THE ROLE OF LIPIDS IN CANCER PROGRESSION AND METASTASIS

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ABSTRACT

Lipids have essential biological functions in the body (e.g., providing energy storage, acting as a signaling molecule, and being a structural component of membranes), yet an excess of lipids can promote tumorigenesis, colonization, and metastatic capacity of tumor cells. To metastasize, a tumor cell goes through different stages that require lipid-related metabolic and structural adaptations. These adaptations include altering the lipid membrane composition for invading other niches and overcoming cell death mechanisms, and promoting lipid catabolism and anabolism for energy and oxidative stress protective purposes. Cancer cells also harness lipid metabolism to modulate the activity of stromal and immune cells to their advantage and to resist therapy and promote relapse. All this is especially worrying given the high fat intake in Western diets. Thus, metabolic interventions aiming to reduce lipid availability to cancer cells or to exacerbate their metabolic vulnerabilities provide promising therapeutic opportunities to prevent cancer progression and treat metastasis.

Introduction

Cancer is the second leading cause of death worldwide, and it will probably become the first one by 2060 (Mattiuzzi and Lippi, 2019). Significantly, 9 out of 10 cancer-associated deaths can be attributed to metastasis, for which there is currently no effective cure (Ganesh and Massagué, 2021; Siegel et al., 2020). The metastatic process involves the escape of cancer cells from the primary tumor and their migration and colonization to other parts of the body, while evading the immune surveillance. However, the mechanisms regulating the metastatic process are not yet fully understood. Recent studies indicate that metastatic tumor genomes have similar mutational landscape and driver genes as their primary tumors (Priestley et al., 2019; Reiter et al., 2018), suggesting that tumor cells require non-mutational cues to metastasize and, therefore, that metabolic alterations play a preponderant role in the metastatic process. Although glucose is likely the major metabolic substrate of rapidly proliferating tumors, other substrates can boost the metastatic process, including glycolytic metabolites (e.g., pyruvate and lactate), amino acids (e.g., glutamine), and especially lipids (Broadfield et al., 2021a). Increasing evidence shows that lipid metabolism is commonly enhanced at different stages of cancer development. These alterations go beyond energetically fueling tumor cells and also trigger signaling and epigenetic events, as well as changes in membrane composition that favor metastasis (Broadfield et al., 2021a). In addition, the tumor microenvironment supports metabolic crosstalk between the tumor and its surrounding cells; for instance, tumor cells can uptake lipids released by stromal cells, which in turn affects the function of the immune cell compartment (Broadfield et al., 2021a). Here we will review what is currently known about the mechanisms underlying how lipids affect the metastatic process.

1. High-fat diets (HFDs), obesity, and cancer progression

Obesity and the excessive consumption of food rich in fat are associated with certain types of cancers and their aggressiveness (Deng et al., 2016; Petrelli et al., 2021). Importantly, an absence of "excess body fatness" lowers the risk of cancer (Lauby-Secretan et al., 2016; Solans et al., 2020). Obesity is also an independent risk factor for the development of distant metastasis, resistance to therapy and death in certain types of cancer (Ewertz et al., 2011). This is especially worrying, as approximately 25% of adults in industrialized countries are clinically obese, and 60% are overweight, with future projections showing an even worse scenario (OECD, 2017). Intriguingly, persons with obesity have improved survival as compared to normal-weight persons for some tumor types, such as melanoma, (McQuade et al., 2018; Petrelli et al., 2021). However, this paradox might depend on histology, stage, treatment, and sex of the person (Greenlee et al., 2017).

HFDs and tumor initiation

At least in animal models, we know that HFDs can directly alter the metabolism and cellular states in healthy tissues and predispose them to cancer. For instance, in mice, obesity induced by a HFD increases the population of intestinal progenitor stem cells (LGR5+), which adopt an even more stem cell–like fate. This increases their capacity to initiate tumors by activating the ubiquitous lipid-ligand transcription factor PPAR-δ (Beyaz et al., 2016), and ultimately enhancing fatty acid oxidation (FAO) together with other peroxisome proliferator-activated receptor (PPAR) isotypes (e.g., PPAR-α and PPAR-γ, which are predominantly present in liver and adipose tissue, respectively), which in turn also regulates the storage and catabolism of dietary fats (Mana et al., 2021). In a comparison of histologically healthy breast tissue from

