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INTERACTION BETWEEN ADIPOSE TISSUE AND CANCER CELLS: ROLE FOR CANCER PROGRESSION

Jean-François Dumas¹, Lucie Brisson^{1*}

¹ Inserm UMR1069, Nutrition, Growth and Cancer, University of Tours, Tours, France

*corresponding author :

Lucie Brisson

Inserm UMR1069 Nutrition, Croissance et Cancer

Université de Tours,

10 boulevard Tonnellé, 37032 Tours, France

Tel 00 33 2 47 36 62 83, Email lucie.brisson@inserm.fr

Abbreviations

AMPK: AMP-activated protein kinase

ATP: adenosine tri phosphate

COX-2: cyclooxygenase-2

CPT1: carnitine palmitoyltransferase I

EMT: epithelial to mesenchymal transition

FABP: fatty acid binding protein

FATP1: fatty acid transport protein 1

GDF: 15 Growth Differentiation Factor 15

HIF-1: hypoxia inducible transcription factor

IGFBP-2: insulin-like growth factor binding protein-2

IL-6: interleukin 6

JAK: Janus kinase

JNK: c-Jun N-terminal kinase

LD: lipid droplets

MCP-1: macrophage chemoattractant protein

MMP: matrix metalloproteinase

NK: natural killer

PGE2: prostaglandin E2

PLOD2: Procollagen-Lysine,2-Oxoglutarate 5-Dioxygenase 2

PPAR: peroxisome proliferator-activated receptors

ROS: reactive oxygen species

STAT: signal transducer and activator of transcription

TGFβ: Transforming growth factor beta

UCP: uncoupling protein

VHL: von Hippel-Lindau

Abstract

Environment surrounding tumours are now recognised to play an important role in tumour development and progression. Among the cells found in the tumour environment, adipocytes from adipose tissue establish a vicious cycle with cancer cells to promote cancer survival, proliferation, metastasis and treatment resistance. This cycle is particularly of interest in the context of obesity which has been found as cancer risk factor. Cancers cells can reprogram adipocyte physiology leading to an “activated” phenotype characterized by delipidation and secretion of inflammatory adipokines. The adipocyte secretions then influence tumour growth and metastasis which has been mainly attributed to interleukin 6 (IL-6) or leptin but also to the release of fatty acids which are able to change cancer cell metabolism and signalling pathways. The aim of this review is to report recent advances in the understanding of the molecular mechanisms linking adipose tissue with cancer progression in order to propose new therapeutic strategies based on pharmacological or nutritional intervention.

Key words: adipocyte, cancer, adipokines, metabolism, fatty acid, exosome

Declarations

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Conflicts of interest/Competing interests

Authors declare no conflict of interest.

Introduction

Tumours are complex tissues composed of cancer and non-cancer cells in a hypoxic and nutrient-deprived microenvironment. In order to survive tumour cells need to adapt to these harsh conditions. One main property of cancer cells is their capacity to reprogram metabolism and take advantage of substrates available in the surrounding microenvironment [1]. Several types of cooperation have been demonstrated between cancer and non-cancer cells of the tumour such as macrophages or fibroblasts [2]. Recently the interaction of tumours with the surrounding adipose tissue has gain interest. Indeed tumours, locally or during metastatic dissemination, related closely with adipose tissue. In particular, from the first steps of cancer initiation, mammary tumours are in contact with the adipose tissue of the mammary gland, whereas several other cancers (prostate, ovarian, lung...) interact with the subcutaneous or visceral adipose tissue or with the adipocytes from bone marrow in advanced stages when tumours grown outside of the primary site.

Adipose tissue is the largest energy storage in the body. The majority of adult adipose tissue in humans is the white adipose tissue, composed mainly of white adipocytes, which by a high plasticity allows adapting the storage or the release of fatty acids according to the nutritional status. White adipose tissue is mainly separated into subcutaneous adipose tissue and visceral adipose tissue with heterogeneity in composition and structure [3]. Brown adipose tissue, a minority in humans, is specialized in thermogenesis. Unlike white adipocytes, brown adipocytes contain several small lipid droplets and mitochondria with a high expression of the uncoupling protein UCP1. Adipose tissue is not only a quiescent tissue for the storage of fatty acids but has metabolic and endocrine functions with the secretion of lipid or protein factors named adipokines (hormones, cytokines, growth factors, matrix remodelling components) with endocrine and paracrine functions [4, 5]. Recent studies highlighted the bidirectional interactions, based on adipokines and lipids, between white adipose tissue and tumours and their role on cancer progression (later "adipose tissue" will refer to white adipose tissue). In addition, adipocyte secreted factors have been shown to regulate the expression of genes associated with cancer progression (adhesion, invasion, angiogenesis, signal transduction and apoptosis) in non-cancerous mammary cells suggesting a role in cancer initiation [6].

Fatty acids are now recognised as important actors of cancer cell metabolic reprogramming. Cancer cells fulfil their lipid requirements by *de novo* synthesis and by the uptake of free fatty acids and lipoproteins from the extracellular microenvironment. Fatty acid synthesis is upregulated in several cancers which has been associated with tumour progression and

metastasis (for review [7]). In the last decades, it has been demonstrated that besides this increase in fatty acid synthesis, cancer cells develop mechanisms to uptake lipids from the surrounding environment and this may depend on the proximity with the adipose tissue. However, the precise role of fatty acids in tumours is not completely elucidated. Since fatty acids have a high diversity in length and unsaturation, not only the proximity of adipose tissue but also its composition can have an important role on cancer progression. Interestingly the lipid composition of adipose tissue correlates with dietary intakes. It has been estimated that 30-35 % of cancer-related deaths are linked with diet and 14-20% with obesity [8]. Adipose tissue is deeply remodelled by obesity which is characterized by excessive accumulation of lipids in adipocytes and high secretion of proinflammatory adipokines such as IL-6 or TNF- α [9].

This review aims to describe current knowledge in the cooperation between adipose tissue and cancer cells. The role of adipokines and lipids in these interactions will be discussed with a focus on the role of specific lipids. In this review, we will report studies using conditioned medium and co-culture system to represent the interactions between adipose tissue and cancer cells. The systemic effects of some adipokines independently of the proximity of adipocytes have been reviewed previously [10, 11].

