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REVIEW

Advances in "adiponcosis": Insights in the inner mechanisms at the base of adipose and tumour tissues interplay

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Abstract

The epidemic spread of obesity is nowadays recognized as a global health and economic burden, arising great interest in the scientific community. The rate of adult obesity steadily increases concomitantly with the cancer incidence. As has been comprehensively reported, obesity is included among the multiple cancer risk factors and can progressively cause and/or exacerbate certain cancer types, as colorectal and breast cancers. The term *adiponcosis* was forged precisely to emphasize the interconnection between obesity and cancer onset and progression. The underlying mechanisms of adiponcosis have not been fully elucidated yet, may vary on cancer type, and depend on body fat distribution. It has been proposed that insulin resistance and related chronic hyperinsulinemia, increased insulin-like growth factors production, chronic inflammation or increased bioavailability of steroid hormones could be responsible of cancer hallmarks. Additionally, it has been suggested that adipose tissue-derived hormones, cytokines and adipokines, such as leptin, adiponectin and inflammatory markers, may reflect mechanisms linked to tumorigenesis. This review summarizes the current evidence on pathways, hormones, cytokines and low-chronic inflammation subtending adiponconsis, focusing on breast and colorectal cancers. In addition, we analyzed the lifestyle interventions that could attenuate the driving forces of obesity-related cancer incidence and progression. Moreover, current targets and drugs, their pros and cons, as well as new mechanisms and targets with promising therapeutic potential in cancer are discussed. Depicting this complex interconnection will provide insights for establishing new therapeutic approaches to halt the obesity impacts and thwart cancer onset and progression.

Abbreviations: APN, adiponectin; ASCs, adipose stem cells; ATM, adipose-tissue macrophages; BC, breast cancer; BMI, body mass index; CASP9, Caspasi-9; CLS, crown-like structures; CRC, colorectal cancer; ECM, extracellular matrix; eIF4E, eukaryotic initiation factor 4E; EPIC, European Prospective Investigation into Cancer e Nutrition; ER, estrogen receptor; FFA, free fatty acids; FOXO, forkhead box protein O; HIF1a, hypoxia inducible factor 1 subunit alpha; IGF, insulin-like growth factor; IGFBP1/2, insulin-like growth factor-binding protein 1/2; ILC1, innate lymphoid cells group 1; INSR, insulin receptor; IR, insulin resistance; IRS1, insulin receptor substrate 1; LEPR, leptin receptor; MAPK, mitogen-activated protein kinase; MCP-1, monocyte chemoattractant protein-1; MDM2, mouse double minute 2 homolog; MDSCs, myeloid-derived suppressor cells; mTor, mammalian target of rapamycin; PEGLPrA2, pegylated leptin peptide receptor antagonist 2; PI3K, phosphatidylinositol 3 kinase; PPAR-γ, peroxisome proliferator-activated receptor γ; ROS, reactive oxygen species; SHBG, sex-hormones-binding globulin; T2D, type 2 diabetes; TZDs, thiazolidinediones; VEGF, vascular-endothelial growth factor; WCRF, World Cancer Research Fund.

KEYWORDS
adiponcosis, adipokine, breast cancer, cancer, colorectal cancer, inflammation, insulin, obesity, sex hormones, therapy

