Drilling for Oil: Tumor-Surrounding Adipocytes Fueling Cancer

Camille Attané, Catherine Muller

Drilling for oil: tumor-surrounding adipocytes fueling cancer

Camille Attané and Catherine Muller*

Institut de Pharmacologie et Biologie Structurale, IPBS, Université de Toulouse, CNRS, UPS, Toulouse, France ; Equipe Labellisée Ligue Contre le Cancer, Toulouse, France.

*corresponding author: Catherine MULLER, IPBS CNRS UMR 5089, 205 Route de Narbonne, 31077 Toulouse Cedex – Tel: 33-561-17-59-32; e-mail: Catherine.muller@ipbs.fr

Keywords

Adipocyte
Cancer metabolism
Fatty acids
Metabolic crosstalk

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.

Tumor microenvironment: a source of metabolites for cancer cells

Metabolic reprograming 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

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

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

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

Adipocytes are a major component of the tumor microenvironment

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

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

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

9, 21]. Using a coculture system, where the two populations are separated by an insert, we found that adipocytes cocultivated with breast tumor cells for 3 to 5 days exhibited a delipidation and decreased expression of adipocyte markers such as Ap2 (FABP4), adiponectin, and resistin [22]. Cocultivated adipocytes exhibited an activated phenotype marked by up-regulation of pro-inflammatory cytokines such as tumor necrosis factor α (TNFα), interleukin (IL)-6, and IL1β [22] as well as proteins involved in extra-cellular matrix remodeling like matrix metalloproteinase 11 (MMP11) [22, 23]. Such activated phenotypes have been found *in vivo* at the invasive front of human breast tumors [22, 23]. Collectively, these data show that adipocytes are not inert to the surrounding tumor and exhibit specific traits, hence we have named them Cancer-Associated Adipocytes (CAAs). These results initially obtained in breast cancer (BCa), have been confirmed in other models including, prostate [13] and ovarian [14] cancers as well as melanoma [24]. In fact, it is now acknowledged that, in all solid tumors, the invasion of proximal adipose tissue by tumor cells leads to profound delipidation of adipocytes, which could ultimately result in the accumulation of fibroblast-like cells, contributing to the so-called desmoplastic reaction-a dense fibrous tissue present around the tumor [7, 9, 21]. Upon exposure to cancer cells *in vitro*, adipocytes undergo sequential morphological changes: first marked by a decrease in adipocyte size and lipid content as seen above (CAAs) and next by acquiring a fibroblast-like morphology (cells that we named Adipose-Derived Fibroblasts, ADFs) [25]. Tumor cells cocultivated with ADFs in two-dimensional or spheroid culture displayed increased invasive capabilities and the presence of ADFs was confirmed in clinical specimens of breast cancer [25]. Together, these results underline the extensive phenotypic changes of mature adipocytes that surround cancer cells.

Mechanisms of lipid release from tumor-surrounding adipocytes

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

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

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

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

Are BM-Ad transformed into CAAs by tumor cells?

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

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

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

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

Transfer of lipids

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

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

Fatty acid storage and mobilization

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

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

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

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

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

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

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

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

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

Other effects of FFA taken up by tumor cells

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

Concluding Remarks

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

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

Box 1: Metabolic symbiosis in the TME

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

Box 2: Regulation of lipolysis

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

out by ATGL (Adipose Triglyceride Lipase), then HSL (Hormone-sensitive lipase) converts DG into MG and FFA and lastly MG are hydrolyzed into glycerol and FFA by MAGL (Monoacylglycerol lipase) [84].

Lipolysis is activated in the fasted state by catecholamines (adrenaline and noradrenaline). The latter activates beta-adrenergic receptors which promote adenylyl cyclase activation and the production of cyclic adenosine monophosphate (cAMP) followed by protein kinase A (PKA) activation. Natriuretic peptides (atrial natriuretic peptide and brain natriuretic peptide) are also important lipolysis activators. They bind and activate type A natriuretic peptide receptors which possess guanylyl cyclase activity and produce cyclic guanosine monophosphate which activates protein kinase G (PKG). PKA and PKG phosphorylate HSL inducing its translocation to the lipid droplet and perilipin 1 (PLIN1) leading to modification of LD surface that facilitates the action of lipases. In the basal state, PLIN1 sequesters comparative gene identification-58 (CGI-58), an ATGL co-activator. After PLIN1 phosphorylation, CGI-58 is released and interacts with ATGL to allow full activation of the lipase. ATGL is also regulated independently of PKA or PKG through G0/G1 switch gene 2 (G0S2) which acts as a competitive inhibitor in the binding of CGI-58. PKA activation also mediates HSL phosphorylation that favors its association with lipid droplets and its activity. Beside catecholamines and natriuretic peptides, other signals are known to activate lipolysis such as growth hormone and proinflammatory cytokines.