1) Modification of adipose tissue by cancer cells : cancer-associated adipocytes

Adipose tissue is highly regulated by environmental factors. Among these factors, it has been demonstrated that tumour secreted factors influence adipocytes leading to an activated phenotype called cancer-associated adipocytes (**Fig1**). Cancer-associated adipocytes are characterized by a specific phenotype with high lipolysis and overexpression of proteases and proinflammatory cytokines [12, 13]. These adipocytes are part of a vicious circle where cancer cells induce the secretion of lipids and adipokines by adipocytes to promote tumour growth (see later for the effects of adipocytes on cancer cells). The demonstration of adipose tissue modifications by tumours has been made initially in breast [12] and ovarian [13] cancers but the molecular mechanisms have been demonstrated in several other tumour types such as prostate [14], pancreas [15], lung [16], hepatocarcinoma [17] and leukaemia [18]. It has been demonstrated in mammary adipose tissue that cancer proximity decreases adipogenesis-related genes and increases the expression of secretion-related genes [12, 19]. Furthermore fat browning proteins like UCP1 have been observed in breast adipose tissue from cancer patients [19]. Altogether these changes promote metabolic remodelling in adipocytes leading to a higher

glycolytic activity associated with increased fatty acid, lactate, pyruvate and ketone bodies secretion [20, 21]. In addition, it has been proposed that glutamine participates in the crosstalk between adipocytes and cancer cells. In pancreatic cancer model, cancer cells promote the secretion of glutamine by adipocytes through the downregulation of glutaminase in adipocytes [22]. Adipose tissue lipolysis has also been observed in pancreatic cancer [15] where cancer cells promote delipidation of adipocytes and decrease the expression of genes associated with lipid metabolism [23]. Adipocyte lipolysis is also induced by leukemic cells in gonadal adipose tissue [24] and in bone marrow [25]. However, lipolysis might be different between adipocytes from bone marrow, visceral adipose tissue or subcutaneous adipose tissue. Indeed bone marrow adipocytes display a specific lipid metabolic profile compared to subcutaneous adipocytes with cholesterol biosynthesis oriented metabolism [26]. Importantly lipolysis is not induced by calorie restriction in bone marrow adipocyte due to the reduced expression of the monoacylglycerol lipase responsible of the last step of lipolysis; the hydrolysis of monoglycerides to free fatty acids and glycerol [26]. In addition with lipolysis and secretion of pro-inflammatory adipokines, cancer-associated adipocytes display fibroblast-like phenotype with the reorganisation of actin and vinculin cytoskeleton and the secretion of fibronectin and collagen 1 [27].

Among the mechanisms involved in the induction of the activated phenotype of adipocytes by cancer cells, extracellular vesicles and miRNA have been recently described to promote adipocyte lipolysis and inflammation. In lung cancer, extracellular vesicles transfer IL-6 to induce adipocyte lipolysis through STAT3 pathway [16]. In hepatocarcinoma exosomes released by cancer cells activate NF κ B signalling and induce an inflammatory phenotype in adipocytes with the secretion of IL-6, IL-8 and macrophage chemoattractant protein (MCP-1) [17]. In breast cancer, the secretion of miRNA-144 and miRNA-126 by breast cancer cells is involved in adipocyte browning [20]. These miRNA are associated with the peroxisome proliferator-activated receptors PPAR γ , IRS-1 and GLUT-4 downregulation and autophagy marker and HiF-1 α upregulation in cancer-associated adipocytes [20]. In another model PPAR γ is also downregulated by miR-155 secreted by breast cancer cells and could participate to metabolic remodelling in adipocytes [21].

Several other signalling pathways induced by cancer cells have been demonstrated in bone marrow adipocytes but little is known about their involvement in white adipose tissue. Leukemic cells influence bone marrow adipocytes by inducing reactive oxygen species (ROS) and oxidative stress [18] and by inducing lipolysis and a decrease in lipid metabolism gene

expression through the secretion of Growth Differentiation Factor 15 (GDF15) [28]. Bones are the major site for prostate cancer metastasis. It has been demonstrated that prostate cancer cells activate bone marrow adipocytes through IL1- β signalling. Besides its role in lipolysis, IL1- β secreted by prostate cancer cells promotes a proinflammatory phenotype in adipocytes via upregulation of MCP-1 and cyclooxygenase-2 (COX-2) which is involved in the synthesis of the bioactive lipid, prostaglandin E2 (PGE2) from arachidonic acid [29].

Altogether, these studies highlighted to profound remodelling of adipocytes by cancer cells leading to the secretion of fatty acids, metabolic fuels and adipokines.

2) Regulation of tumour microenvironment by adipocytes

The modification of adipocyte phenotype by cancer cells induces a strong effect in tumour cells including macrophages, natural killer cells and endothelial cells (**Fig1**).

One important effect of adipocyte on tumour microenvironment is the activation of macrophages. In hepatocarcinoma it has been demonstrated that inflammatory adipocytes induced by cancer cells promote macrophage migration and their recruitment in tumours [17]. In breast cancer, adipocyte proximity also promotes macrophage migration by increasing the secretion of MCP-1 by cancer cells [30]. In addition, leptin secreted by adipocytes controls the secretion of pro-inflammatory cytokines and chemokines in macrophages and promotes macrophages differentiation [30]. Interestingly more crown-like structures, macrophages surrounding dying adipocytes, are observed in mammary adipose tissue from obese tumour-bearing mice even far from the tumour compared to lean tumour-bearing mice [30, 31].

Beside the promotion of macrophages inflammatory phenotype and tumour promotion, adipocyte – tumour crosstalk regulates anti-tumour immune response by natural killer (NK) cells. Adipocytes decrease the natural killer cell toxicity against castration-resistant prostate cancer cells [32]. PD-L1/PD-1 and NKG2D ligand/NKG2D pathways mediate NK cell interaction with cancer cells. Secretion of leptin and IL-6 by adipocytes activates the Janus kinase (JAK)-signal transducer and activator of transcription 3 (STAT3) pathway in prostate cancer cells leading to upregulation of PD-L1 and downregulation of NKG2D ligands in prostate cancer cells. This regulation of cancer cell recognition by NK cells decreases NK cytotoxicity and promotes immune escape in castration resistant prostate cancer [32]. Also adipocytes inhibit trastuzumab-mediated antibody dependent cellular cytotoxicity by natural

killer cells [33]. In this model NK cell cytotoxicity is not affected by adipocyte secreted factor but adipocytes reduce sensitivity of tumour cells to antibody-dependent cellular cytotoxicity through upregulation of survival pathways [33].