1 | INTRODUCTION

The term *adiponcosis*, derived from the fusion of the words *adiposis* and *oncosis*, was proposed in 2013 to highlight the increasing evidence linking obesity to enhanced cancer risk.[1] However, the molecular mechanisms subtending adiponcosis are still to be deepen. Worldwide, the burden of cancer attributable to obesity is 11.9% in men and 13.1% in women,[2] and overweight/obesity are the main preventable determinants of the increasing incidence and prevalence of cancer, surpassing smoking as a significant cause of cancer.[3] The onset and progression of several solid tumors, such as colorectal, breast, ovarian, thyroid and certain brain cancers, as well as hematologic malignancies, have been associated with excess body weight.[4-7] Accordingly, reduction of overweight/obesity may decrease the burden of postmenopausal breast cancer (BC) and colorectal cancer (CRC), which represent two of the most frequent malignancies worldwide. Ectopic fat deposition, as the pathological expansion of white adipose tissue at intrahepatic, intra-abdominally, intramyocellular level may affect metabolic, inflammatory and immunologic pathways. This produce alterations of DNA repair, gene function, cell mutation rate as well as epigenetic changes enabling malignant transformation and progression.[8,9] The positive energy balance linked with obesity induces a variety of systemic changes including altered levels of insulin, insulin-like growth factor-1 (IGF), leptin, adiponectin (APN), steroid hormones and cytokines. Each of these factors alters the nutritional milieu and has the potential to create an environment that favors tumor initiation and progression. It is known that the prevalence of overweight and obesity, mostly assessed by various anthropometric measures including body mass index (BMI), is continuously increasing, reaching pandemic proportions. Carcinogenesis and tumor progression induced by excess body weight are linked to the production and secretion by the adipose tissue of numerous hormones, growth factors and proinflammatory molecules able to act both locally in the adipose tissue and at systemic level in other organs.[10] In cancer, several oncogenic mutations, alter cellular metabolism to support the biomass and energy demands of the hyperproliferative state. The chronic caloric excess is stored as lipid in adipose tissue and may accumulate in other metabolic organs (such as the liver) and skeletal muscle. An increased amount of lipid significantly alters the normal metabolic milieu and creates an environment that chronically transmits a signal of nutrient excess to the cell. As a result, signaling cascades that drive glucose uptake, cell growth, cell proliferation and angiogenesis are activated and may lead to oncogenic transformation.[11] This review summarizes the current evidence on pathways, hormones, cytokines and low-chronic inflammation subtending adiponconsis, focusing on breast and CRCs. In addition, we analyzed the lifestyle interventions that could attenuate the driving forces of obesity-related cancer incidence and progression. In addition, current targets and drugs, their pros and cons, as well as new mechanisms and targets with promising therapeutic potential in cancer are discussed, providing potential suggestions for further investigation.

2 | BIOLOGICAL MECHANISMS LINKING OBESITY TO CANCER

2.1 | Hyperinsulinemia/insulin resistance

Several factors including adipokines, inflammatory cytokines, growth hormones, hyperinsulinemia, impaired insulin signaling and the reduced peripheral target tissues response to insulin (insulin resistance, IR) have the potential to significantly contribute to cancer development and progression through the regulation of several signaling pathways: this mechanism has been reported for liver and pancreatic cancer. However, the cause/effect relationship linking cancers to obesity is not completely understood.[12]

A chronic hyperinsulinemia in basal/fasting condition and/or as an enhancement of postprandial insulin secretion, resulting by insulin hypersecretion and/or reduced systemic insulin clearance, is frequently observed in obesity.[13] It is commonly accepted that obesity induces hyperinsulinemia, to overcome the induced IR. IR is triggered by a complex genetic and environmental factors interplay. Several genetic alterations in insulin receptor (INSR) and insulin signalling pathway components have been identified. For example, INSRs overexpression is frequently observed in liver cancer cells, maybe for a gene transcription dysregulation [[14] and refs therein]. However, the abnormal visceral fat accumulation in genetic susceptibility people is considered the main IR driver. In addition, obesity causes IR by promoting chronic inflammation.[15]

Insulin and IGFs represent growth and survival factors for many cell types; they are able to bind to each other's receptors, INSR and IGF-1 receptors (IGFRs), and exert their oncogenic potential, by activating several downstream signaling including phosphatidylinositol 3 kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) and mitogen-activated protein kinase (MAPK) pathway to promote cancer cell growth, survival, motility, differentiation, angiogenesis and metastasis (Figure 1) [[16] and refs therein]. Particularly, obesity causes increased levels of insulin and IGFs activating common downstream signaling including PI3K/Akt/mTOR and MAPK pathway that promote cancer cell growth, survival, motility, differentiation, angiogenesis and metastasis. AKT phosphorylates BCL2, CASP9 and the transcription factor FOXO to inhibit apoptosis. AKT also phosphorylates the MDM2 proto-oncogene that inhibits the tumor suppressor TP53. AKT phosphorylates mTOR that activate the substrates S6 kinase

