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1 **Drilling for oil: tumor-surrounding adipocytes fueling cancer**

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Abstract

Over the past decade, it has become apparent that metabolic reprogramming is a key event in tumor progression. The tumor microenvironment is a source of metabolites for tumor cells. Lipid filled mature adipocytes are frequently found in the proximity of invasive human tumors and release free fatty acids through lipolysis. These free fatty acids are taken up by tumor cells and used to promote tumor progression by mechanisms that include mitochondrial fatty acid oxidation. This review discusses recent advances in our understanding of this metabolic symbiosis between adipocytes and cancer cells and underlines the differences in this metabolic crosstalk between the varying types of cancers and their localization.

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Tumor microenvironment: a source of metabolites for cancer cells

Metabolic reprogramming is a hallmark of cancer, as defined in 2011 by Hanahan and Weinberg [1], and is a very active research field in the development of new anti-cancer drugs. The metabolic phenotype of cancer cells depends on intrinsic factors such as genetic alterations, specificities of tissue origin and tumor state, but also on extrinsic factors that comprise interactions with the tumor microenvironment (TME) [2]. The metabolic flexibility of cancer cells allows them to use different metabolites to produce energy, maintain their redox status and obtain intermediate metabolites needed for synthesis of biomolecules and cell signaling (for review [2]). The TME is an important source of metabolites that benefit cancer cells, referred to here as metabolic symbiosis (Box 1). These metabolites provided by the TME are used by cancer cells to promote tumor progression [2]. Besides glucose and glutamine, the role of lipids in cancer progression is increasingly highlighted [3]. Initially, while most attention was focused on *de novo lipogenesis* (using glucose and glutamine as substrates), it is now apparent that cancer cells can acquire exogenous free fatty acids (FFA). Recent studies have shown that exogenous FFAs, rather than *de novo lipogenesis* appear to be the predominant lipid source for cancer cells [4-6].

In the TME, the mature adipocytes -the major component of white adipose tissue (WAT)- are a tremendous reservoir of lipids for cancer cells. Distributed throughout the body, WAT is found in close proximity to various invasive solid cancers in humans such as breast, prostate, colon and kidney cancers and melanoma [7-10]. WAT is specialized in storing and delivering, when needed, energy to demanding tissues (such as liver, muscle or heart). Such functions are ensured by metabolically active cells, the adipocytes. Additionally, WAT is an important endocrine organ that secretes hormones, cytokines, chemokines and growth factors, termed adipokines [11]. WAT has recently emerged as a main actor in tumor progression [7-9]. Several soluble factors (such as chemokines or pro-inflammatory cytokines) have been involved in the cross-talk between tumor cells and surrounding WAT, of which some have also been secreted by other components of the TME (such as cancer-associated fibroblasts or tumor-associated macrophages) [12]. One of the most specific and emerging mechanisms regarding the role of WAT in the TME involves the ability of cancer cells to advantageously exploit the nourishing role of adipocytes. This metabolic symbiosis has now been demonstrated in a wide range of models such as breast, ovarian and prostate cancers and melanoma [13-16]. The known

1 association between obesity and cancer mortality clearly reinforces the interest for this research
2 area [17]. Obesity is characterized by increased adipose depot size, associated to changes at
3 tissue level, including metabolic dysfunctions and is characterized by a sub-inflammatory state
4 [18]. Investigations are now beginning to be conducted on whether this state affects metabolic
5 symbiosis.

6 However, the simple concept of using lipids to provide energy to tumor cells in order to sustain
7 tumor progression is more complex than we initially thought. In this review, we will discuss
8 how tumor cells force adipocytes to deliver lipids and how these lipids promote tumor
9 progression. A particular focus will be on the differences observed in this metabolic symbiosis
10 depending on the cancer type and localization.

11

12 **Tumor-surrounding adipocytes: a source of lipids for tumor cells**

13 **Adipocytes are a major component of the tumor microenvironment**

14 Mature adipocytes are one of the main components of many TMEs. WAT is found in close
15 proximity to invasive cancers such as breast (mammary adipose tissue, MAT), prostate
16 (periprostatic adipose tissue, PPAT), colon (visceral adipose tissue, VAT) or melanoma
17 (subcutaneous adipose tissue, SAT) and cancer cells come into contact with WAT upon
18 crossing the basement membrane. Adipocytes are also present in the TME of hematological
19 malignancies such as acute myeloid leukemia (AML) and multiple myeloma (MM). In fact, the
20 bone marrow (BM) contains bone marrow adipocytes (BM-Ad) that represent around 10% of
21 the total fat mass [19]. In addition, during the metastatic process, solid tumors might localize
22 to adipocyte-rich microenvironments such as the omentum, a large intra-peritoneal fat pad that
23 extends from the stomach and covers the bowel [14]. Omental metastases are frequently
24 observed for ovarian, gastric and pancreatic cancers. Furthermore, solid tumors that frequently
25 metastasize to the bones, such as prostate, breast, lung, kidney or melanoma are found in near
26 proximity to BM-Ad. Finally, hematological malignancies also disseminate to VAT, at least in
27 mouse models [20].