Although the mechanism is controversial, cancer-associated adipocytes promote tumour growth through modulation of endothelial cells and tumour vascularization. It has been demonstrated in hepatocarcinoma that cancer-associated adipocytes enhance endothelial cell tube formation and vascularisation in tumours [17]. Interestingly it has been demonstrated in obese mice that the activation of macrophages by adipocytes through MCP-1 IL1- β and CXCL12 promotes vascularization and angiogenesis [31]. However in breast cancer model, high secretion of IL-6 and FGF-2 in obese condition is associated with reduced vascularization and hypoxia leading to resistance to anti-VEGF therapy [34]. In addition, resistance to anti-angiogenic therapy is mediated by adipose tissue lipolysis and lipid metabolic reprogramming in cancer cells (FFA uptake and FAO) [35]. Therefore it has been proposed to target both angiogenesis and FAO which have shown promising tumour growth reduction [35].

Because of its wide range of effect, adipose tissue highly influence tumour microenvironment by promoting macrophage infiltration, tumour inflammation and regulating immune cell cytotoxicity and angiogenesis. More studies are needed to better characterize the role of cancer-associated adipocytes on tumour cells. Nevertheless, combination therapy acting on both adipose tissue and tumour microenvironment could be promising strategies to reduce the impact of cancer-associated adipocytes and limit treatment resistance.

3) Regulation of cancer cells by adipocytes

Besides its effect on tumour microenvironment, cancer-associated adipocytes influence cancer cells *per se* leading to tumour growth, metastasis and treatment resistance. These effects are mediated by the wide range of adipokines, glutamine, ketone bodies, extracellular vesicles and fatty acids secreted by cancer-associated adipocytes (**Table 1** and **Fig1**).

a) adipokines

Several hormones, cytokines or growth factors secreted by adipocytes have been associated with cancer cell properties and tumour progression.

i) Leptin

1 Leptin, one major adipokine secreted by adipocytes, stimulates the proliferation and the
2 migration of cancer cells [36, 37]. Mechanistically leptin through its fixation to its receptor ObR
3 in cancer cells activates pro-survival pathways like JAK/STAT3, Akt and c-Jun N-terminal
4 kinase (JNK) [37, 38]. The activation of these signalling pathways induces the transcription of
5 genes involved in cellular proliferation and invasiveness like the telomerase reverse
6 transcriptase, IL-6, transforming growth factor β (TGF β), matrix metalloproteinases (MMP)
7 MMP9 and MMP13 [39]. Interestingly the expression of leptin receptor is increased in tumours
8 compared to normal tissues [39]. Leptin is also secreted by adipose stem cells and promotes
9 cancer cell proliferation, migration, invasion and metastasis [40]. Moreover these effects are
10 more pronounced with adipose stem cells from obese patients [40]. As a consequence mice
11 lacking the leptin receptor display a reduced tumorigenicity, tumour growth and metastasis
12 appearance through a reduction of the ERK1/2 and JAK/STAT3 signalling [41]. Interestingly
13 leptin signalling is also associated with metabolic remodelling in cancer cells. Mammary cancer
14 cells lacking the leptin receptor show a decrease in glycolysis and an increase in mitochondrial
15 oxidation [41].

16 Besides its important role on cancer growth and metastasis, the activation of leptin pathway in
17 cancer cells is also associated with resistance to therapy. In melanoma cells, the proximity of
18 adipocytes induces the activation of Akt and MEK/ERK pathways by leptin and leptin receptor
19 ObR. Consequently, the activation of these signalling pathways reduces apoptosis induced by
20 chemotherapeutic drugs, including the alkylating agent cisplatin, the anti-microtubule agent
21 docetaxel, and the histone deacetylase inhibitor SAHA [42]. It has also been demonstrated that
22 mature adipocytes in bone marrow protect myeloma cells against chemotherapy through
23 autophagy activation. The secretion of leptin and adiponectin by bone marrow adipocytes increases
24 the expression of autophagic proteins and reduces apoptosis induced by melphalan (alkylating
25 agent), bortezomib (proteasome inhibitor), dexamethasone (corticosteroid) or doxorubicin
26 (topoisomerase inhibitor) in myeloma cells [43].

27 ii) Adiponectin

28 In addition to leptin, nutrient and energy homeostasis are regulated by another important
29 adipokine, the adiponectin. It has been demonstrated in hepatocarcinoma that adiponectin
30 antagonizes the effects of leptin in the activation of STAT3 and Akt and consequently in the
31 stimulation of proliferation, migration, invasion and tumour growth [38]. The balance between
32 leptin and adiponectin seems to be an important factor for the proliferation of cancer cells [44].

1 This could be an important parameter for the effect of obesity in cancer promotion since the
2 level of leptin is often found increased and adiponectin decreased in obese patients.

3 The reduction in adiponectin levels in colorectal cancer patients compared to healthy control
4 was associated with an increase in colon tumour development [45, 46]. Adiponectin
5 downregulation was linked with an increase in cytokine secretion, STAT3 activation and a
6 decrease in AMP-activated protein kinase (AMPK) activation [46]. Reciprocally, adiponectin
7 supplementation mediates apoptosis of colon cancer cells through the activation of caspase-3
8 via increased activation of JNK and AMPK [47]. However, the role of adiponectin in cancer
9 seems to be more complex. Some studies suggested on the opposite that a high level of
10 adiponectin is associated with increased risk of breast cancer development [48]. The
11 discrepancy in the effects of adiponectin in cancer might be due to the presence of two
12 adiponectin forms. Adiponectin exists in the full-length form and in the truncated form named
13 globular adiponectin, which contains the carboxy-terminal globular domain. Unlike the full-
14 length form, globular adiponectin promotes breast cancer cell invasive morphology, migration
15 and invasion. Although the mechanisms are not completely described, autophagy induction
16 participates in the promotion of cancer cell invasiveness by globular adiponectin [49].

17 Altogether, these studies demonstrated the complex roles of leptin and adiponectin in cancer
18 progression. Because of the opposite effects of lectin and adiponectin on obesity and on cancer
19 cells, studies investigating both adipokines will be more informative than separate studies.
20 These studies are needed to better clarify the influence of these important adipokines and to
21 develop the targeting of these signalling pathways to reduce cancer growth.