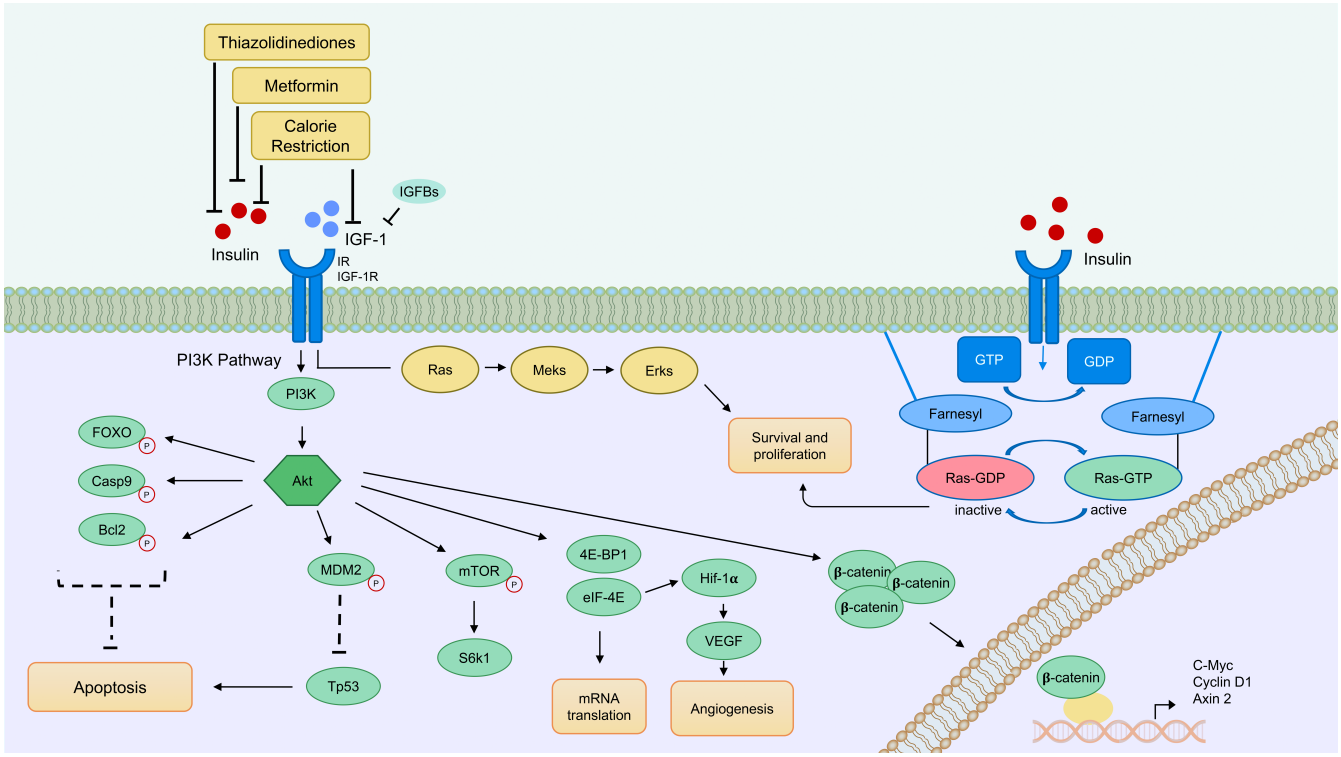

FIGURE 1 Pathways activated by INS/IGF-1 in obesity [Color figure can be viewed at wileyonlinelibrary.com]

1 and eIF4E-binding protein 1, which regulate mRNA translation initiation and progression to control cell growth. Moreover, activation of IR/PI3K/Akt signaling pathway stimulates β-catenin translocation into the nucleus, increases the levels of VEGF, thus impacts the various tumor cell behaviours. Insulin and IGF signaling impact cell survival and proliferation through the RAS/RAF/MAPK kinase/ERK cascade. Insulin augments the amount of farnesylated RAS available for GTP loading in response to stimulation by other growth factors, by phosphorylating and activating the enzyme farnesyltransferase, involved in RAS isoprenylation. Therefore, pharmacological and lifestyle interventions to prevent/treat obesity and/or drugs targeting leptin and IGFs signalling may reduce breast and CRC risk, improve clinical outcomes of patients and control other comorbidities (Figure 1).

The major insulin signaling pathway components are frequently mutated in cancer cells thus affecting cell proliferation and survival.[17,18] In addition, INSR downregulation by receptor internalization is lost in cancer cells, considering their insensitivity to hyperinsulinemia.[14] Chronic hyperinsulinemia could also mediate tumorigenesis indirectly by decreasing hepatic production of IGF-binding proteins 1 and 2 (IGFBP1/2), resulting in an IGF-1 and IGF-2 tissue bioavailability increase able to activate mitogenic signalling pathways in several cell types.[19,20]