Box 3: Transfer and fate of lipids in tumor cells

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

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

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

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

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

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

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

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

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

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

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

Acknowledgement:

The authors thank Charlotte Somes for English editing of the manuscript. Studies performed in our laboratory are supported by the "Fondation de France, the « Fondation ARC (Association pour la recherche sur le cancer) », the « Fondation Toulouse Cancer Santé », « Ligue Contre le Cancer » and the « Société Française de Dermatologie ».

References

1. Hanahan, D. and R.A. Weinberg, *Hallmarks of cancer: the next generation.* Cell, 2011. **144**(5): p. 646-74.
2. Martinez-Outschoorn, U.E., et al., *Cancer metabolism: a therapeutic perspective.* Nat Rev Clin Oncol, 2017. **14**(1): p. 11-31.
3. Beloribi-Djefaflia, S., S. Vasseur, and F. Guillaumond, *Lipid metabolic reprogramming in cancer cells.* Oncogenesis, 2016. **5**: p. e189.
4. Balaban, S., et al., *Extracellular Fatty Acids Are the Major Contributor to Lipid Synthesis in Prostate Cancer.* Mol Cancer Res, 2019. **17**(4): p. 949-962.
5. Balaban, S., et al., *Adipocyte lipolysis links obesity to breast cancer growth: adipocyte-derived fatty acids drive breast cancer cell proliferation and migration.* Cancer Metab, 2017. **5**: p. 1.
6. Hosios, A.M., et al., *Amino Acids Rather than Glucose Account for the Majority of Cell Mass in Proliferating Mammalian Cells.* Dev Cell, 2016. **36**(5): p. 540-9.
7. Duong, M.N., et al., *The fat and the bad: Mature adipocytes, key actors in tumor progression and resistance.* Oncotarget, 2017. **8**(34): p. 57622-57641.
8. Lengyel, E., et al., *Cancer as a Matter of Fat: The Crosstalk between Adipose Tissue and Tumors.* Trends Cancer, 2018. **4**(5): p. 374-384.