22 iii) IL-6

23 Among adipokines, the pro-inflammatory cytokine IL-6 has been widely linked with cancer
24 progression. IL-6 secretion by adipocytes has been associated with increased breast cancer cell
25 aggressiveness [12, 50]. Adipocyte proximity leads to more aggressive morphology in breast
26 cancer cells associated with epithelial to mesenchymal transition (EMT), a high invasiveness
27 *in vitro* and metastasis *in vivo* (Dirat et al., 2011). IL-6 secreted by adipocytes is involved in
28 these pro-invasive effects (Dirat et al., 2011). In another study IL-6 and MCP-1 secreted by
29 adipocytes promote breast cancer cell migration *in vitro*, however adipocytes lead to an increase
30 in epithelial marker E-Cadherin (Fujisaki et al., 2015). Interestingly in these studies breast
31 cancer cell invasiveness is promoted by cancer-associated adipocytes compared to normal
32 breast adipocytes isolated from patients [12, 50].

The effects of IL-6 in cancer cells are mainly mediated by STAT3 activation [51, 52]. In breast cancer cells the activation of STAT3 and Akt signalling by leptin and IL-6 increases the expression of the Procollagen-Lysine,2-Oxoglutarate 5-Dioxygenase 2 (PLOD2) (He et al., 2018). This protein, involved in collagen deposition, is important for matrix remodelling in extracellular tumour environment. Therefore the expression of PLOD2 induced by adipocytes promotes cancer cell migration, invasiveness and EMT (He et al., 2018). Interestingly PLOD2 downregulation decreases tumour growth and metastasis in mice and high PLOD2 expression is associated with poor prognosis in breast cancer patients (He et al., 2018). In ovarian cancer, the activation of STAT3 by adipocyte-derived IL-6 is associated with chemoresistance. It has been demonstrated that adipocytes promote the expression of the pro-survival member of the BCL-2 family, BclXl and induce resistance to carboplatin [51]. In addition, IL-6 secreted by adipocytes is associated with resistance to radiotherapy in breast cancer cells. Adipocytes increases the activation of the DNA-damage response protein Chk1 after irradiation through IL-6 and STAT3 activation [53].

iv) Other adipokines

Several other adipokines have been associated recently with cancer progression mainly in breast cancer such as resistin, adipsin, Lipocalin-2 or insulin-like growth factor binding protein-2 (IGFBP-2). In breast cancer cells, resistin activates the TLR4/NF- κ B/STAT3 pathway to stimulate EMT and stemness. Consequently resistin increases migration, invasion, anoikis resistance and tumour growth [54]. Importantly high level of resistin is found in breast cancer patients and correlates with cancer progression and poor prognosis [54]. Adipsin (complement factor D) is a complement factor that cleaves complement factor B into Ba and Bb leading to the cleavage of C3 into C3a and C3b to activate the alternative complement pathway. It has been demonstrated that Adipsin/C3a pathway activates the C3a receptor in breast cancer cells, which increases cell proliferation and sphere forming efficiency. In mice experiments, adipsin is involved in tumour growth promotion by adipocytes [55]. Lipocalin-2, which secretion by adipocytes is increased in obesity, has been shown to promote breast cancer cell proliferation and migration. Although the mechanism is not clearly understood, the effects of Lipocalin-2 seem to be linked with the expression of 3-hydroxybutyrate dehydrogenase 2, an enzyme involved in iron metabolism [56]. Among the adipokines involved in cancer progression, IGFBP-2 secreted by adipocytes in proximity with breast cancer cells stimulates breast cancer cell invasiveness. IGFB-2 is associated with increased expression of MMP2 by breast cancer cells [57]. Matrix proteases are also increased by adipocytes conditioned medium in several

cancer models such as MMP9 and MMP2 in melanoma and colon cancer cells [58] and cell-surface urokinase-type plasminogen activator in breast cancer cells [6] to promote cancer cell migration and invasiveness. It has been demonstrated in an interesting model of obesity independent of high-fat diet or leptin deficiency that the secretion of osteopontin is associated with prostate cancer cell invasiveness [59]. In this model p62 (an autophagic cargo) deficiency in adipose tissue increases adiposity and metabolic remodelling of adipose tissue. The migration and invasion of prostate cancer cells were enhanced in presence of p62 deficient adipocyte conditioned medium. The effect of osteopontin secreted by adipocytes was mediated by an increase in the carnitine palmitoyltransferase I (CPT1) expression and fatty acid oxidation (FAO) [59].

Like leptin and IL-6, besides these important roles on cancer progression and metastasis, the other adipokines have been linked with resistance to chemotherapy. It has been demonstrated that adipocytes promote resistance to trastuzumab in HER2- positive breast cancer cells through the secretion of GDF15, which activates the Akt survival pathway. In the same model Leptin promotes resistance to lapatinib but not to trastuzumab [60]. Adipose tissue and obesity are also associated with the relapse of acute lymphoblastic leukaemia. In murine models, leukaemia cells migrate through adipose tissue. The authors demonstrate *in vitro* that Stromal derived factor-1 secreted by adipocytes promotes the migration of leukaemia cells towards adipocytes. The localisation of leukaemia cells in adipose tissue protects them from the chemotherapeutic drugs daunorubicin and vincristine [61].

Altogether these studies demonstrated that through the secretion of a wide range of adipokines, adipocytes play a major role in cancer growth, metastasis and treatment resistance.

b) Glutamine and ketone bodies

Although the mechanism is not entirely described, it has been demonstrated that cancer-associated adipocytes secrete glutamine, which is taken up by prostate cancer cells. Glutamine secreted by adipocytes increases the proliferation of pancreatic cancer cells likely through its metabolic function [22]. This secretion of glutamine by adipocytes can be important for leukaemia which are highly dependent on glutamine metabolism and for which L-asparaginase is used as treatment. Indeed it has been demonstrated that the expression of glutamine synthetase is increased in bone marrow adipocytes after L-asparaginase treatment and that

adipocyte secretion of glutamine protects leukaemia cells from L-asparaginase cytotoxicity [62].