28

29 **The delipidation of adipocytes is observed at the invasive front of human tumors**

30 Adipocytes neighboring cancer cells display profound phenotypic and functional alterations
31 (Figure 1). Histological images of solid tumors have consistently shown a decrease in both
32 number and size of adipocytes, located at the invasive front compared to adipocytes distant
33 from the tumor (for review [7, 9, 21]). Moreover, at the tumor center, there are elevated
34 fibroblast-like cells suggesting a “dedifferentiation” of adipocytes induced by cancer cells [7,

1 9, 21]. Using a coculture system, where the two populations are separated by an insert, we found
2 that adipocytes cocultivated with breast tumor cells for 3 to 5 days exhibited a delipidation and
3 decreased expression of adipocyte markers such as Ap2 (FABP4), adiponectin, and resistin
4 [22]. Cocultivated adipocytes exhibited an activated phenotype marked by up-regulation of pro-
5 inflammatory cytokines such as tumor necrosis factor α (TNF α), interleukin (IL)-6, and IL1 β
6 [22] as well as proteins involved in extra-cellular matrix remodeling like matrix
7 metalloproteinase 11 (MMP11) [22, 23]. Such activated phenotypes have been found *in vivo* at
8 the invasive front of human breast tumors [22, 23]. Collectively, these data show that adipocytes
9 are not inert to the surrounding tumor and exhibit specific traits, hence we have named them
10 Cancer-Associated Adipocytes (CAAs). These results initially obtained in breast cancer (BCa),
11 have been confirmed in other models including, prostate [13] and ovarian [14] cancers as well
12 as melanoma [24]. In fact, it is now acknowledged that, in all solid tumors, the invasion of
13 proximal adipose tissue by tumor cells leads to profound delipidation of adipocytes, which
14 could ultimately result in the accumulation of fibroblast-like cells, contributing to the so-called
15 desmoplastic reaction—a dense fibrous tissue present around the tumor [7, 9, 21]. Upon exposure
16 to cancer cells *in vitro*, adipocytes undergo sequential morphological changes: first marked by
17 a decrease in adipocyte size and lipid content as seen above (CAAs) and next by acquiring a
18 fibroblast-like morphology (cells that we named Adipose-Derived Fibroblasts, ADFs) [25].
19 Tumor cells cocultivated with ADFs in two-dimensional or spheroid culture displayed
20 increased invasive capabilities and the presence of ADFs was confirmed in clinical specimens
21 of breast cancer [25]. Together, these results underline the extensive phenotypic changes of
22 mature adipocytes that surround cancer cells.

23

24 ***Mechanisms of lipid release from tumor-surrounding adipocytes***

25 The occurrence of CAAs and ADFs is the result of at least two processes, dedifferentiation and
26 induction of lipolysis. In both cases, the characterization of the mechanisms involved is
27 incomplete. In BCa, we have shown a reactivation of the Wnt/ β -catenin pathway in mature
28 adipocytes, in response to tumor-cell-secreted Wnt3a [25]. This has also been demonstrated in
29 CAAs in pancreatic cancer [26]. It is known that this pathway negatively regulates adipose
30 progenitor differentiation along the adipose lineage [25]. So, Wnt/ β -catenin pathway activation
31 is used to induce a dedifferentiated state of mature adipocytes that appear to be highly plastic
32 [25, 26]. An important mechanism contributing to the delipidation of CAAs is the ability of
33 tumor cells to activate lipolysis in adipocytes [5, 13-15, 27-30]. Adipocytes are cells dedicated
34 to storing and releasing lipids, an energy-dependent process known as lipolysis (Box 2). The

1 breakdown of triglycerides (TG) involves the intervention of three consecutive lipases ATGL
2 (Adipose Triglyceride Lipase), HSL (Hormone-sensitive lipase) and MAGL
3 (Monoacylglycerol lipase) ultimately leading to the release of FFA and glycerol. Of note,
4 palmitic, oleic and linoleic acids are the main FFA released through lipolysis [31] but the nature
5 of the FFA released could be different depending on the adipose depot (MAT, PPAT, VAT or
6 SAT) or in obese compared to lean subjects [32]. Release of these FFA is observed when *in*
7 *vitro* differentiated adipocytes or isolated primary adipocytes are incubated with conditioned
8 medium from breast, prostate or ovarian cancer cell lines [5, 13-15]. In addition to acute
9 stimulation of lipolysis through phosphorylation and activation of HSL [15, 27, 28], tumor cells
10 can extend lipolysis activation through upregulation of the expression of HSL [8, 29] and/or
11 ATGL [28-30]. While it is now admitted that tumor induced lipolysis occurs in adipocytes, the
12 lipolytic factor(s) involved remain(s) to be determined (Figure 1). Catecholamines are major
13 hormones involved in lipolysis induction and have been implicated in the activation of lipolysis
14 by ovarian cancer cell lines [14] but not in BCa and prostate cancer (PCa) models [13, 15]. Pro-
15 inflammatory cytokines are also able to cause lipolysis of WAT, a pathway that has been
16 involved in the disappearance of adipose mass during cancer cachexia [33]. In mouse models,
17 Ye *et al* proposed that the lipolysis induced by leukemic stem cells, relocated to VAT, might
18 be due to the secretion of pro-inflammatory cytokines, such as IL-1 α , IL-1 β , Colony
19 Stimulating Factor 2 (CSF2) and TNF α despite no direct demonstration of this effect having
20 been provided [20]. Finally, signals emanating from tumor cells could be contained in tumor-
21 released extracellular vesicles (EV). In pancreatic cancer, EV-contained adrenomedullin lead
22 to phosphorylation and activation of HSL [27]. Thus, even if some tumor secreted factors have
23 been proposed to induce lipolysis in adipocytes, these results should be interpreted with caution.
24 The lipolytic signals could be different depending on the tumor considered and further studies
25 are clearly needed to clarify this issue.