2.2 | Obesity and low chronic inflammation

A chronic low-grade inflammation is associated with obesity and provide an additional link with cancer. The enlarged visceral fat tissue adipocytes shift their secretome to a pro-inflammatory profile in which cytokines and other mediators increase cell susceptibility to cancer initiation or progression.[21] In obesity, the expansion of adipose tissue leads to the formation of hypoxic areas, where a limited supply of oxygen triggers chronic low-grade inflammation and IR. In this scenario, HIF1a upregulation induces ECM (Extracellular Matrix) dysregulation with consequent chronic fibrosis, vascular inflammation and an increased number of macrophages with a proinflammatory phenotype recruitment in adipose tissue has been observed. MCP-1 drives the macrophages and immune cells migration to the adipose tissue that can modulate cancer transformation and progression.[22-24] Adipose-tissue macrophages (ATMs) are significantly increased in both obese humans and mice where remove dead adipocytes.[25,26] In obesity, ATMs show a polarization towards the M1 proinflammatory phenotype (M1 ATMs).[27] Cytokines such as TNF-α, IFNγ, IL-1β and IL-6 and pro-inflammatory immune cells, including various granulocytes, group 1 innate lymphoid cells (ILC1), B cells and $CD8^{+}$T cells, accumulate in microenvironment to sustain chronic inflammatory responses.[28] Chronic hypoxia can lead to adipocytes stress or death, after hypertrophy and hyperplasia. Macrophages surround dead or dying adipocytes promoting the development of crown-like structures (CLS). CLS-associated macrophages promote both vascular permeability, producing high levels of cytokines and myofibroblast activation, contributing to increased tissue stiffness in the obese adipose tissue microenvironment.[29] The CLS formation in the obese adipose tissue microenvironment is proposed as a hallmark of adipose tissue inflammation and is correlated with IR and metabolic syndrome.[30] The growing interest in using CLS as a prognostic biomarker is due to the association of such structures with poorer prognosis in cancer

patients. Indeed, both in breast and prostate cancer, a positive status of CLS is associated with higher BMI and systemic markers of the metabolic syndrome.[31,32] Of note, CLS was positively associated with increased aromatase activity in breast tissues. CLS presence was related with high activity of NF-κB, able to regulate the expression of several genes, such as TNFα, IL-1β, IL-6 and COX-2-derived PGE2, associated to increased aromatase activity in adipose tissue and other oncogenic mechanisms.[33] Once inflammation is established in adipose tissue, neutrophils participate to the network with several immune cells such as NKs, lymphocytes, macrophages and dendritic cells. For example, the serine protease neutrophil elastase cleaves insulin receptor substrate 1 (IRS1), preventing its to binding to PI3K, thus leading to IR in response to adipose inflammation.[34]

Chronic adipocyte hypertrophy and hyperplasia, through inhibition of canonical WNT-β-catenin and PPARγ signalling, can induce a chronic activation of dendritic cells, with consequent T cell exhaustion.[35] On the other hand, an impaired $CD8^+$ T cell surveillance and accelerated tumor onset and progression was reported in BC models, where PDL-1 upregulation was observed in myeloid-derived suppressor cells (MDSCs) after IFNγ release from tumor cells.[36] Moreover, mast cells, by producing IL-6 and IFNγ induce various proteases such as cathepsin S, able to promote cancer progression and therapeutic resistance to cytotoxic therapies. Mice treated with clinically available mast cell-stabilizing agents showed reduced obesity and diabetes, highlighting the potential of multiple new treatment targets going forward for these common human metabolic diseases.[37] Noteworthy, as in acute lymphoblastic leukemia adipocytes and macrophages can sequester and catabolize chemotherapeutic agents, reducing their therapeutic efficacy. So, a treatment aimed to control both cancer growth and adiposity may improve patient's survival, the quality of life and the response to chemotherapy.[38,39] In addition, IL-6 could induce cancer proliferation via STAT signaling.[40] TNF-α released by macrophages triggers the NFκB and JNK-MAP4K4-AP1 (activator protein 1) pathways, thus amplifying the mitogenic signals.[41-43] In addition, high free fatty acid (FFA) levels can amplify the proinflammatory response via NFκB signalling and increased secretion of pro-inflammatory cytokines such as IL-6, IL-1, TNF-α and MCP-1.[44] Furthermore, NFκB may induce the expression of target genes involved in cell migration, apoptosis, angiogenesis and cell proliferation.