In addition to the secretion of adipokines, fatty acids or glutamine by adipocytes, the secretion of ketone bodies such as β -hydroxybutyrate could have an important role on epigenetic regulation of gene expression and cancer progression [63]. It has been demonstrated that β -hydroxybutyrate secreted by breast adipocytes, promotes breast cancer cell proliferation and tumour growth in cells expressing its transporter MCT2. β -hydroxybutyrate through HDAC inhibition induces the expression of tumour promoting genes such as IL-1 β and Lipocalin-2 in cancer cells. MCT2, IL-1 β and Lipocalin-2 high expression was associated with poor prognosis in breast cancer patients [63].

c) Extracellular vesicles

Recently the demonstration of the secretion of extracellular vesicles by adipocytes has provided new evidence for the understanding of the interactions between adipocytes and tumours. Extracellular vesicles carries proteins, RNAs or lipids and are important mechanism for cellular communications.

In melanoma it has been demonstrated that extracellular vesicles carry proteins involved in fatty acid and glucose oxidation along with metabolic substrates inducing metabolic reprogramming in cancer cells [64, 65]. These extracellular vesicles are involved in the promotion of cancer cell migration and invasion by adipocytes [64, 65]. Furthermore adipocytes grown in high-fat diet have a higher secretion of extracellular vesicles which induce a more pronounced effect on fatty acid oxidation in cancer cells due to enhanced lipid transfer but not through protein transfer [64, 65].

It has been demonstrated that extracellular vesicles secreted by adipocytes can also carry proteases. In a lung cancer model, adipocyte exosomes are used to transfer MMP3 in cancer cells. MMP3 activates MMP9 and promotes cellular invasiveness and metastasis *in vivo*. In lung tumour patients the protein level of MMP3 was increased in obese patients compared with non-obese patients, suggesting that obesity can amplify this mechanism of MMP3 secretion through exosomes to promote metastatic dissemination [66].

Extracellular vesicles are important carriers of non-coding RNA. Adipocyte exosomes contains miR-23a and miR-23b, which are transferred in hepatocellular carcinoma cells. The von Hippel-

1 Lindau (VHL) protein is a direct target of these miRNA. Consequently, miR23a/b increases
2 hypoxia inducible transcription factor (HIF-1) signalling in cancer cells leading to an increase
3 in cell proliferation, migration, resistance to 5-FluoroUracil and tumour growth. miR23a/b was
4 found enriched in exosomes from high body fat hepatocellular carcinoma patients. Moreover
5 VHL low expression and HIF-1 α high levels was associated with poor patient prognosis [67].
6 In another study, the transfer of miR-21 from adipocyte exosomes to ovarian cancer cells
7 promotes paclitaxel resistance through targeting the Apoptotic protease activating factor 1 [68].

8 9 d) Fatty acids

10 It is now well described that fatty acids released by adipocytes in proximity with tumours are
11 up taken by cells from breast cancer [69], ovarian cancer [13], prostate cancer [70], melanoma
12 [71], colon cancer [72], pancreatic cancer [15] and leukaemia cells [24]. Fourier transform
13 infrared (FTIR) microspectroscopy has allowed to evidence the lipid translocation from
14 adipocytes to prostate cancer cells [73]. In addition *in vitro* co-culture pulse chase assays has
15 shown a direct transfer of fatty acids from adipocytes to melanoma cells [74]. To avoid
16 lipotoxicity excess free fatty acids are often stored esterified in lipid droplets (LD) which are
17 intracellular organelles formed of a phospholipid monolayer surrounding neutral lipids
18 (triacylglycerol and sterol esters). LD accumulation have been observed in several tumours and
19 is associated with aggressiveness and poor prognosis [75]. This accumulation of LD depends
20 also on tumour microenvironment factors like hypoxia, which is associated with LD
21 accumulation through upregulation of fatty acid binding proteins FABP7 and FABP3. LD are
22 essentials for ROS removal, NADPH production and survival in condition of reoxygenation
23 [76]. Free fatty acids up taken from the tumour environment or released from lipid droplets
24 exert major roles for membrane structures, metabolism as substrates for fatty acid oxidation
25 (FAO) and signalling through transcription factor or oxidative stress.

26 i) Metabolic roles

27 Fatty acids are substrates for FAO to fuel the citric acid cycle and the mitochondrial electron
28 transport chain. Interestingly the rate-limiting enzyme of FAO CPT1, involved in the delivery
29 of fatty acids to mitochondria, are upregulated in cancers [77]. Furthermore in non-glycolytic
30 tumours, as prostate adenocarcinoma, fatty acid uptake could be the major energetic source [69,
31 78].

1 The interaction between adipocytes and cancer cells through fatty acid transfer is well described
2 in breast and ovarian cancers. In breast cancer cells, it has been demonstrated that co-culture
3 with adipocytes increases lipid droplet number. Interestingly fatty acids stored in lipid droplets
4 in cancer cells are released over time through the action of the adipose triglyceride lipase
5 (ATGL) or through lysosomal-dependent pathway; the lipophagy [64]. These fatty acids induce
6 profound changes in breast cancer cell metabolism with an increase in FAO, and in glucose and
7 glutamine oxidation [69, 79, 80]. Unexpectedly this increase in mitochondrial oxidation is
8 uncoupled to ATP production which comes mainly from glycolysis [69]. This uncoupled
9 mitochondrial oxidation leads to a decrease in ATP content and consequently AMPK activation
10 and ACC phosphorylation redirects lipids towards FAO instead of fatty acid synthesis leading
11 to a metabolic remodelling oriented towards fatty acid oxidation [69].

12 The metabolic effect of adipocyte proximity is also observed in colon and ovarian cancers and
13 leukaemia. Adipocytes induce an accumulation of lipid droplets and metabolic remodelling
14 with an increase in oxygen consumption from FAO and a decrease in oxygen consumption from
15 glucose in colon cancer cells. This study provides mechanistic details linking AMPK activation
16 with autophagy and survival under nutrient deprivation [72]. Fatty acids are also transferred
17 from adipocytes into ovarian cancer cells and used for FAO inducing AMPK activation [13].
18 In this model ACC is inhibited by AMPK activation but also by the activation of the salt-
19 inducible kinase SIK2 to promote fatty acid oxidation [81]. Indeed this study demonstrates that
20 fatty acids transferred from adipocytes increase the intracellular calcium concentration in
21 ovarian cancer cells through the activation of G-protein coupled fatty acid receptor and
22 subsequent phospholipase C activation. SIK2 is activated by the rise in intracellular calcium
23 leading to ACC phosphorylation and the activation of the PI3K/Akt pro-survival pathway [81].
24 In leukaemia cells, adipocytes promote also metabolic changes with enhanced FAO and glucose
25 metabolism but again uncoupled to ATP production and associated with AMPK activation and
26 autophagy markers. The authors proposed that fatty acids might activate PPAR γ transcription
27 factor to induce the expression of fatty acid transporters FABP4 and CD36 and anti-apoptotic
28 proteins [82]. Altogether, these studies shown that AMPK activation and mitochondrial
29 uncoupling seems to be key mechanisms in cancer metabolic reprogramming induced by
30 adipocytes. This suggests important roles of mitochondrial metabolites, apart from energy
31 production through ATP, for cancer cell metabolism and might be favourable to resistance to
32 cell death and survival as demonstrated in leukaemia [83].