26 More recently, studies have proposed that lipid transfer from adipocytes to cancer cells could
27 also happen through EV. We have recently demonstrated that mature adipocytes liberate
28 continuously, independently of lipolytic stimuli, EV-containing FFA [34] which are taken up
29 by tumor cells (see below). The liberation of EV-containing FFA is amplified
30 by α -adrenergic stimulation suggesting that this process might also be involved in lipid
31 transfer upon energy deprivation [34]. EV are known to transport a large panel of lipid species
32 such as sphingomyelin, cholesterol, lysophosphatidylcholine and eicosanoids [35, 36] whose
33 implications in adipocytes/cancer crosstalk have never been explored. Finally, Ferrante's team
34 recently showed that adipocytes release EV containing small pieces of lipid droplets (composed

1 of TG and cholesterol ester) that are directly transferred to macrophages in WAT [37]. Again,
2 although this mechanism has not been investigated in cancer, all these innovative studies
3 highlight that the EV “route” should not be neglected in the context of metabolic symbiosis.

4 5 **Are BM-Ad transformed into CAAs by tumor cells?**

6 As mentioned above, the primary tumor site for hematological malignancies and metastatic site
7 for some cancers is the BM which contains BM-Ad. When considering BM biopsies, the
8 delipidation of BM-Ad at close proximity of cancer cells is not clear. In MM, an increase in the
9 number of preadipocytes as well as increased BM-Ad size have been reported in comparison to
10 control subjects [38]. A recent study challenged these results by showing a decrease in
11 adipocyte number with only a slight decrease in BM-Ad area in patients with evolutive disease
12 when compared to controls [39]. While BM-Ad certainly plays a role in the development of
13 MM, favoring local dissemination and growth [38] or the occurrence of osteolytic lesions [39],
14 the key features of CAAs are not observed *in vivo*. In AML, slightly different results have been
15 observed. In a study, comparing control samples to those of patients exhibiting refractory
16 diseases or in remission (70 samples in each group), the patients with active disease were
17 reported to have an increase in the number of small adipocytes yet lacked significant changes
18 in the representation of medium/large BM-Ad [40]. By contrast, a dramatic decrease in
19 adipocyte size was observed in VAT colonized by AML cells *in vivo* [20] or when AML cells
20 were engrafted in SAT [41]. Using human samples and mouse models, Boyd *et al* reported
21 decreased adipocyte size and frequency in the presence of AML cells in haematopoietically
22 active “red” marrow whilst adipocytes from haematopoietically inactive “yellow” marrow were
23 unaffected [41]. The observed changes in BM-Ad favored leukemic cell outgrowth while
24 negatively affecting normal hematopoiesis [41]. Absence of decrease in the medium/large
25 adipocytes [40] and the elective decrease of BM-Ad in the “red” marrow area [41], where there
26 is a constant accumulation of newly formed adipocytes [42], suggests that AML cells are more
27 likely to induce a defect of adipogenesis rather than an activation of a lipolytic process in
28 already-formed mature adipocytes. These results are not surprising when the physiology of BM-
29 Ad is considered. Recent reports highlight that BM-Ad are deficient in lipolysis in both mouse
30 [43] and human [44] models in accordance with the fact that this fat depot is not sensitive to
31 energy deprivation [45]. In addition, we demonstrated that the bone marrow mesenchymal stem
32 cells (MSC), differentiated *in vitro* using classical protocols for *in vitro* adipogenesis, do not
33 recapitulate the metabolic phenotype of primary human BM-Ad and display effective lipolytic
34 activity [44]. Therefore, all studies demonstrating a lipid transfer through FFA release between

1 tumor cells (both hematological malignancies and solid tumors) and *in vitro* differentiated MSC
2 should be interpreted with caution [28, 29, 46, 47]. In conclusion, robust results show the
3 occurrence of a lipolytic process with liberation of FFA in various AT at the vicinity of solid
4 tumors, but metabolic symbiosis, if it exists, might be of a different nature in the BM.

6 **Transfer and fate of lipid in tumor cells, a matter of tumor type?**

7 We have seen that tumor-surrounding adipocytes are able to release FFA [5, 13-15, 48] or EV-
8 containing FFA [34]. We will now describe how these lipids are transferred into tumor cells,
9 their metabolic fate inside tumor cells and how they promote tumor progression (Box 3).

11 **Transfer of lipids**

12 Once released by adipocytes, FFA are transferred to cancer cells. This transfer has been
13 demonstrated in several models using isotopically labeled adipocytes [5, 15] or staining with
14 fluorescent dyes [14, 24, 34, 48-51]. Down-regulation of ATGL or HSL expression in
15 adipocytes inhibit the accumulation of lipids in cocultivated BCa cells as compared to control
16 adipocytes [5]. This decrease in lipid transfer is associated to a decreased effect of adipocytes
17 on BCa cell proliferation and migration, thereby demonstrating that adipocytes alter cancer cell
18 behavior through FFA release [5]. Identifying the membrane transporters involved in FFA
19 uptake is another approach to demonstrate their direct implication in tumor progression. Several
20 fatty acid transporters have been involved in FFA transfer into cancer cells suggesting cancer
21 type differences. CD36 (FAT, Fatty acid translocase), has been proposed as a prognostic marker
22 in various cancers, mostly of epithelial origin (breast, prostate, ovary and colon) as well as in
23 hepatic carcinoma and gliomas [52-55]. Ovarian cancer cells co-cultured with primary human
24 omental adipocytes express high levels of CD36 and down-regulation of CD36 expression or
25 function prevented the deleterious effect of adipocytes on tumor progression [56]. Similar
26 effects are observed in PCa when CD36 is inhibited [55]. The role of long-chain fatty acid
27 transport protein (FATP), in particular FATP1, has been shown to transfer FFA from adipocytes
28 to melanoma cells. Pharmacological inhibition of FATPs with the small molecule Lipofermata
29 abrogates this transfer and reduces melanoma growth and invasion [24]. Oncomine analysis
30 shows that high FATP1 expression is correlated with decreased survival in melanoma [24]
31 while it is not the case for PCa [55]. Finally, fatty acid binding proteins (FABPs), small proteins
32 that bind FFA and facilitate their intracellular transport, have also been involved in lipid transfer
33 from adipocytes to ovarian cancer cells. Nieman and collaborators were the first to show that
34 FABP4 is overexpressed in ovarian cancer cells cocultivated with adipocytes and its inhibition