2.3 | Sex hormones

In the peripheral adipose tissue androgens and their precursors are converted to estradiol by aromatase. Adipose tissue hyperplasia/hypertrophy is responsible of high aromatase expression and activity that induce high circulating estrogens levels.[45,46] Estrogens via ERs control cell proliferation, differentiation, apoptosis and cell migration.[47] High estrogens concentration and ERα signaling dysregulation are related to the incidence and mortality of hormone receptors positive BC in postmenopausal women.[48,49] Insulin/IGF-1 and estrogen signaling often exert a synergistic effect in carcinogenesis. Estrogens elicit both insulin signalling, by increasing expression and activity of insulin/IGF-I pathway components[50,51] and IGF-1 production, stimulating endometrial tissue tumorigenesis.[52] Hyperinsulinemia can affect the hepatic sex-hormones-binding globulin (SHBG) synthesis, thereby increasing the sex steroids bioavailability that positively influence cancer development and progression.[53]

3 | ADIPONCOSIS: DEEPEN THE GAP IN OBESITY-ASSOCIATED BREAST AND COLORECTAL CANCERS KNOWLEDGE

The comprehensive understanding of the contribution of body composition to the pivotal mechanisms inducing BC and CRC development is challenging. In the past several decades, many studies have been carried out to clarify the role of external factor in the cancer pathogenesis: for this purpose, smoking, stress and obesity have been widely investigated. According to the World Health Organization, obesity is defined by excessive and atypical accumulation of adipose tissue, dangerous for the individual's health. Chronic low-grade inflammation and alteration of adipokines synthesis and secretion are often reported in overweight/obese patients. The infiltration of innate and adaptive immune system cells enhances the secretion of both proinflammatory cytokines and adipokines: the result is a chronic low-grade inflammation state and the creation of a microenvironment advantageous for cancer development.[54] Adipokines are actively secreted by adipocytes and evidence suggests their involvement in cancer progression and proliferation. Among them, leptin and APN have been extensively investigated.[55] APN, one of the most abundant protein hormones secreted by the adipose tissue, is implicated in the regulation of glucose blood concentration, controlling its cellular uptake. APN acts as insulin sensitizing hormone and its blood concentration is inversely proportional to obesity.[56] APN exerts its function by activating AMPK and inhibiting the PI3K/AKT/mTOR pathways, resulting in cell cycle arrest and induction of apoptosis. Moreover, APN inhibits STAT3, whose activation is linked to high proliferation and survival of tumor cells.[57]

3.1 | Obesity and breast cancer

Globally, BC is one of the most frequently diagnosed cancer.[58] Nowadays, besides family history and gene mutations, many environmental factors are recognized as cancerogenic, and previous research showed that overweight/obesity and physical inactivity play a pivotal role in BC development.[59] There are several possible mechanisms subtending adiponcosis in BC: estrogen alteration levels, chronic adipose tissue inflammation, leptin and insulin/IGF-1 signalling pathway activation. Almost all women life is orchestrated by biological and functional alteration of sex steroid hormones levels (pregnancy or menopause, for example) that are often associated to body composition modifications.[60,61] In premenopausal women, estrogens are predominantly synthesized by the ovary. During menopause the production of estrogens is performed at extra-glandular level, by characteristic cells of adipose

tissue like the undifferentiated adipose fibroblasts: here plasma androstenedione secreted by the adrenal glands is converted by Cytochrome P450 aromatase complex in estrone.[62] For obese postmenopausal women, the abundant adipose tissue become the main estrogen synthesis site responsible of the increase in its concentration.[63] The aromatase enzymatic complex is expressed also within normal and cancer breast cells.[64] It is notable that in breast tumour microenvironment, the local estrogen concentration is much higher than blood.[56] Moreover, the SHBG levels decrease and consequentially increased level of free estrogens that can be correlated to a higher BC risk is observed.[65] The molecular pathway linking estrogens to BC, should be investigated firstly in estrogens metabolism that leads to the production of catechol metabolites. Its oxidative metabolism induces the production of estrogen 3,4-quinone, an unstable product able to produce DNA damage.[66] In addition, the activation of the estrogen receptors (ERs) signaling pathway needs to be deeply investigated. The activation of ERs results in an increased cellular proliferation and apoptosis inhibition. Previous studies reported that Adipose Stem cells (ASCs), occasionally found in tumour microenvironment, contribute to the establishment and growth of BC. The IL-6 and CCL5 secretion by ASCs is involved not only in BC tumorigenesis, but also in metastasis formation.[67]