9. Park, J., et al., *Obesity and cancer--mechanisms underlying tumour progression and recurrence.* Nat Rev Endocrinol, 2014. **10**(8): p. 455-465.
10. Clement, E., et al., *Obesity and melanoma: could fat be fueling malignancy?* Pigment Cell Melanoma Res, 2017. **30**(3): p. 294-306.
11. Fasshauer, M. and M. Blüher, *Adipokines in health and disease.* Trends in Pharmacological Sciences, 2015. **36**(7): p. 461-470.
12. Quail, D.F. and J.A. Joyce, *Microenvironmental regulation of tumor progression and metastasis.* Nat Med, 2013. **19**(11): p. 1423-37.
13. Laurent, V., et al., *Periprostatic Adipose Tissue Favors Prostate Cancer Cell Invasion in an Obesity-Dependent Manner: Role of Oxidative Stress.* Mol Cancer Res, 2019. **17**(3): p. 821-835.
14. Nieman, K.M., et al., *Adipocytes promote ovarian cancer metastasis and provide energy for rapid tumor growth.* Nat Med, 2011. **17**(11): p. 1498-503.
15. Wang, Y.Y., et al., *Mammary adipocytes stimulate breast cancer invasion through metabolic remodeling of tumor cells.* JCI Insight, 2017. **2**(4): p. e87489.
16. Lazar, I., et al., *Adipocyte Exosomes Promote Melanoma Aggressiveness through Fatty Acid Oxidation: A Novel Mechanism Linking Obesity and Cancer.* Cancer Res, 2016. **76**(14): p. 4051-7.
17. Renehan, A.G., M. Zwahlen, and M. Egger, *Adiposity and cancer risk: new mechanistic insights from epidemiology.* Nat Rev Cancer, 2015. **15**(8): p. 484-98.
18. Kahn, C.R., G. Wang, and K.Y. Lee, *Altered adipose tissue and adipocyte function in the pathogenesis of metabolic syndrome.* J Clin Invest, 2019. **129**(10): p. 3990-4000.
19. Cawthorn, William P., et al., *Bone Marrow Adipose Tissue Is an Endocrine Organ that Contributes to Increased Circulating Adiponectin during Caloric Restriction.* Cell Metabolism, 2014. **20**(2): p. 368-375.
20. Ye, H., et al., *Leukemic Stem Cells Evade Chemotherapy by Metabolic Adaptation to an Adipose Tissue Niche.* Cell Stem Cell, 2016. **19**(1): p. 23-37.
21. Nieman, K.M., et al., *Adipose tissue and adipocytes support tumorigenesis and metastasis.* Biochim Biophys Acta, 2013. **1831**(10): p. 1533-41.
22. Dirat, B., et al., *Cancer-associated adipocytes exhibit an activated phenotype and contribute to breast cancer invasion.* Cancer Research, 2011. **71**(7): p. 2455-65.
23. Andarawewa, K.L., et al., *Stromelysin-3 is a potent negative regulator of adipogenesis participating to cancer cell-adipocyte interaction/crosstalk at the tumor invasive front.* Cancer Res, 2005. **65**(23): p. 10862-71.
24. Zhang, M., et al., *Adipocyte-Derived Lipids Mediate Melanoma Progression via FATP Proteins.* Cancer Discov, 2018. **8**(8): p. 1006-1025.
25. Bochet, L., et al., *Adipocyte-derived fibroblasts promote tumor progression and contribute to the desmoplastic reaction in breast cancer.* Cancer Res, 2013. **73**(18): p. 5657-68.
26. Chirumbolo, S. and G. Bjorklund, *Can Wnt5a and Wnt non-canonical pathways really mediate adipocyte de-differentiation in a tumour microenvironment?* Eur J Cancer, 2016. **64**: p. 96-100.
27. Sagar, G., et al., *Pathogenesis of pancreatic cancer exosome-induced lipolysis in adipose tissue.* Gut, 2016. **65**(7): p. 1165-74.
28. Shafat, M.S., et al., *Leukemic blasts program bone marrow adipocytes to generate a protumoral microenvironment.* Blood, 2017. **129**(10): p. 1320-1332.
29. Diedrich, J.D., et al., *Bone marrow adipocytes promote the Warburg phenotype in metastatic prostate tumors via HIF-1alpha activation.* Oncotarget, 2016. **7**(40): p. 64854-64877.