1 Interestingly, the expression of the actors of these fatty acid induced pathways is upregulated
2 in cancer cells. ATGL is overexpressed in breast tumours compared to normal tissues and
3 correlates with aggressiveness [69]. Moreover ATGL expression is increased in breast tumours
4 in contact with the adipose tissue [69]. SIK2 is overexpressed in ovarian cancer cells
5 metastasised in adipose tissue compared to cells from the primary tumour [81]. Lastly the
6 expression of CPT1 is increased by high fatty acid condition [79]. In human cancer patients
7 CPT1 gene alteration is associated with poor prognosis in ER positive breast cancer patients
8 [79].

9 The metabolic role of fatty acids transferred from adipocytes in cancer cells is associated with
10 cancer survival and metastases. Fatty acids derived from adipocytes induce morphology
11 changes in cancer cells associated with EMT [15, 69, 72] and relocalization of lipid droplets
12 and mitochondria in cellular protrusions [64]. This phenotype promotes cancer cell migration
13 [15, 64, 72, 80], invasiveness and metastasis [69, 81]. However in a breast cancer model fatty
14 acids promote cancer cell proliferation but the increase in migration depends on adipokines
15 [79]. In colon cancer cells the stimulation of autophagy by adipocyte proximity promotes
16 survival in nutrient-deprivation condition through the metabolic use of fatty acids [72].

17 18 ii) Oxidative stress and survival

19 Besides their metabolic roles, fatty acids are well known signalling molecules through free-
20 fatty acid sensing G-protein coupled receptors (FFA1-4) and intracellular transcription factors
21 of the PPAR family.

22 Therefore, fatty acids are involved in cell death protection and particularly in cancer treatment
23 resistance. In several cancer types, adipocytes provide protection against cancer treatment by
24 providing metabolic fuels [24] and preventing apoptosis [15, 84]. Fatty acids, through the
25 functioning of electron transport chain in mitochondria and through modulation of NADPH
26 oxidase have been associated with either the promotion or the reduction of oxidative stress and
27 ROS [85]. In leukaemia cells adipocytes promote survival by reducing oxidative stress induced
28 by daunorubicin and by radiation [18]. In this model, leukaemia cells promote a Nrf2-mediated
29 oxidative stress in adipocytes with an increase in glutathione synthesis which is partially
30 involved in adipocyte protection of leukaemia [18]. Secreted factor induced by oxidative stress
31 in adipocytes are involved in the reduction of oxidative stress induced by daunorubicin and by
32 radiation in leukaemia cells [18]. In gastric cancer cells, adipocyte proximity decreases

oxidative stress induced by cell detachment through increase in NADPH production and glutathione leading to anoikis resistance and metastasis in mice [86].

However fatty acids and FAO are also associated with enhanced oxidative stress and ROS production. Indeed adipocyte proximity induces fatty acid metabolic remodelling and increases ROS and lipid peroxidation in ovarian cancer cells. Although the mechanism was not described, the FAO and ROS production induced by adipocytes are associated with proliferation and resistance to carboplatin [87]. In prostate cancer cells intracellular ROS are also increased by adipocyte proximity and lipid transfer [70]. In this model ROS are produced by NOX5 which expression increases in presence of adipocytes and in human tumours close to adipose tissue. ROS production is associated with HIF-1 signalling, MMP14 expression and cancer cell invasiveness [70]. This lipid/ROS/HIF signalling pathway is potentiated by obese adipocytes [70]. In another model of prostate cancer it has been found that bone marrow adipocyte promotes the expression of glycolytic genes and glycolytic metabolism through the stabilisation of HIF-1 α [14]. HIF-1 α target genes are increased in prostate cancers in contact with bone adipocytes compared to subcutaneous tumours and also with high fat diet [14]. The same team demonstrated that ROS produced by adipocyte proximity are associated with overexpression of the oxidative stress enzyme Heme oxygenase 1 and ER-stress protein BIP in prostate cancer cells. These oxidative and ER-stress pathways promote cancer cell invasion and survival in bone [88].

4) Targeting fatty acid transporters

Since fatty acids play a major role on cancer progression, reducing fatty acid transport from adipocytes to cancer cells might be an attractive target for cancer therapy

For a long time it has been thought that, fatty acids diffuse freely through the plasma membranes and integrate to the phospholipid bilayer. However it is now clear that several membrane transporters are involved in lipid uptake such as CD36, Fatty Acid Binding Proteins (FABPs) and Fatty Acid transport proteins (FATs) which have all been found upregulated in cancer [89]. Furthermore, hypoxia, a common marker of tumour microenvironment has been linked with fatty acid transporter expression. Indeed the expression of several FA transporters is increased in hypoxia through HIF-1 α signalling like FABP7, FABP3 [76] and FABP4 [90].

Obviously fatty acid transporters have been involved in the interactions between adipocytes and cancer cells and represent interesting targets to reduce cancer promotion by adipose tissue. CD36 is one of the most characterized transporter in cancer cells. Interestingly CD36 is highly expressed in metastasis compared to primary tumour and its expression in metastasis-initiating cells is associated with metastasis dissemination and poor prognosis [91, 92]. It has been demonstrated that CD36 expression is induced in ovarian and breast cancer cells by adipocyte proximity [91, 93]. Lipid transport through CD36 is involved in the regulation of cancer cell metabolism and in the stimulation of cancer progression and metastasis [91, 93]. Interestingly the inhibition of CD36 expression or activity using blocking antibody or Sulfo-N-succinimidyl oleate reduces adipocyte-induced fatty acid uptake and subsequent migration, invasion, tumour growth and metastasis [91, 93].