Leptin shows an increased level in obese people, and it is positively correlated with overall weight.[68] To our knowledge, BC onset can be influenced by leptin in an endocrine, paracrine and autocrine manner. Leptin stimulates pro-inflammatory cytokines secretion thus plumping low chronic inflammation.[69] The leptin binding to its receptor (Leptin receptor, LEPR) activates three distinct signalling pathways: the JAK/STAT pathway that induce cancer progression; the MAPK pathway that enhance cell proliferation and the PI3K pathway that increase proliferation, migration and invasion.[70] Insulin and IGF-1 can also increase the expression of leptin and its receptor in mammary epithelial tissues, that is associated with worse prognosis in BC.[71] In addition, leptin increases the BC development risk, particularly in postmenopausal women, that result in estrogen synthesis stimulation, by aromatase activating.[68]

In BC an increase in circulating insulin and estrogen concentration with an APN expression level reduction have been reported.[72] However, the precise mechanism of action of APN has not been fully understood and conflicting results have been described.[73] It has been demonstrated that APN affects BC growth, aggressiveness and behaviour.[74,75] In ERα-negative human BC cell line MDA-MB-231, APN shows an antiproliferative effect by modulating the expression of genes that control cell cycle progression, activates AMPK, inhibits Wnt/beta-catenin and PI3K/AKT pathways.[72,76] In addition, mounting evidence shows the existence of a crosstalk between APN/AdipoR1, IGF-IR and ERα in BC. It has been demonstrated that low APN concentrations enhances the association of IGF-1R with AdipoR1, APPL1, ERα, IGF-IR and c-Src, leading to MAPK activation and BC cell proliferation.[77]

3.2 | Obesity and colorectal cancer

CRC is one of the most recurrent cancers with poor prognosis worldwide. Several mechanisms have been proposed to explain adiponcosis in CRC. Altered adipokines production and the anomalous expression of their receptors in obese patients promotes CRC risk and affects CRC carcinogenesis.[78] For example, a correlation between overweight, low APN level and increased CRC risk has been proposed.[79] In vitro, it has been demonstrated that APN is capable of inhibit CRC cell proliferation by activating AMPK pathway and consequently inhibiting mTOR pathway. In the last decades, several studies investigated leptin as a possible CRC inducer. As previously mentioned, leptin exerts its biological function through JAK/STAT signalling pathway activation, contributing to cell cycle progression. This signalling pathway results overstimulated in CRC where LEPR expression level is increased compared with the normal tissue.[80]

In vitro studies revealed that the crosstalk among tumour microenvironment adipocytes and CRC cells enhances their proliferation and migration.[81] In addition, the increased expression level of insulin/IGF-1 and their receptors observed in obesity represents a major driver in CRC pathogenesis, leading to CRC cells proliferation and migration by PI3K/Akt and Src signal pathway activation.[82,83]

The role of estrogen in obesity-associated CRC is complicated. Some cohort studies indicated that estrogens play a protective role in CRC pathogenesis, as revealed by estrogen replacement therapy.[84] However, several studies have shown that high BMI increased the CRC risk in men and premenopausal women, but not in postmenopausal women.[85] The ER-α expression is increased in CRC, and positively correlates with CRC stages and worse survival.[84] The ER-β expression, instead, is lower in CRC cells and inversely correlates with CRC, indicating that ER-β mediates the estrogens protective effect on CRC tumorigenesis.[86] This hypothesis is supported by the observation that ER-β overexpression induced cell-cycle arrest and inhibited cell proliferation and growth in SW480 cells and mouse xenografts model.[87]

Inflammation also shows an important role in CRC by activating proliferation, migration and metastasis.[88] Indeed, TNF-α stimulates NF-κB pathway activation that is indispensable for CRC carcinogenesis.[89] Again, TNF-α induces the malignant transformation of intestinal stem cells through the NF-κB and Wnt/β-catenin signaling pathways activation.[90] Tumour-associated macrophage induced inflammation is related to CRC poor prognosis.[91] For example, CCL2 knockout in ApcMin/+ mice inhibited CRC growth and immune infiltration; CCL2 promotes the MDSCs accumulation into the tumour microenvironment and increased MDSC-mediated inhibition of T cells in a STAT3-dependent manner. In addition, blocking CCL2 using antibodies reduced tumour growth and MDSC infiltration in a murine model of colitis-associated CRC.[92]

4 | CURRENT THERAPEUTIC STRATEGIES TARGETING THE INTERPLAY AMONG ADIPOSE TISSUE AND CANCER

Adipose tissue interacts and supports tumorigenesis in different ways. Current therapeutic strategies aim to interfere with adiponcosis by targeting the molecular crosstalk between cancer cells and adipocytes,

inflammation status, lowering the excessive amount of adipose tissue and/or by modulating the altered signalling pathways involved in adiponcosis.