30. Wang, C., et al., *Human adipocytes stimulate invasion of breast cancer MCF-7 cells by secreting IGFBP-2.* PLoS ONE, 2015. **10**(3): p. e0119348.
31. Hellmuth, C., et al., *Association between plasma nonesterified fatty acids species and adipose tissue fatty acid composition.* PLoS ONE, 2013. **8**(10): p. e74927.
32. Yew Tan, C., et al., *Adipose tissue fatty acid chain length and mono-unsaturation increases with obesity and insulin resistance.* Sci Rep, 2015. **5**: p. 18366.
33. Das, S.K., et al., *Adipose triglyceride lipase contributes to cancer-associated cachexia.* Science, 2011. **333**(6039): p. 233-8.
34. Clement, E., et al., *Adipocyte extracellular vesicles carry enzymes and fatty acids that stimulate mitochondrial metabolism and remodeling in tumor cells.* The EMBO journal, 2020. **In press**.
35. Lazar, I., et al., *A new role for extracellular vesicles: how small vesicles can feed tumors' big appetite.* J Lipid Res, 2018. **59**(10): p. 1793-1804.
36. Record, M., et al., *Exosomes as new vesicular lipid transporters involved in cell-cell communication and various pathophysiologies.* Biochim Biophys Acta, 2014. **1841**(1): p. 108-20.
37. Flaherty, S.E., 3rd, et al., *A lipase-independent pathway of lipid release and immune modulation by adipocytes.* Science, 2019. **363**(6430): p. 989-993.
38. Trotter, T.N., et al., *Adipocyte-Lineage Cells Support Growth and Dissemination of Multiple Myeloma in Bone.* Am J Pathol, 2016. **186**(11): p. 3054-3063.
39. Liu, H., et al., *Reprogrammed marrow adipocytes contribute to myeloma-induced bone disease.* Sci Transl Med, 2019. **11**(494).
40. Lu, W., et al., *Small bone marrow adipocytes predict poor prognosis in acute myeloid leukemia.* Haematologica, 2018. **103**(1): p. e21-e24.
41. Boyd, A.L., et al., *Acute myeloid leukaemia disrupts endogenous myelo-erythropoiesis by compromising the adipocyte bone marrow niche.* Nat Cell Biol, 2017. **19**(11): p. 1336-1347.
42. Scheller, E.L., et al., *Region-specific variation in the properties of skeletal adipocytes reveals regulated and constitutive marrow adipose tissues.* Nat Commun, 2015. **6**: p. 7808.
43. Scheller, E.L., et al., *Bone marrow adipocytes resist lipolysis and remodeling in response to beta-adrenergic stimulation.* Bone, 2019. **118**: p. 32-41.
44. Attané, C., et al., *Human bone marrow is comprised of adipocytes with specific lipid metabolism* Cell Reports, 2020. **In press**.
45. Devlin, M.J., et al., *Caloric restriction leads to high marrow adiposity and low bone mass in growing mice.* Journal of Bone and Mineral Research, 2010. **25**(9): p. 2078-2088.
46. Herroon, M.K., et al., *Bone marrow adipocytes promote tumor growth in bone via FABP4-dependent mechanisms.* Oncotarget, 2013. **4**(11): p. 2108-23.
47. Tabe, Y., et al., *Bone Marrow Adipocytes Facilitate Fatty Acid Oxidation Activating AMPK and a Transcriptional Network Supporting Survival of Acute Monocytic Leukemia Cells.* Cancer Research, 2017. **77**(6): p. 1453-1464.
48. Wen, Y.A., et al., *Adipocytes activate mitochondrial fatty acid oxidation and autophagy to promote tumor growth in colon cancer.* Cell Death Dis, 2017. **8**(2): p. e2593.
49. Gazi, E., et al., *Direct evidence of lipid translocation between adipocytes and prostate cancer cells with imaging FTIR microspectroscopy.* J Lipid Res, 2007. **48**(8): p. 1846-56.
50. Kwan, H.Y., et al., *Subcutaneous adipocytes promote melanoma cell growth by activating the Akt signaling pathway: role of palmitic acid.* J Biol Chem, 2014. **289**(44): p. 30525-37.

