

Table 1
Therapeutic strategies targeting peritumoral adipose tissue in cancer.

	Mechanism of Action	Examples of Interventions	Cancer Types	Clinical Evidence and Challenges
Leptin and Leptin Receptors	Promotes tumor proliferation, angiogenesis, metastasis via JAK/STAT3 and PI3K/AKT pathways	Monoclonal antibodies, leptin receptor antagonists	Breast, Renal	Systemic side effects and leptin overexpression in obesity
Fatty Acid Synthase (FASN)	Impairs lipid transfer from adipocytes to tumor cells	FASN inhibitors (cerulenin, Orlistat, TVB-3166, TVB-2640)	Breast	Promising antitumoral activity and increased tolerability with new inhibitors
Aromatase Activity in CAAs	Reduces estrogen biosynthesis	Aromatase inhibitors	Breast	Established cornerstone in estrogen receptor-positive breast cancer therapy
CD36 Fatty Acid Transportes	Reduces regulatory T cells, enhances effector T cell infiltration, and improves immunotherapy outcomes	CD36 inhibitors combined with checkpoint inhibitors	Breast	Enhanced antitumor activity in preclinical evidence but needs further clinical validation
Reactive Oxygen Species (ROS)	Mitigates oxidative stress and obesity-driven RCC progression	Antioxidants, NADPH oxidase (NOX) inhibitors	Renal	Potential to limit PRAT-induced tumorigenesis
Adipose Derived Cytokines	Disrupts immunosuppressive milieu driven by IL-6, TNF-α, regulatory T cells, and myeloid-derived suppressor cells (MDSCs)	Anti-inflammatory agents in combination with checkpoint inhibitors	Renal	Combination therapies (anti-IL-1β + anti-PD-L1) show promise in preclinical models
Metabolic Modulation	Reduces systemic inflammation and adipocyte metabolism	Metformin, thiazolidinediones (PPAR-γ activators)	Breast, Renal	Demonstrated anticancer properties but needs further clinical validation
Gene Editing	Silences genes related to adipokine signaling and lipid metabolism	Targeting FABP4	Breast, Renal	Emerging preclinical data but feasibility and long-term safety are an issue
Stromal Remodeling Enzymes (MMPs)	Reduces extracellular matrix modifications driven by adipose-tumor interactions	MMP inhibitors	General	May inhibit cancer cell migration but requires validation in cancer-specific models
Lifestyle and Dietary Interventions	Reduces systemic insulin levels and modulates adipokine profiles	Caloric restriction, ketogenic diets	General	Adjuncts to standard therapies but prospective clinical trials needed to establish feasibility and long-term benefits.

linked to epithelial-mesenchymal transition (EMT) and increased metastatic potential [88]. In this context, therapeutic strategies targeting adipokine signaling pathways, particularly leptin and adiponectin imbalance are of paramount importance. The inhibition of leptin signaling has shown promise in reducing EMT-associated gene expression and impeding RCC invasiveness [89]. Leptin receptor antagonists or downstream inhibitors of the JAK2/STAT3 pathway could be pivotal in reducing tumor aggressiveness [90,91]. Additionally, targeting oxidative stress mediators such as reactive oxygen species (ROS) with antioxidants or inhibitors of NADPH oxidase (NOX) has demonstrated potential in mitigating obesity-related RCC progression [92,93]. Another promising approach involves modulating the immune microenvironment influenced by PRAT. Adipose-derived cytokines, including IL-6 and TNF-α, promote an immunosuppressive milieu characterized by increased regulatory T cells and myeloid-derived suppressor cells (MDSCs) [94]. Immunotherapeutic strategies combining checkpoint inhibitors with anti-inflammatory agents that disrupt these adipose-driven immune modulations are currently under exploration. Indeed, combining anti-IL-1β and anti-PD-L1 antibodies has been shown to reduce MDSC levels and block tumor progression [95].

However, beyond direct adipokine or cytokine inhibition, repurposing metabolic drugs to target adipose-tumor interactions has shown significant promise and could represent a more immediate answer to targeting PAT (Table 1). Agents such as metformin, which modulate insulin resistance and systemic inflammation, have demonstrated anticancer properties by indirectly affecting adipocyte metabolism and reducing IGF signaling in both breast and renal cancer [96]. Similarly, thiazolidinediones, which activate (PPAR-γ), offer potential benefits by promoting adipocyte differentiation and reducing the pro-inflammatory phenotype of CAAs [97]. Nevertheless, novel gene-editing technologies, including CRISPR-Cas9, present interesting avenues for silencing adipokine-related genes or metabolic enzymes critical to lipid transfer [98]. For instance, targeting FABP4, a lipid chaperone involved in fatty acid transport, has shown potential in reducing cancer cell lipid uptake and proliferation [99]. Additionally, inhibition of stromal remodeling enzymes such as matrix metalloproteinases (MMPs) could curtail the adipose-driven ECM modifications that facilitate cancer cell migration [100]. Finally, lifestyle, exercise and dietary interventions aimed at reducing adiposity and metabolic dysregulation remain essential complementary strategies [101]. Caloric restriction and ketogenic diets, which influence systemic insulin levels and adipokine profiles, have been proposed as adjuncts to standard therapies [102]. Prospective clinical trials are needed to validate the long-term benefits and feasibility of integrating these approaches into routine cancer care.

5. Conclusions

It is widely accepted that patients with obesity are at increased risk for the development, growth and progression of several cancers, but the influence of excessive adiposity on the efficacy of cancer treatment has not been fully elucidated for established or newer therapies. One emerging model is that cancer cells reprogram adipocytes into CAAs to support tumour growth. Once reprogrammed, CAAs provide a pro-tumour microenvironment by releasing inflammatory and angiogenic factors, as well as various metabolites that promote tumour growth and metastasis. The identification of interactions between adipocytes and cancer cells through paracrine signalling may lead to the identification of new targets for cancer therapy. In this context, it is not surprising that targeting AT with anti-obesity and/or anti-diabetic agents, such as metformin and thiazolidinediones, has shown great promise and may provide a more immediate answer to the treatment of overweight or obese cancer patients. Lifestyle and dietary interventions for the reduction of adiposity and metabolic dysregulation remain essential complementary strategies. Although a better mechanistic understanding of the contribution of dysfunctional adipose tissue to cancer progression will certainly provide new molecular targets for cancer treatment in obese patients, in an era of individualised cancer therapy, the need to develop targeted therapeutic approaches for patients with obesity and cancer remains.

Declaration of Competing Interest

The authors declare no conflicts of interest.

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Data availability

No data was used for the research described in the article.

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