1 reduced both lipid accumulation in cancer cells and adipocyte-mediated invasion *in vitro* or
2 metastasis *in vivo* [14]. Other FABPs are likely to facilitate the uptake of exogenous FFA into
3 cancer cells, in particular FABP5 and FABP7 as they influence lipid uptake in BCa cell lines
4 [57, 58]. The FFA contained in EV are also taken up by tumor cells [34]. We can therefore
5 conclude that several transmembrane and intracellular transporters are involved in lipid
6 transfer. Once clinically validated, targeting FFA uptake may be an effective strategy for
7 treating invasive solid tumors that evolved in an adipocyte-rich microenvironment.

9 **Fatty acid storage and mobilization**

10 Once taken up, FFAs can act directly as substrates for a range of metabolic pathways including
11 mitochondrial oxidation (as discussed below) or converted into neutral lipids (mainly TG) and
12 stored in small lipid droplets (LD) as observed in breast [5, 15], prostate [4, 13, 55] and ovarian
13 [14] cancers and melanoma [16, 24, 34] to avoid cytotoxicity induced by FFA [59]. The ability
14 of tumor cells to progressively liberate FFA, locally or at distance, is key to the support of tumor
15 progression. Recent evidence showed that cancer cells possess lipolytic activity (Box 3).
16 Expression of ATGL is upregulated in BCa cells cocultivated with adipocytes *in vitro* and in
17 cancer cells that are in close contact to adipocytes at the invasive front of human BCa *in vivo*
18 [15]. Decreasing ATGL expression in cocultivated BCa cells impaired lipolysis and reduced
19 the pro-invasive effect of adipocytes [15]. A higher ATGL expression was also observed in
20 pancreatic tumors from obese patients (with increased visceral adiposity) and exhibiting higher
21 tumor-surrounding desmoplasia [60]. It has to be noted that, independently of coculture of
22 adipocytes, the role of ATGL in tumor progression is largely debated with elevated expression
23 in some tumor types whereas down-regulation has been reported in others (for review [61]).
24 Very few data are available on the function of HSL in the context of adipocyte/cancer cell
25 crosstalk, with the exception of its upregulation in BCa cells when cocultivated with adipocytes
26 *in vitro* [15]. Compelling arguments demonstrate that MAGL, the enzyme involved in the last
27 step of lipolysis, is overexpressed in aggressive cancers including melanoma, ovarian, prostate
28 and breast cancer [62, 63]. These initial studies by Nomura *et al* have clearly highlighted that
29 FFA, taken up or newly synthesized in cancer cells, are immediately converted into neutral lipid
30 stores and that their intracellular utilization is dependent on their release [62, 63]. The
31 importance of MAGL in cancer progression has been confirmed by other studies [64, 65]. The
32 regulation of MAGL function and expression in cancer cells cocultivated with adipocytes has
33 only been studied once and showed a slight upregulation of its expression in cocultivated cells
34 [15].

1 Beside classic lipolysis, lipophagy defined by the lysosomal degradation of TG carried out by
2 lysosomal acid lipase, is an alternate mechanism allowing TG hydrolysis which was initially
3 demonstrated in hepatocytes [66]. Some preliminary studies suggest that lipophagy might be
4 used by cancer cells [67]. In colon cancer, mobilization of intracellular lipid stores in cells
5 cocultivated with adipocytes result from such a process [48]. We recently demonstrated that
6 adipocyte EV-derived FFA taken up and stored in LD by melanoma cells are released by
7 lipophagy and not by lipolysis [34]. In conclusion, LD act as switches that coordinate lipid
8 storage and liberation in order to support cancer progression. The mechanisms involved are
9 under characterization and are accompanied by new and exciting potential therapeutic targets
10 [68].

11

12 **Fatty acid oxidation: coupled or non-coupled to ATP production?**

13 Adipocyte-released FFA taken up by cancer cells or released from TG stores can be transferred
14 to mitochondria to be oxidized, a metabolic pathway called fatty acid oxidation (FAO) (Box 3).
15 The last decade of studies has underpinned the role of this metabolic pathway in cancer [69].
16 Coculture with adipocytes lead to increased FAO in an array of cancers including melanoma
17 [24], ovarian [14], prostate [4, 13], breast [5, 15], colon [48] and gastric [51] cancers. The
18 entry of FFA into mitochondria is dependent on carnitine palmitoyltransferase 1 (CPT1). The
19 expression of the CPT1a isoform is increased by adipocytes in breast [5, 15] and ovarian [14]
20 cancers. Moreover, increased mitochondria biogenesis is observed in BCa cells cocultivated
21 with adipocytes [15]. All these mechanisms are likely to contribute to increased FAO. Treating
22 BCa cells with a pharmacological inhibitor of CPT1a, etomoxir (ETO), in addition to down-
23 regulating its expression, inhibits the invasive capacities of the cancer cells *in vitro* as well as
24 their metastatic capacities *in vivo* [15]. Pharmacological inhibition of CPT1 also restores the
25 sensitivity of colon cancer to antiangiogenic therapies [70]. In fact, treatment-induced hypoxia
26 increases the expression of lipid transporters and FAO-related genes that rescues cell death only
27 in tumors adjacent to adipose depots [70]. These results directly demonstrate the link between
28 the FAO activity and effects of adipocytes. By contrast, while coculture increases FAO in PCa
29 cells, only a slight decrease of invasiveness of cocultivated tumor cells was observed in ETO-
30 treated cells [13]. These results demonstrated that transferred FFA are not only used for FAO
31 but promote invasive capacities by different mechanisms (see below). Regarding EV, exposure
32 of melanoma cells to adipocyte-secreted EV (Ad-EV) was found to induce lipid accumulation
33 and stimulates FAO and mitochondrial biogenesis [16, 34]. Ad-EV contains FFA as well as
34 proteins involved in FAO [e.g., HADHA (trifunctional enzyme subunit alpha) and HCDH