51. Tan, Y., et al., *Adipocytes fuel gastric cancer omental metastasis via PITPNC1-mediated fatty acid metabolic reprogramming.* Theranostics, 2018. **8**(19): p. 5452-5468.
52. Hale, J.S., et al., *Cancer stem cell-specific scavenger receptor CD36 drives glioblastoma progression.* Stem Cells, 2014. **32**(7): p. 1746-58.
53. Nath, A. and C. Chan, *Genetic alterations in fatty acid transport and metabolism genes are associated with metastatic progression and poor prognosis of human cancers.* Sci Rep, 2016. **6**: p. 18669.
54. Pascual, G., et al., *Targeting metastasis-initiating cells through the fatty acid receptor CD36.* Nature, 2017. **541**(7635): p. 41-45.
55. Watt, M.J., et al., *Suppressing fatty acid uptake has therapeutic effects in preclinical models of prostate cancer.* Sci Transl Med, 2019. **11**(478).
56. Ladanyi, A., et al., *Adipocyte-induced CD36 expression drives ovarian cancer progression and metastasis.* Oncogene, 2018. **37**(17): p. 2285-2301.
57. Bensaad, K., et al., *Fatty acid uptake and lipid storage induced by HIF-1alpha contribute to cell growth and survival after hypoxia-reoxygenation.* Cell Rep, 2014. **9**(1): p. 349-365.
58. Guaita-Esteruelas, S., et al., *The peritumoural adipose tissue microenvironment and cancer. The roles of fatty acid binding protein 4 and fatty acid binding protein 5.* Mol Cell Endocrinol, 2018. **462**(Pt B): p. 107-118.
59. Petan, T., E. Jarc, and M. Jusovic, *Lipid Droplets in Cancer: Guardians of Fat in a Stressful World.* Molecules, 2018. **23**(8).
60. Grace, S.A., et al., *Adipose Triglyceride Lipase (ATGL) Expression Is Associated with Adiposity and Tumor Stromal Proliferation in Patients with Pancreatic Ductal Adenocarcinoma.* Anticancer Res, 2017. **37**(2): p. 699-703.
61. Vegliante, R., et al., *Hints on ATGL implications in cancer: beyond bioenergetic clues.* Cell Death Dis, 2018. **9**(3): p. 316.
62. Nomura, D.K., et al., *Monoacylglycerol lipase exerts dual control over endocannabinoid and fatty acid pathways to support prostate cancer.* Chem Biol, 2011. **18**(7): p. 846-56.
63. Nomura, D.K., et al., *Monoacylglycerol lipase regulates a fatty acid network that promotes cancer pathogenesis.* Cell, 2010. **140**(1): p. 49-61.
64. Hu, W.R., et al., *Monoacylglycerol lipase promotes metastases in nasopharyngeal carcinoma.* Int J Clin Exp Pathol, 2014. **7**(7): p. 3704-13.
65. Zhang, J., et al., *Monoacylglycerol Lipase: A Novel Potential Therapeutic Target and Prognostic Indicator for Hepatocellular Carcinoma.* Sci Rep, 2016. **6**: p. 35784.
66. Singh, R., et al., *Autophagy regulates lipid metabolism.* Nature, 2009. **458**(7242): p. 1131-5.
67. Maan, M., et al., *Lipid metabolism and lipophagy in cancer.* Biochem Biophys Res Commun, 2018. **504**(3): p. 582-589.
68. Attane, C., et al., *Metabolic remodeling induced by adipocytes: a new Achilles' heel in invasive breast cancer?* Curr Med Chem, 2018.
69. Carracedo, A., L.C. Cantley, and P.P. Pandolfi, *Cancer metabolism: fatty acid oxidation in the limelight.* Nat Rev Cancer, 2013. **13**(4): p. 227-32.
70. Iwamoto, H., et al., *Cancer Lipid Metabolism Confers Antiangiogenic Drug Resistance.* Cell Metab, 2018. **28**(1): p. 104-117 e5.
71. McDonnell, E., et al., *Lipids Reprogram Metabolism to Become a Major Carbon Source for Histone Acetylation.* Cell Rep, 2016. **17**(6): p. 1463-1472.
72. Sivanand, S., I. Viney, and K.E. Wellen, *Spatiotemporal Control of Acetyl-CoA Metabolism in Chromatin Regulation.* Trends Biochem Sci, 2018. **43**(1): p. 61-74.