The expression of FABP4 is also increased by adipocyte proximity in ovarian cancer [13, 87, 90]. Furthermore FABP4 expression is also upregulated in adipocytes by leukaemia cells [25]. Fatty acid transport through FABP4 participates in tumour growth, metastasis and resistance to carboplatin in ovarian cancer [13, 87] and survival in leukaemia [25]. Downregulation of FABP4 expression reduces leukemic cell viability and metastasis in ovarian cancer model [13, 87]. A small molecule has been developed to inhibit FABP4, BMS309403 and shows promising reduction in tumour growth in breast cancer and metastasis in ovarian cancer models [87, 94]. Unexpectedly FABP4 has also been linked with DNA methylation in acute myeloid leukaemia [95]. FABP4 activates NFκB/IL-6/STAT3 pathway leading to an increase in the expression of DNA methyltransferase 1. FABP4 induces tumour suppressor genes silencing by hypermethylation and leads to aggressive leukaemia [95]. High expression of FABP4 in acute myeloid leukaemia patients is associated with poor patient survival [95]. Interestingly high circulating FABP4 was found in obese breast cancer patients and promotes cancer stemness and aggressiveness [94]. FABP5 is also overexpressed by breast cancer cells in contact with adipocytes [78]. FABP5 is involved in fatty acid trafficking after ATGL-dependant lipolysis leading to increased migration and invasiveness by cancer cells [78]. High FABP5 expression in human breast cancer patients correlates with high grade and ER negative and triple negative tumours [78].

Lastly the fatty acid transport protein 1 (FATP1) has been involved in fatty acid transfer from adipocytes to melanoma cells [74]. In melanoma patients FATP1 expression is higher in metastasis close to subcutaneous adipose tissue compared to primary tumour. FATP1 inhibition by the small-molecule inhibitor Lipofermata decreases cancer cell growth and invasion [74]. In

clear renal cell carcinoma high FATP4 expression is found in cancer compared with normal tissue and is associated with poor prognosis [96].

Altogether these studies provide the proof of concept that fatty acid transport protein might be promising molecular targets to disrupt the interaction of tumours with the surrounding adipose tissue. This could be of major interest in the context of obesity. These proteins represent interesting avenues for diagnosis and also as therapeutic targets to reduce tumour growth and metastasis.

5) Modification of adipose tissue composition

The interaction between adipocytes and cancer cells involves mainly adipokines and fatty acids. Most of the studies have focused on fatty acid quantity, however the composition of adipose tissue and tumours in fatty acid length and unsaturation could have important role. Indeed the structural and signalling roles of fatty acids highly depend on the different lengths and degrees of unsaturation of fatty acids which are associated with oxidative stress, membrane fluidity and specific membrane domains as the lipid rafts [97]. The role of saturated and unsaturated fatty acids in cancer is still controversial. On one hand some studies show that a high level of saturated fatty acids in tumours are associated with aggressive breast cancers [98]. On the other hand other studies have shown that mono and polyunsaturated fatty acids are associated with cancer aggressiveness since higher polyunsaturated fatty acids level was associated with epithelial to mesenchymal transition in breast cancer cells [99]. In addition the expression of stearoyl CoA desaturase-1, enzyme catalysing the conversion of saturated fatty acids into monounsaturated fatty acids, have been found increased in different tumour type and associated with lipid metabolism and cancer progression [100].

Adipocyte proximity induces global change in lipid composition in cancer cells [87, 101], however mechanisms involving specific lipids have been demonstrated. Among fatty acids modified in cancer cells by adipocyte proximity, palmitic acid has been found increased and associated with high proliferation in melanoma cells [71]. It has been demonstrated that palmitic acid activates Akt survival pathway leading to increased proliferation of melanoma cells [71]. In gastric cancer cells, adipocyte proximity induces an increase in oleic acid which promotes cancer cell invasiveness through AKT activation [102]. Arachidonic acid found in conditioned media from adipocytes activates Akt in ovarian cancer cells and contributes to chemoresistance by inhibiting cisplatin induced apoptosis [103]. Arachidonic acid metabolite PGE2 was also

1 associated with chemoresistance in prostate cancer cells. PGE2 provided by adipocytes induces
2 prosurvival pathway and resistance to docetaxel [29]. Lastly it has been shown that mammary
3 adipose tissue contains lysophosphatidic acid (LPA) and lysophosphatidylcholine (LPC) for
4 which breast cancer cells express the receptor LPAR1/3 [104]. LPA activates Akt in cancer
5 cells leading to proliferation and protection from cell death [104].

6 Therefore the role of fatty acids in the interaction between adipose tissue and tumours seems
7 complex. The study of adipose tissue composition could be more interesting than its quantity
8 in the context of cancer progression as demonstrated by the lipidome analysis of breast and
9 prostate adipose tissue that can be used to predict the risk of cancer progression [105, 106].
10 Interestingly the lipid composition of adipose tissue correlates with past dietary intakes and
11 therefore can be changed by dietary supplements or dietary restrictions in lipids. For breast
12 cancer, it has shown that a low level of long-chain n-3 polyunsaturated fatty acids (PUFA,
13 eicosapentaenoic acid, EPA and docosahexaenoic acid, DHA) in breast adipose tissue is
14 associated with tumour multifocality [107], parameter associated with poor prognosis. In
15 prostate cancer, the fatty acid profile is differently associated with cancer aggressiveness in
16 Africane Caribbeans and Caucasians [106]. Among fatty acids associated with prostate cancer
17 aggressiveness, linoleic acid and eicosapentaenoic acid exert anticancer effects by reducing
18 cancer cell migration through regulation of calcium signalling and the EMT transcription factor
19 Zeb1 [108].

21 Conclusion

22 Altogether these studies highlight the recent demonstration of the reciprocal interaction of
23 adipose tissue with tumours. Among factors secreted by adipocytes, a wide range of adipokines
24 and fatty acids has been involved. All these studies have been done on in co-culture models or
25 using conditioned media. The recent development of 3D models will brings more information
26 about the relationship in complex tissues. These models have been developed for prostate
27 cancer using 3D culture of prostate cancer spheroids with bone marrow-derived adipocytes
28 [109] or with preadipocytes for breast cancer [110, 111]. First studies using 3D models have
29 confirmed the effects of adipocytes on cancer cells. In 3D cultures adipocyte proximity induces
30 a change in prostate cancer morphology and increases Akt signalling and proliferation [112].
31 In 3D model of breast tumour, leptin and leptin receptor was expressed and adipocyte proximity
32 induces major transcriptional changes in breast cancer cells including genes involved in cell

1 proliferation, angiogenesis and IL-6 pathway [110]. These 3D models including cells from
2 tumour microenvironment such as macrophages, endothelial cells or fibroblast will be useful to
3 better characterize the effects of adipose tissue proximity on tumours. In addition, studies
4 investigating the effects of fatty acid composition on cancer cells are needed. For example
5 Raman microspectroscopy have been used to investigate lipid droplet composition in prostate
6 cancer cells [113].