1 (Hydroxyacyl-coenzyme A dehydrogenase)], thus providing both the enzyme and substrate to
2 tumor cells, in order to increase their migratory and invasive capacities [16, 34]. In obesity, the
3 heightened effect of Ad-EV on melanoma aggressiveness does not depend on increased
4 expression of FAO-related enzymes but is due to an increased content and transport of FFA
5 [16, 34]. As EV diffuse through tissues and circulate throughout the organism, they may
6 influence tumors not only at proximity to AT, but also at distance to help establish metastatic
7 niches. Further experiments are needed to explore this promising hypothesis.

8 Convincing results have now been obtained in a wide range of models that link coculture with
9 adipocytes or exposure to Ad-EV to increased FAO, a metabolic remodeling that promotes
10 cancer progression *in vitro* and *in vivo*. A question remains: how does increased FAO promote
11 cancer progression?

12 FAO generates coenzymes used by the electron transport chain to produce ATP (Box 3). FAO
13 produces twice as much ATP per mole as oxidation of glucose [69]. In the first article reporting
14 a lipid transfer between tumor-surrounding adipocytes and cancer cells, Nieman's team
15 proposed that the increased FAO is used for energy production in order to promote tumor
16 growth, despite ATP production not being measured [14]. This concept, validated in wider
17 studies, directly demonstrates enhanced ATP production in melanoma [24, 34], omental
18 metastasis of gastric cancer [51], and in colorectal cancer growing in an adipose environment
19 [70]. Increased ATP production stimulates tumor growth and invasion [24, 34], promotes
20 resistance to cell-death induced anoikis [51] and confers resistance to antiangiogenic drugs [70]
21 (Figure 2A).

22 However, in other models, FAO could be uncoupled with ATP production, despite the fact that
23 inhibiting FAO by ETO inhibits invasion [15]. In BCa cells cocultivated with adipocytes, a
24 decrease in mitochondrial respiration associated to decreased ATP content was observed [15].
25 This uncoupling was due to enhanced expression of the uncoupling protein 2 as well as the
26 ATPase inhibitory factor 1 [15]. Adipocytes also induced FAO without increasing respiration
27 or ATP production in CD36+ leukemic cells that colonized VAT [20] or in cocultivated colon
28 cells [48]. Thus, in these models, increased FAO by adipocytes was not used for ATP
29 production to promote invasive capacities [15], growth [48] or to confer drug resistance [20].
30 Increased FAO associated to decreased mitochondrial respiration could therefore contribute to
31 accumulation of acetyl-CoA. Increasing evidence demonstrates the links between acetyl-CoA,
32 histone acetylation and control of gene expression [71, 72]. Thus, this FAO-derived product
33 could contribute to epigenetic changes favoring the pro-invasive effect of adipocytes [15, 20,
34 48]. Moreover, acetyl-CoA is also involved in the synthesis of ketone bodies, FFA and

1 cholesterol [73] which could also influence tumor behavior. FAO also contributes to the
2 NADPH pool, critical for regeneration of the GSH antioxidant system to maintain redox balance
3 and survival [69, 74] (Figure 2B).

4 5 **Other effects of FFA taken up by tumor cells**

6 As mentioned above, we showed that FAO induced by coculture with adipocytes is not always
7 the key event responsible for the increased aggressiveness of cancer cells. This is particularly
8 the case in PCa where FFA taken up by tumor cells increase the expression of the pro-oxidant
9 enzyme NADPH oxidase 5 (NOX5) leading to elevated reactive oxygen species (ROS) [13].
10 ROS subsequently activate the HIF1/MMP14 (Hypoxia Inducible Factor 1/Matrix
11 Metalloproteinase 14) signaling pathway, which is responsible for the increased tumor cell
12 invasion induced by adipocytes (Figure 2C). Interestingly, this study is one of the first to show
13 that the metabolic symbiosis might be magnified by obesity [13]. In obesity, tumor-surrounding
14 adipocytes, isolated from PPAT of lean and obese patients, are more prone to deliver lipids to
15 tumor cells and to activate the NOX5/HIF1/MMP14 signaling pathway. Finally, the expression
16 of NOX5 and MMP14 is upregulated at the invasive front of human tumors where cancer cells
17 are in close proximity to adipocytes and this process is amplified in obese patients, underlining
18 the clinical relevance of our results. Lastly, FFA can also bind to transcriptional factors,
19 regulating their function and leading to a transcriptional regulation of cancer cells towards
20 acquisition of more aggressive traits (for review [75]). These numerous studies emphasize that,
21 despite increased FAO seeming like the most evident pathway explaining the link between lipid
22 transfer and tumor progression, other mechanisms might exist. The different mechanisms
23 coupling FFA transfer to tumor progression are summarized in Figure 2.