73. Pietrocola, F., et al., *Acetyl coenzyme A: a central metabolite and second messenger.* Cell Metab, 2015. **21**(6): p. 805-21.
74. Pike, L.S., et al., *Inhibition of fatty acid oxidation by etomoxir impairs NADPH production and increases reactive oxygen species resulting in ATP depletion and cell death in human glioblastoma cells.* Biochim Biophys Acta, 2011. **1807**(6): p. 726-34.
75. Comba, A., et al., *Basic aspects of tumor cell fatty acid-regulated signaling and transcription factors.* Cancer Metastasis Rev, 2011. **30**(3-4): p. 325-42.
76. Sonveaux, P., et al., *Targeting lactate-fueled respiration selectively kills hypoxic tumor cells in mice.* J Clin Invest, 2008. **118**(12): p. 3930-42.
77. Martinez-Outschoorn, U.E., M.P. Lisanti, and F. Sotgia, *Catabolic cancer-associated fibroblasts transfer energy and biomass to anabolic cancer cells, fueling tumor growth.* Semin Cancer Biol, 2014. **25**: p. 47-60.
78. Huang, C.K., et al., *Adipocytes promote malignant growth of breast tumours with monocarboxylate transporter 2 expression via beta-hydroxybutyrate.* Nat Commun, 2017. **8**: p. 14706.
79. Yang, L., et al., *Targeting Stromal Glutamine Synthetase in Tumors Disrupts Tumor Microenvironment-Regulated Cancer Cell Growth.* Cell Metab, 2016. **24**(5): p. 685-700.
80. Meyer, K.A., et al., *Adipocytes promote pancreatic cancer cell proliferation via glutamine transfer.* Biochem Biophys Rep, 2016. **7**: p. 144-149.
81. Ehsanipour, E.A., et al., *Adipocytes cause leukemia cell resistance to L-asparaginase via release of glutamine.* Cancer Res, 2013. **73**(10): p. 2998-3006.
82. Lyssiotis, C.A. and A.C. Kimmelman, *Metabolic Interactions in the Tumor Microenvironment.* Trends Cell Biol, 2017. **27**(11): p. 863-875.
83. Zhao, H., et al., *Tumor microenvironment derived exosomes pleiotropically modulate cancer cell metabolism.* Elife, 2016. **5**: p. e10250.
84. Lafontan, M. and D. Langin, *Lipolysis and lipid mobilization in human adipose tissue.* Prog Lipid Res, 2009. **48**(5): p. 275-97.
85. Cadenas, S., *Mitochondrial uncoupling, ROS generation and cardioprotection.* Biochim Biophys Acta Bioenerg, 2018. **1859**(9): p. 940-950.