4.1 | Present and potential drugs targeting adiponcosis

Metformin is a drug used for type 2 diabetes (T2D) treatment[79]; it is also a potent insulin sensitizer, activating the INSR through enhanced tyrosine phosphorylation. Metformin can improve obesity-associated metabolic dysregulation by reducing the inflammation status associated with the adipose tissue.[80] Metformin is able to influence the inflammation by reducing the production of proinflammatory cytokines through the inhibition of M1 ATMs and upregulation of the anti-inflammatory M2 macrophages.[93] Furthermore, it has also been demonstrated that Metformin limits the adipocyte tumor-promoting effect on ovarian cancer.[94]

Peroxisome proliferator-activated receptor γ (PPAR-γ) is implicated in lipid metabolism.[95,96] Indeed, its activation lowers circulating lipids, by promoting their uptake and storage.[97] PPAR-γ is also involved in several signaling pathways modulating immune responses towards cancer cells.[96] As for Metformin, PPAR-γ ligands influence the macrophage polarization, inhibit the expression of pro-inflammatory molecules meanwhile promotes the maturation of anti-inflammatory M2 macrophages.[97,98] This ability to regulate both inflammation and immunity shows the potential of PPAR-γ as a novel therapeutic target for adiponcosis. TZDs, also known as glitazones, are PPAR-γ agonists.[99] Pioglitazone, a TDZ used in T2D treatment, reduces hyperinsulinaemia and showed interesting effects in obese mice where it reduced the inflammation associated with the periprostatic white adipose tissue.[100] Additionally, PPAR-γ synthetic ligands have been shown to increase APN levels in preclinical models and in humans.[101] Although the leptin displays a well-established role in promoting cancer growth, no pharmacological approaches targeting leptin signalling are currently available for cancer prevention or treatment. The pegylated leptin peptide receptor antagonist 2 (PEGLPrA2) inhibited leptin signalling pathways and BC growth both in vitro and in vivo experiments.[102] Interestingly, metformin has been shown to decrease leptin levels in BC patients.[103]

APN is a cytokine normally produced by the fat tissue and found in human serum at concentrations of 2 to 20 μg/ml.[104-108] It has been demonstrated that APN has ameliorative effects against IR, inflammation and cancer, such as breast cancer.[108-111] For this reason, the development of new agonists mimicking the APN function in obese individuals showing low APN levels could be a potential therapeutic approach for adiponcosis. ADP 355, the first APN receptor agonist, showed promising activity and stability in biological fluids as well as acceptable toxicity.[112]

Strategies targeting IGF1R for cancer treatment have been investigated in some studies and clinical trials. However, they showed limited efficacy and often several side effects. Further investigations are warranted to assess the applicability of strategies acting on IGF1R.[113-116]

IGFs targeting represents an additional potential strategy. Monoclonal antibodies able to bind IGFs, as dusigitumab and xentuzumab have demonstrated promising anti-tumour activity with a well-tolerated toxicity.[117,118] Specific aromatase inhibitors have showed efficacy for ER+ BC prevention and treatment.[119] In addition, it has been demonstrated that metformin and APN are endowed with the potential to inhibit aromatase expression.[120,121]

4.2 | The impact of diet and physical activity on adiponcosis

The recognition of obesity as a leading modifiable risk factor for cancer development and mortality has triggered an active area of investigation and a rationale for testing anti-obesity interventions in oncology. Weight loss strategies targeting overweight or obese individuals account for most of these interventions. In the last decades, lifestyle has increasingly become the subject of study for its correlation with cancer. Diet, nutrition, physical activity, metabolic syndrome and obesity are important players in cancer incidence worldwide.[6,122]

Several epidemiologic studies highlighted the link between lifestyle modification, and in particular differences in dietary pattern, and cancer incidence and prognosis.[123-125] On the other hand, nutrition and physical activity, certainly influence normal homeostasis. Thus, a careful control of energy balance (intended as relationship between energy consumed, expended and stored in adipose tissue) could be considered a successful strategy to improve both incidence, prognosis and survival in cancer patients.