24 25 **Concluding Remarks**

26 Adipocytes are major components of the TME in a large number of cancers and their role in
27 tumor progression is increasingly recognized. Although growing evidence shows that cancer
28 cells are likely using this lipid reservoir in order to promote tumor progression, several
29 questions remain unanswered (see Outstanding Questions). Most studies reported in this review
30 use adipocytes obtained from pre-adipocyte cell lines or isolated adipose progenitors
31 differentiated *in vitro*, very useful as “first step” models to decipher adipocyte-cancer cell
32 crosstalk. However, these models do not completely reflect the physiology of mature adipocytes
33 within the organism. Additionally, accumulating work pinpoints the existence of adipose depots
34 specificity in terms of secretion patterns and metabolic behavior, as exemplified here in BM-

1 Ad. Further experiments are clearly needed using primary adipocytes isolated from specific
2 adipose depots surrounding each tumor type. Current studies also suggest that cancer type
3 matters for the transfer and fate of FFA delivered by adipocytes, an issue that needs to be
4 addressed more systematically. Finally, it is important to consider that evidence of this
5 metabolic symbiosis existing in animal and human tumors *in vivo*, or amplified in an obese state
6 is still sparse. Once well established, the metabolic symbiosis between cancer cells and
7 adipocytes will undoubtedly offer new therapeutic avenues in the treatment of cancer in obese
8 and non-obese patients.

9 10 **Box 1: Metabolic symbiosis in the TME**

11 Sonveaux and colleagues were the first to demonstrate metabolic cooperation within the TME.
12 Indeed, they showed that, in hypoxic regions, cancer cells use glucose to produce lactate which
13 is then transferred and used in cancer cells present in well-oxygenated regions [76]. Then,
14 Lisanti's group proposed that cancer-associated-fibroblasts (CAFs) displayed increased
15 anaerobic glycolysis in response to tumor cell signaling leading to lactate release which is in
16 turn used in tumor cells, a process known as the "Reverse Warburg effect" [77]. Lactate taken
17 up by oxidative cancer cells is converted into pyruvate to fuel tricarboxylic acid (TCA) cycle
18 and this effect is associated with increased tumor growth [76, 77]. More recently, beta
19 hydroxybutyrate, a ketone body produced from acetyl CoA, was also shown to be involved in
20 the metabolic crosstalk between BCa cells and adipocytes. Indeed, mammary adipocytes release
21 beta hydroxybutyrate which is taken up by cancer cells and promotes tumorigenesis through
22 regulation of histone acetylation and gene expression [78]. In addition to lactate and beta
23 hydroxybutyrate, cells present in the TME can release amino acids. Ovarian cancer cells induce
24 glutamine release by CAFs which is transferred in cancer cells to promote tumor growth [79].
25 Adipocytes can also release glutamine which is taken up by cancer cells to support proliferation
26 in pancreatic cancer [80] or to induce resistance to chemotherapy in leukemia cells [81]. Other
27 amino acids such as alanine, arginine and cysteine are involved in the metabolic symbiosis in
28 the TME (for review [82]). Importantly, EVs released by cells of the TME can also carry
29 metabolites including amino acids, lipids and TCA cycle intermediates that are utilized by
30 cancer cells to promote tumor growth [83].

31 32 **Box 2: Regulation of lipolysis**

33 Lipolysis corresponds to the hydrolysis of TG in three sequential steps producing glycerol and
34 three molecules of FFA. The first step consists of the hydrolysis of TG to DG and FFA carried

1 out by ATGL (Adipose Triglyceride Lipase), then HSL (Hormone-sensitive lipase) converts
2 DG into MG and FFA and lastly MG are hydrolyzed into glycerol and FFA by MAGL
3 (Monoacylglycerol lipase) [84].
4 Lipolysis is activated in the fasted state by catecholamines (adrenaline and noradrenaline). The
5 latter activates beta-adrenergic receptors which promote adenylyl cyclase activation and the
6 production of cyclic adenosine monophosphate (cAMP) followed by protein kinase A (PKA)
7 activation. Natriuretic peptides (atrial natriuretic peptide and brain natriuretic peptide) are also
8 important lipolysis activators. They bind and activate type A natriuretic peptide receptors which
9 possess guanylyl cyclase activity and produce cyclic guanosine monophosphate which activates
10 protein kinase G (PKG). PKA and PKG phosphorylate HSL inducing its translocation to the
11 lipid droplet and perilipin 1 (PLIN1) leading to modification of LD surface that facilitates the
12 action of lipases. In the basal state, PLIN1 sequesters comparative gene identification-58 (CGI-
13 58), an ATGL co-activator. After PLIN1 phosphorylation, CGI-58 is released and interacts with
14 ATGL to allow full activation of the lipase. ATGL is also regulated independently of PKA or
15 PKG through G0/G1 switch gene 2 (G0S2) which acts as a competitive inhibitor in the binding
16 of CGI-58. PKA activation also mediates HSL phosphorylation that favors its association with
17 lipid droplets and its activity. Beside catecholamines and natriuretic peptides, other signals are
18 known to activate lipolysis such as growth hormone and proinflammatory cytokines.

19

20 **Box 3: Transfer and fate of lipids in tumor cells**

21 Several trans-membrane transporters or proteins involved in FFA intra-cellular trafficking have
22 been involved in the transfer of lipids into tumor cells. Once taken up, FFA can be stored as
23 neutral lipids in lipid droplets. Tumor cells possess the ability to liberate FFA overtime to
24 support tumor progression. This mainly involves the lipolytic pathway, although some recent
25 studies also report the implication of lipophagy.