Figure I (box 3)

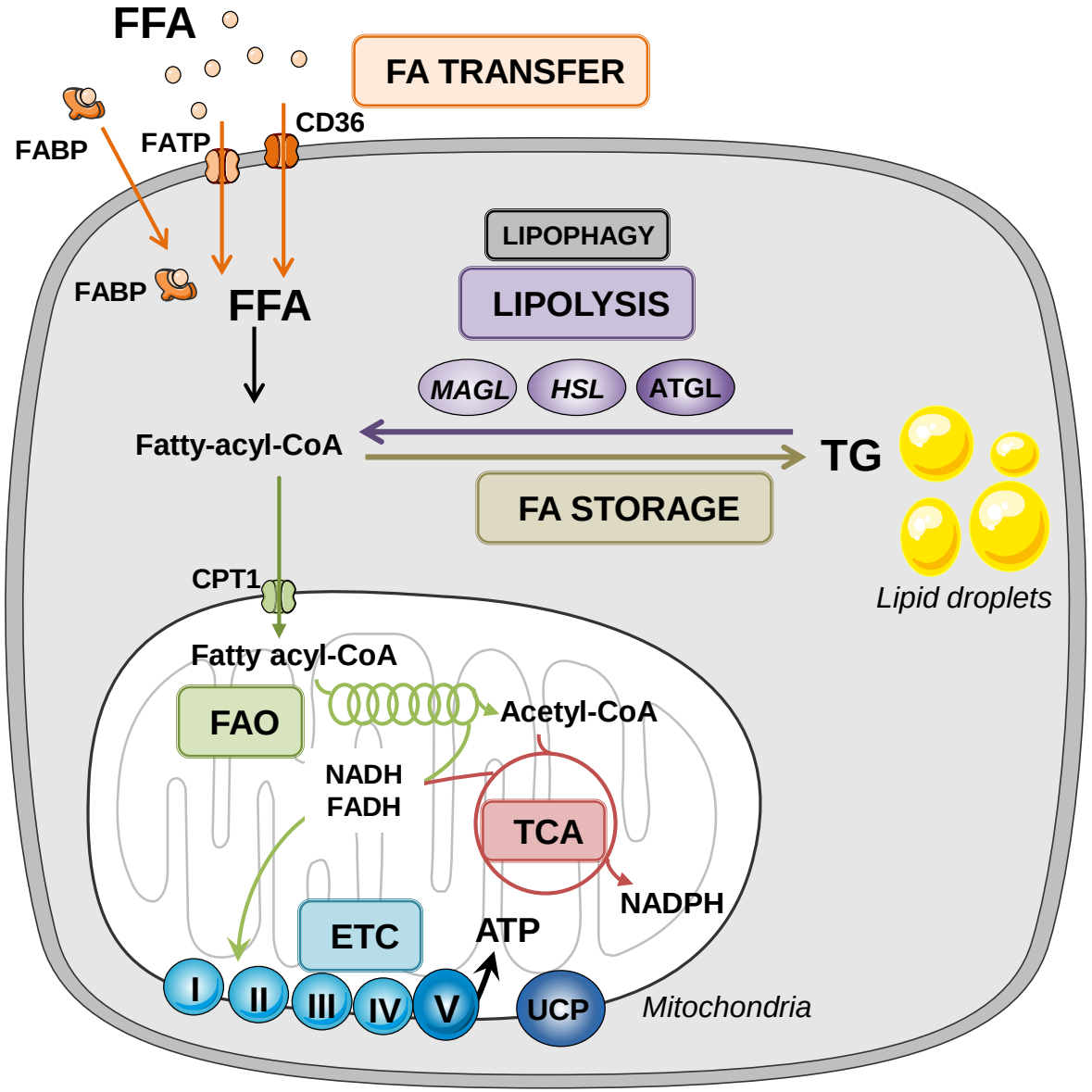


Figure 1

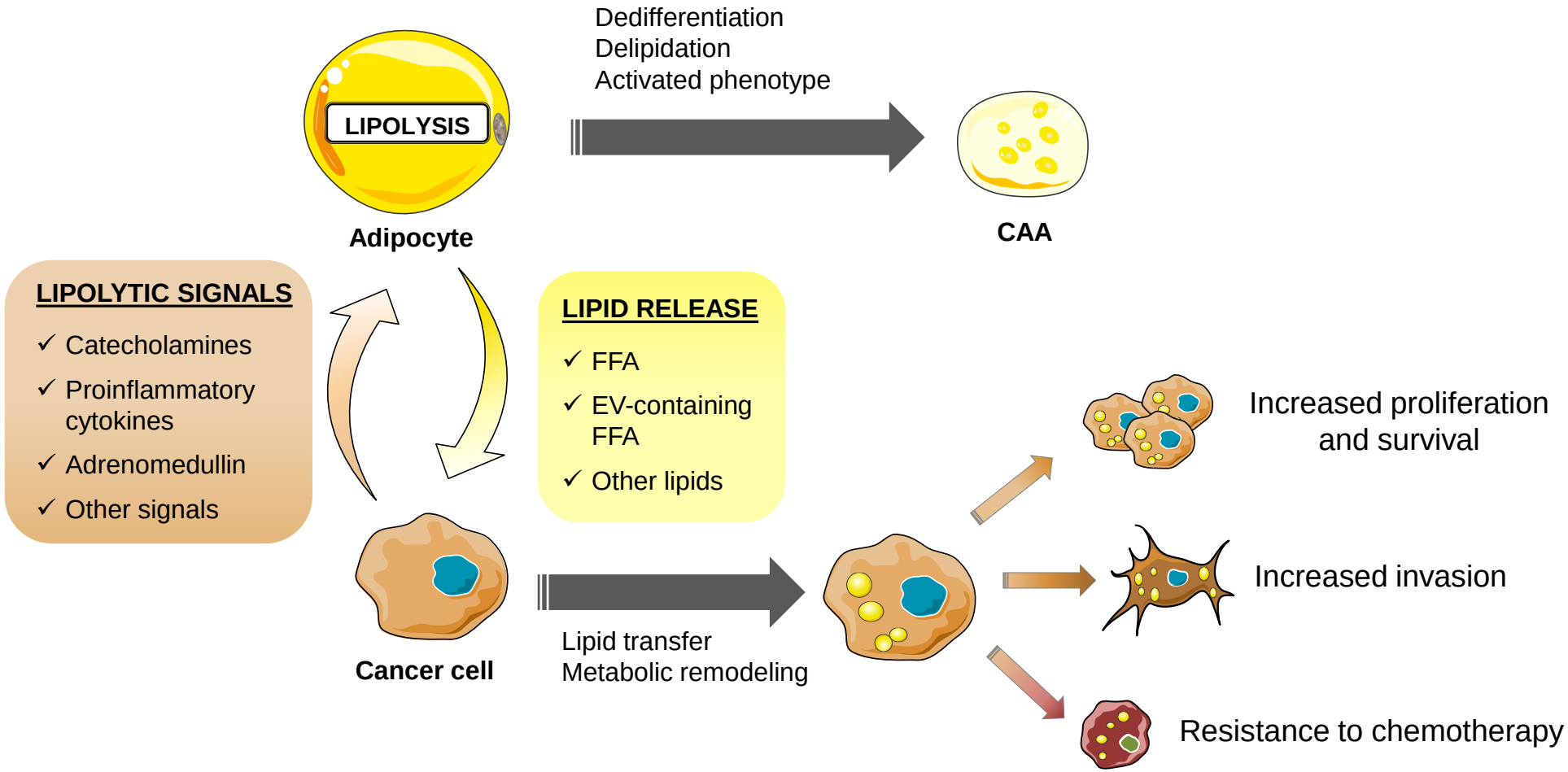
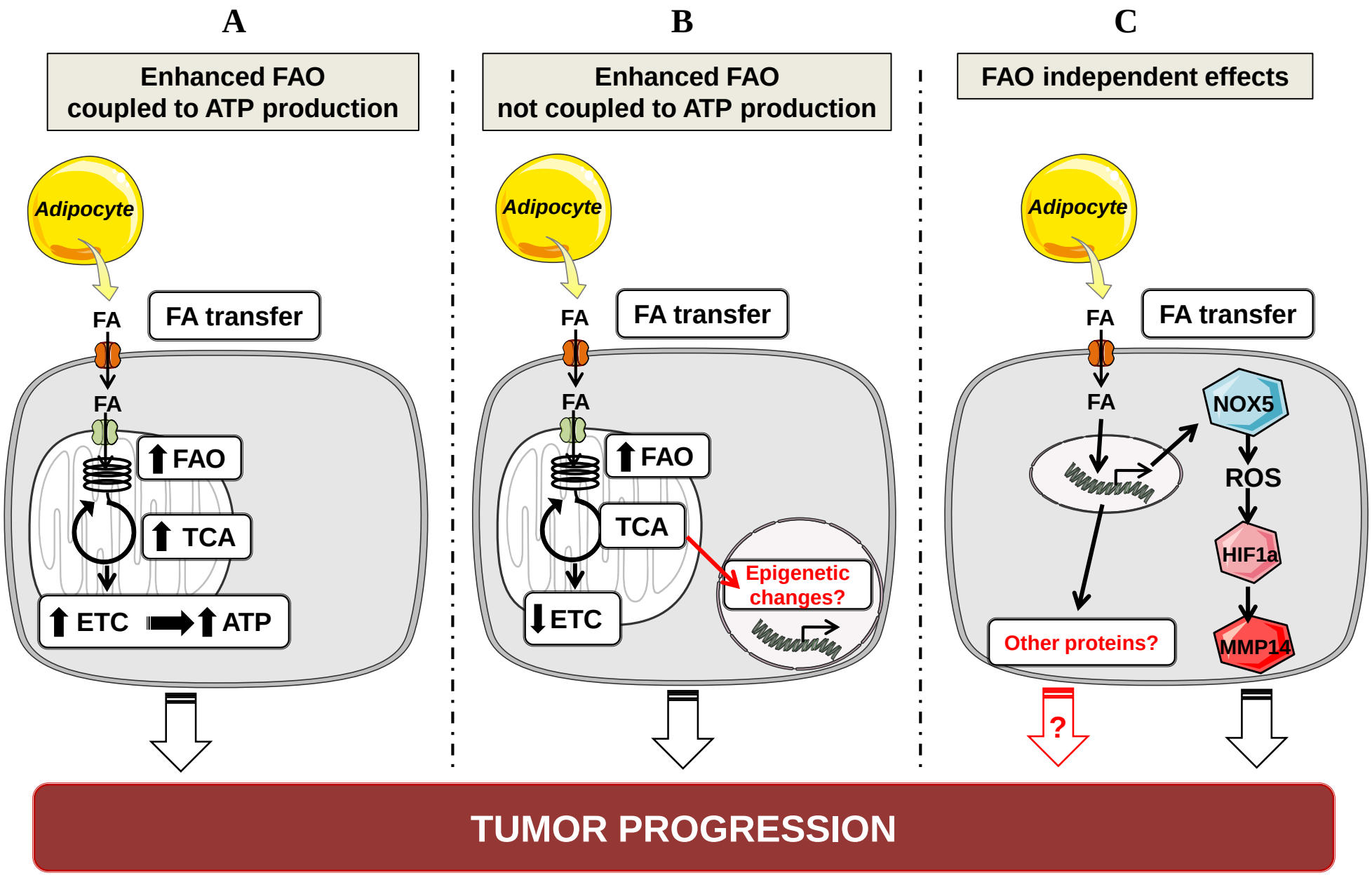

LIPOLYSIS
Adipocyte
Dedifferentiation
Delipidation
Activated phenotype
CAA
LIPOLYTIC SIGNALS
✓ Catecholamines
✓ Proinflammatory cytokines
✓ Adrenomedullin
✓ Other signals
LIPID RELEASE
✓ FFA
✓ EV-containing FFA
✓ Other lipids
Cancer cell
Lipid transfer
Metabolic remodeling
Increased proliferation and survival
Increased invasion
Resistance to chemotherapy

Figure 2


A
Enhanced FAO
coupled to ATP production
Adipocyte
FA
FA transfer
FA
FAO
TCA
ETC
ATP
B
Enhanced FAO
not coupled to ATP production
Adipocyte
FA
FA transfer
FA
FAO
TCA
ETC
Epigenetic
changes?
C
FAO independent effects
Adipocyte
FA
FA transfer
FA
NOX5
ROS
HIF1a
MMP14
Other proteins?
?
TUMOR PROGRESSION