Recently, the contribution of the European Prospective Investigation into Cancer and Nutrition (EPIC) study, has been reviewed to identify key factors linking dietary factors and other lifestyle exposures such as alcohol, BMI and physical activity with cancer mortality.[124] Dietary patterns, more than some individual foods, are associated with lower cancer mortality. Of note, high adherence to Mediterranean diet constitutes a protective factor, reducing overall cancer mortality risk. Vegetarians/vegans diet or scarce meat consumers and fish eaters was associated with a significant reduction of mortality from pancreatic cancers, lymphatic/hematopoietic tissue cancers and all cancers combined. Also, high pre-diagnosis intake of Vitamin D, have protective effect on CRC mortality, while lignans protect from BC mortality. Processed meat and alcohol increase the risk of cancer mortality. Accordingly, in the Third Expert Report, the WCRF (World Cancer Research Fund) exhaustively summarized the impact of diet, nutrition and physical activity on cancer-related biological processes. Vegetables and fruit intake provide micronutrients and phytochemicals (eg, fibers, carotenoids, flavonoids, folates and vitamins) that have anti-tumor activity in several cancers. On the contrary, red and processed meats allow to intake mutagenic compounds like heme iron, heterocyclic amines and polycyclic aromatic hydrocarbons that induce DNA-damaging. Alcohol consumption is associated with production of carcinogenic compounds, like acetaldehyde and ROS (Reactive oxygen species). Moreover, increased estradiol production and changes in hormone metabolism are pro-tumorigenic consequence of alcohol intake.[124]

Healthy lifestyle and a minimum of 150 min/week of moderate intensity physical activity had a protective effect against overall cancer mortality. It is reported that aerobic activity decreases oxidative stress and enhances DNA repair mechanisms, as well as stimulates innate and acquired immunity and improves insulin sensitivity.[124] Interestingly, in overweight or obese survivors of BC, aerobic exercise affects metabolic syndrome biomarkers, like insulin, IGF-1, leptin and APN, suggesting that physical activity could be beneficial also in patients with BC that experienced postdiagnosis weight gain.[125]

Last but not least, high BMI (>35 kg/m^2) and high waist circumference increase the risk of overall cancer mortality.[124] However, according to the so-called "obesity-paradox", high BMI has been often associated with reduced mortality.[6] Hence, studies limited to measurements of BMI may be inappropriate, incomplete or misleading, since BMI does not consider age, sex, race, cancer-induced illness and does not reflect biology and quality of adipose tissue. Certainly, weight-gain allow to metabolic and inflammatory changes in adipose tissue microenvironment that are strongly connected to cancer development. Therefore, keeping body weight and the volume of adipose tissue under control through caloric restriction and exercise, could be a valid therapeutic approach to contrast obesity-associated dysfunction.[7] Of course, different tumors might differentially respond to caloric restriction. Consequently, additional studies are claimed to understand and optimize this approach for effective clinical benefits.

5 | CONCLUSIONS

The relationship among obesity and cancer, resembled in adiponcosis, is complex and multifactorial. The augmentation of adipose tissue shows not only local effects, but also acts at systemic level, where it can trigger several mechanisms that could be correlated to cancer onset and progression. Strong and robust associations have been reported for BC and CRC. The translation of these findings into effective clinical strategies is urgently needed to halt the accelerating global burden of obesity-related cancer. Further studies should be conducted to better elucidate the mechanisms underlying adiponcosis and to discover additional targets that could be therapeutically exploited to improve obesity-related cancer risk and outcomes. Several drugs could be repurposed for obesity-related cancers prevention and treatment. Lifestyle interventions, including an equilibrated diet and a regular physical activity, also represent potential anticancer strategies. However, additional efforts are needed to identify and optimize a patient- and/or cancer-specific therapeuticstrategies.

AUTHOR CONTRIBUTIONS

Cristina Pagano designed the content of this review article. Cristina Pagano, Erika di Zazzo, Giorgio Avilia, Beatrice Savarese, Giovanna Navarra, Maria Chiara Proto and Donatella Fiore wrote the review. M.R. analyzed the literature and drew the figure. Cristina Pagano, Erika di Zazzo, Patrizia Gazzerro, Chiara Laezza and Maurizio Bifulco, revised the review. More, all authors have approved the submitted version and agree to be personally accountable for ensuring that published literature has been fairly considered. All authors have read and agree to the published version of the manuscript. The work reported in the paper has been performed by the authors, unless clearly specified in the text.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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