26 Fatty acyl CoA present in the cytoplasm can be transported into the mitochondria through CPT1
27 and CPT2 to be oxidized and to produce energy. Acyl-CoA are oxidized by a series of cycles.
28 Each cycle consists of four reactions cleaving two carbons from the acyl-CoA to release acetyl-
29 CoA, FADH₂ and NADH (Figure I). Acetyl-CoA enters the TCA cycle, which comprises a
30 series of chemical reactions producing redox coenzymes FADH₂ and NADH through the
31 oxidation of acetyl-CoA. These coenzymes and those produced by each FAO cycle are then
32 used in the electron transport chain (ETC, aka oxidative phosphorylation) to produce adenosine
33 triphosphate (ATP). The ETC is composed of four large complexes labeled I to IV that couple
34 transferred electrons with the transfer of protons across a membrane. This creates an

1 electrochemical proton gradient that drives the synthesis of ATP by ATP synthase (aka complex
2 V). Mitochondrial oxidative phosphorylation is incompletely coupled with ATP production
3 when the proton gradient is dissipated by the mitochondrial inner membrane proton channels,
4 uncoupling protein (UCP). This results in a proton leak across the inner mitochondrial
5 membrane and return to the mitochondrial matrix independently of ATP synthase and thereby
6 without ATP production.

7 Importantly, mitochondria are a main source of cellular reactive oxygen species (ROS) and
8 mitochondrial uncoupling was proposed as a protective mechanism against mitochondrial
9 oxidative damage by reducing the production of ROS (for review [85]).

11 **Figure I. Transfer and fate of lipids in tumor cells.**

12 FFA can be taken up by several membrane transporters and stored as TG or directly transferred
13 in the mitochondria to be oxidized. Tumor cells can also release FFA overtime through TG
14 store mobilization through lipolysis or lipophagy. Once inside mitochondria, FFA are oxidized
15 to produce redox coenzymes and acetyl-CoA which enter the TCA cycle. Redox coenzymes
16 are finally used in the ETC for ATP production.

19 **Figure 1. Tumor progression promoted by tumor cell lipid uptake released by adipocytes 20 at the invasive front.**

21 Tumor cells release lipolytic signals (e.g., catecholamines, proinflammatory cytokines,
22 adrenomedullin, or other unknown signals) to transform adipocytes into CAAs that exhibit
23 dedifferentiation, delipidation, and an activated phenotype. Delipidation is mainly due to the
24 ability of cancer cells to activate lipolysis in adipocytes. In turn, adipocytes liberate FFA (and
25 potentially other lipids), but also EV-containing FFA. Such lipids are internalized by tumor
26 cells and trigger lipid metabolic reprogramming to promote tumor progression.

29 **Figure 2. Involvement of FAO and beyond in tumor progression: current mechanisms.**

30 Depending on the type of cancer, FFAs transferred to tumor cells promote tumor progression
31 through different mechanisms. (A) In melanoma, ovarian, metastatic or gastric cancer models,
32 the increased FAO induced by coculture has been described to be coupled to ATP production,
33 resulting in metabolic remodeling and leading to enhanced tumor progression. (B) In BCa,
34 AML, and colon cancer, FAO could be uncoupled to ATP production despite the fact that

1 inhibiting FAO by ETO inhibits tumor progression. Accumulation of metabolites, such as
2 acetyl-CoA, resulting from this uncoupling could then induce epigenetic changes, however, this
3 hypothesis has not been directly demonstrated. (C) Eventhough the metabolic remodeling
4 induced by FFAs is the predominant hypothesis that links the transfer of FFA into tumor cells,
5 FAO-independent effects have been reported. In PCa, the transfer of FFAs induced by the
6 overexpression of the pro-oxidant enzyme NOX5 stimulates a signaling pathway promoting
7 tumor progression. This last mechanism is one of the only mechanisms shown to be amplified
8 by obesity. FFAs can potentially prompt transcriptional regulation involved in tumor
9 progression.

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- 31
32

Figure I (box 3)