7 Although several mechanisms involving adipokines or lipids have been discovered to play a
8 major role on cancer progression some studies are still needed to understand the role of fatty
9 acid transport and composition in order to propose innovative therapies, based on nutritional
10 adjuvant interventions, or on the targeting of new signalling pathways to interfere with this
11 cellular cooperation.

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Finally, we wish to apologize to all researchers whose relevant works, owing to the limited length of this article format, could not be cited in this review.

Figure legend

Fig1: Molecular interplay between adipocytes, cancer and non-cancer cells in tumours. Cancer cells induce an activated phenotype in adipocytes characterized by delipidation and increase in the secretion of pro-inflammatory adipokines (blue ↓ and ↑). These cancer-associated adipocytes promote tumour growth, metastasis and treatment resistance through the secretion of a wide range of adipokines and metabolites including fatty acids. The orange arrows indicate the adipocytes secretions and the black arrows the main mechanisms demonstrated in cancer cells. In addition, cancer-associated adipocytes also act on tumour macrophages, natural-killer cells and endothelial cells (indicated in green). LD: lipid droplet, FA: fatty acid, EV: extracellular vesicles, TF: transcription factor, ROS: reactive oxygen species, TG: triglyceride, PL: phospholipid.

Tissue	Secretion involved	Molecular mechanism	Effect on tumour	Reference
Breast	FA	FA uptake	proliferation, migration, invasion	[93]
	FA	metabolic remodelling, EMT	invasion, metastasis	[69]
	FA (LPA)	pAkt	proliferation, survival	[104]
	FA and other	metabolic remodelling	proliferation (FA), migration (other)	[79]
	IL6, MMP9, MMP11, PAI	partial EMT	invasion, metastasis	[12]
	Resistin	TLR4/NF- κ B/STAT3 pathway, EMT	migration, invasion, anoikis resistance, tumour growth	[54]
	Adipsin	C3a/C3aR	proliferation, sphere forming ability, tumour growth	[55]
	IL-6	DNA damage response	radioresistance	[53]
	IL-6 MCP-1	EMT	migration	[50]
	IL6, Leptin	JAK/STAT3 Akt PLOD2	migration, invasion, EMT, tumour growth and metastasis	[52]
	Leptin	macrophages migration	tumour growth	[30]
	Leptin		resistance to lapatinib	[60]
	IGFBP2	MMP2, Ecadherin	migration, invasion	[57]
	Lipocalin 2		proliferation, migration	[56]
	adiponectin	autophagy	invasion	[49]
	GDF15	Akt	resistance to trastuzumab	[60]
	β -hydroxybutyrate	epigenetic	tumour growth	[63]
	uPa	pAkt	migration	[6]
	?	metabolic remodelling,	proliferation, migration	[80]
Leukemia	FA	metabolism	survival, tumour growth	[25]
	FA	metabolism	survival, chemoresistance	[24]
	FA, Adiponectin	AMPK, metabolism	survival	[82]
	Leptin	?	proliferation, migration	[36]
	SDF1	?	migration, chemoresistance	[61]
	soluble factors	ROS	chemoresistance	[18]
	?	?	chemoresistance	[84]
	?	?	chemoresistance	[114]
Ovarian	FA	metabolism	migration, invasion, metastasis	[13]
	FA	Ca dependant activation of SIK2, metabolism	metastasis	[81]
	FA (arachidonic acid)	Akt, cisplatin-induced apoptosis	chemoresistance	[103]
	FA	FABP4 expression, metabolism, ROS	metastasis, chemoresistance	[87]
	FA	CD36, metabolism	invasion, migration, adhesion, clonogenicity, metastasis	[91]
	IL6	STAT3	chemoresistance	[51]

	Exosome	miR-21	chemoresistance	[68]
Prostate	FA (palmitic acid)	ROS, metabolism	invasion	[70]
	FA (PGE2)	HIF	chemoresistance	[14, 29]
	osteopontin	metabolism	proliferation, migration, invasion	[59]
	Leptin and IL6	JAK/STAT	immune escape	[32]
	Leptin	JNK	proliferation of androgen independent cells	[37]
	?	metabolism, HIF	migration	[14]
	?	ER stress, ROS	survival, invasion, tumour growth	[88]
Melanoma	FA (palmitic acid)	Akt, metabolism	proliferation, tumour growth	[71]
	FA	metabolism, FATP expression	proliferation, invasion, metastasis, tumour growth	[74]
	Leptin	Akt, mTor, ERK/MEK	chemoresistance	[42]
	exosome	metabolism	migration, invasion, metastasis	[65]
	extracellular vesicles	metabolism	migration	[64]
	?	Akt, mTor	proliferation, migration, invasion	[58]
Hepatocarcinoma	Adiponectin	AMPK, C-Jun	apoptosis	[47]
	Adiponectin deficiency	inflammation	tumour growth	[46]
	Adiponectin, Leptin	Adiponectin antagonizes leptin activation STAT3, Akt	proliferation, migration, invasion, tumour growth	[38]
	Leptin	STAT3, hTERT	proliferation, invasion	[39]
	exosome	microRNA-23a/b, HIF	tumour growth, chemoresistance, migration, proliferation	[67]
	exosome	?	tumour growth, angiogenesis macrophage infiltration, proliferation , migration	[17]
Pancreas	FA	?	migration, invasion, EMT and gemcitabine resistance	[15]
	glutamine	?	proliferation	[22]
	?	?	migration	[23]
Colon	FA (oleic acid)	metabolism, autophagy, EMT	survival, migration, tumour growth	[72]
	?	Akt, mTor	proliferation, migration, invasion	[58]
Gastric	FA (oleic acid)	Akt	invasiveness	[102]
Myeloma	adipsin, leptin	autophagy activation and apoptosis reduction	chemoresistance	[43]
Lung	exosome	MMP3, MMP9	migration, invasion, metastasis	[66]

Table 1: Molecular mechanisms involved in the effects of adipocytes on cancer cells. Fatty acid: FA

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