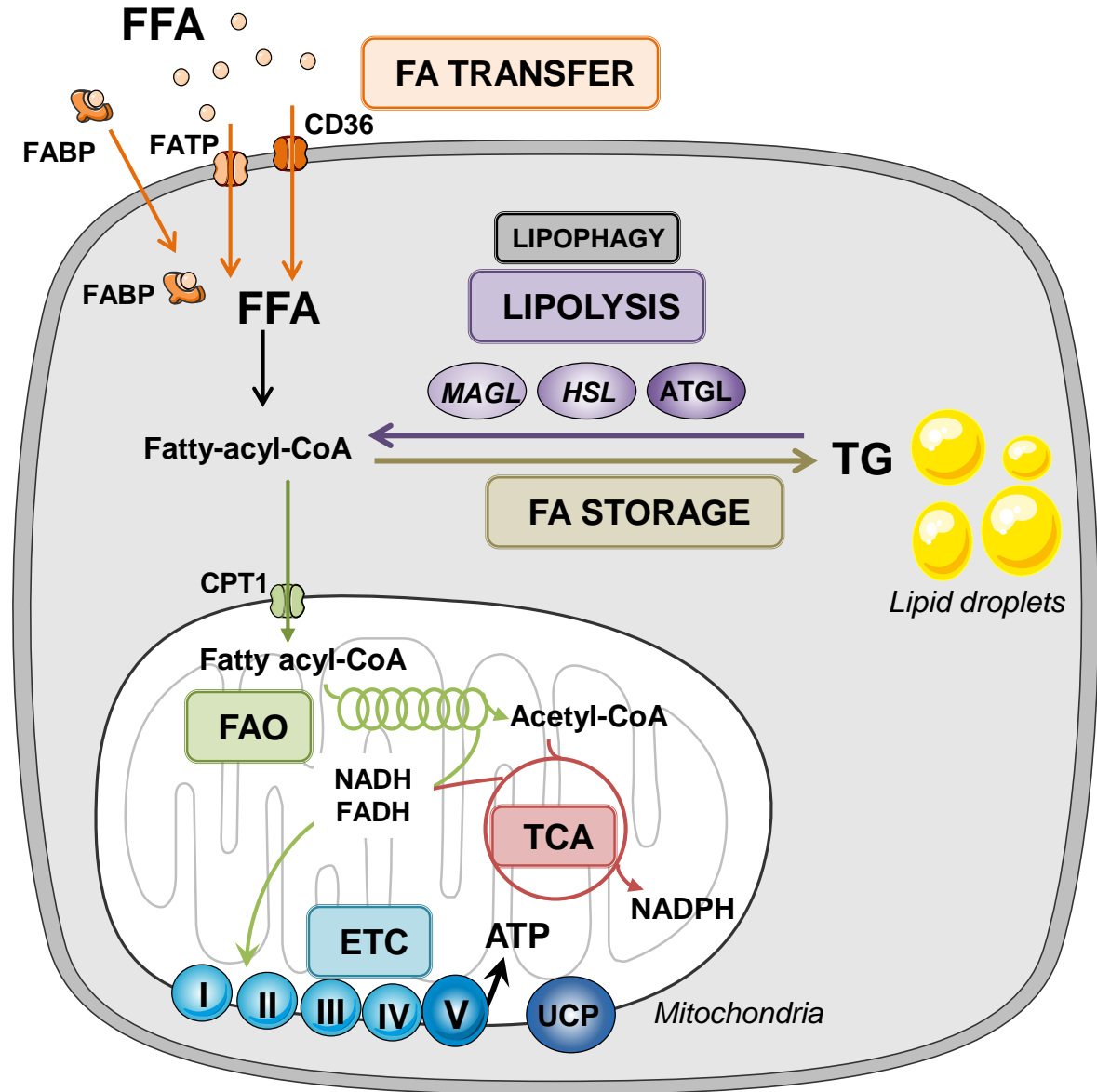


Figure 1

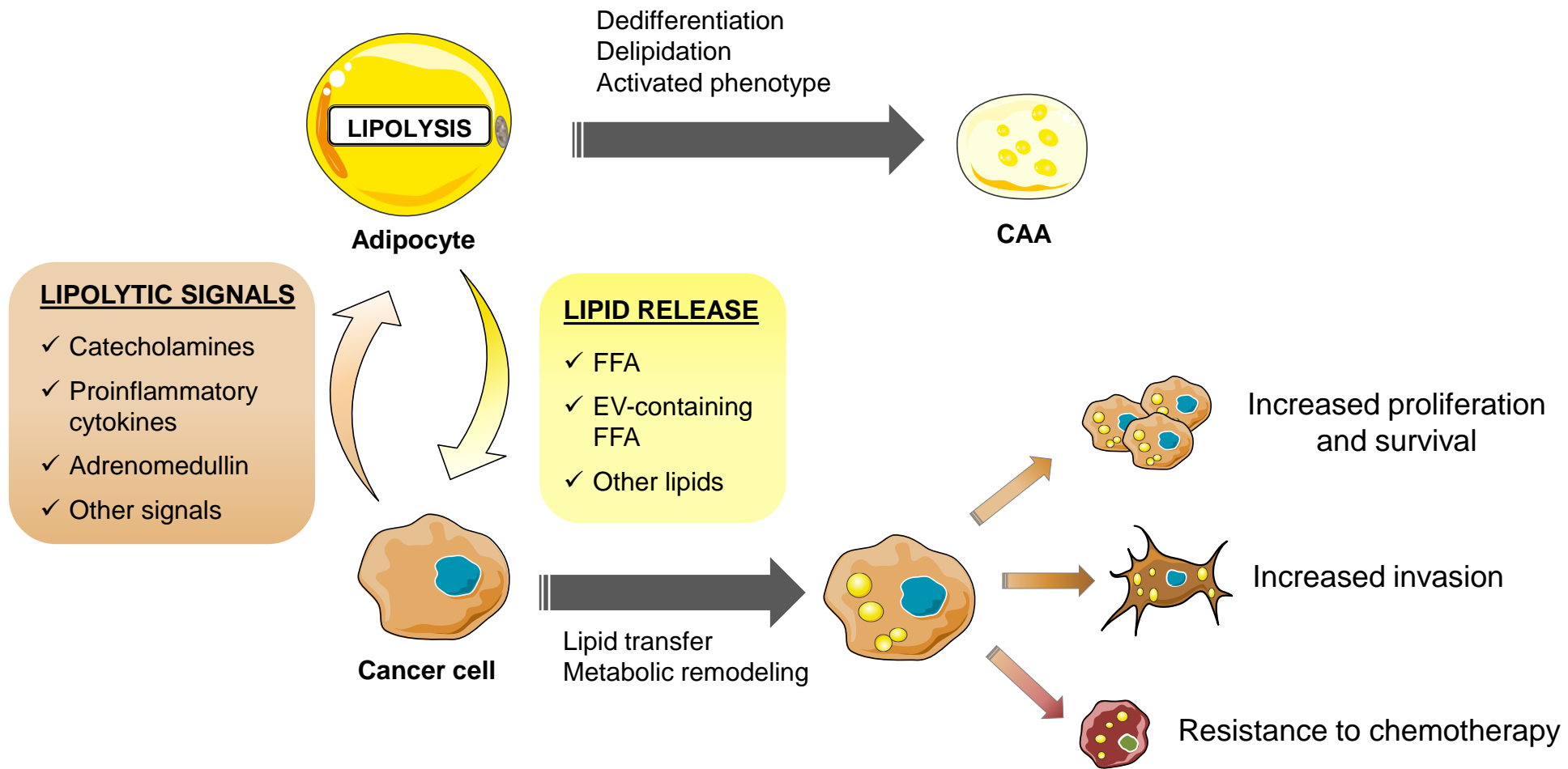


Figure 2