women at-risk or not-at-risk for breast cancer, tissue from at-risk women (but not from not-at-risk women) showed lipid metabolism alterations, with upregulation of lipid transporters (CD36 and AQP7), lipolysis (LIPE) and lipid-detoxifying (AKR1C1) proteins in their epithelium, together with increased crosstalk with the adipose tissue and a reduction of active natural-killer cells and lymphocytes (Marino et al., 2020). In other words, these tissues are "primed" for exposure to a HFD. In mice, excessive fat consumption, even over the short term, can also enhance glucose metabolism in hepatocytes and alter their lipid composition, predisposing them to cancer development. In fact, the metabolic alterations observed in non-transformed hepatocytes upon HFD resemble those characterizing hepatocellular carcinoma (Broadfield et al., 2021b). All these results suggest that early activation of lipid metabolism in cancer-free tissues by excess fat consumption can favor tumor initiation; a similar preconditioning could also occur in secondary sites of metastasis.

HFDs and immune system

After eating fat-enriched food, the amount of circulating fats in the body increases dramatically, which dampens immune surveillance and favors tumor progression (Kulkarni and Bowers, 2021). For instance, the innate antitumor response of NK cells against melanoma is impaired in obese mice fed a HFD, as evidenced by the reduction in the production of perforins and apoptosis-inducing granzymes (Michelet et al., 2018). This is a consequence of PPAR-α/δ-driven accumulation of lipids in NK cells, which inhibits mTOR-mediated glycolysis, the main energy pathway sustaining NK cell function (Michelet et al., 2018). Similarly, HFD-induced obesity results in the exhaustion of CD8+ tumor infiltrating lymphocytes (TILs) by reducing the production of granzyme and cytokines (interferon-gamma, TNF-alpha), which ultimately accelerates tumor growth in murine models of colorectal and breast cancer (Kado et al., 2019; Ringel et al., 2020; Wang et al., 2018b). TILs are also functional repressed in obese mice on a HFD via suppression of amino acid metabolism, which increases cancer burden and, importantly, can be partially reverted by losing weight (Dyck et al., 2022). HFDs alter the lipid composition of the tumor microenvironment, making tumor cells more efficient by upregulating lipid uptake and oxidation, and in parallel limiting nutrient availability for CD8+ T-cells, thus impairing their function (Ringel et al., 2020). This HFD-mediated metabolic reprogramming is regulated by the repression of the hypoxia factor PHD3 in tumor cells and preventing this metabolic reprogramming in obese mice improves antitumor immunity (Ringel et al., 2020). HFD also restrains activation of CD4+ T helper cell by inhibiting autophagy (Guerrero-Ros et al., 2020). HFD-induced obesity also enhances the amount of myeloid-derived suppressor cells (MDSCs) in circulation and their accumulation in the tumor microenvironment (TME), which favors tumor growth and spontaneous metastasis by inhibiting tumor-reactive T cells and enhancing immunotherapy resistance, as observed in several models of renal, oral, and breast cancers (Clements et al., 2018; Gibson et al., 2020; Hale et al., 2015; Peng et al., 2021). HFD can also produce dysfunction of dendritic cells (DC), which play important roles in the initiation and maintenance of the immune response against tumors, by promoting the accumulation of intracellular lipids (Gao et al., 2015; James et al., 2012). Furthermore, chronic inflammation caused by HFD-induced obesity produces lung neutrophilia and promotes lung metastasis in a mouse model of breast cancer which, again, can be reverted by weight loss (Quail et al., 2017). Apart from generating an immunosuppressive environment that favors tumor growth and metastasis, excessive lipid consumption can also facilitate the extravasation of circulating cancer cells from blood to other organs; for instance, in obese mice on a HFD, extravasation of circulating breast cancer cells to the lung is promoted by the neutrophil-mediated production of extracellular DNA traps and oxidative species, which ultimately leads to disrupted endothelial junctions and loss of vascular integrity (McDowell et al., 2021). Importantly,

this effect can be reversed in preclinical models of obesity by enhancing the antioxidant response, decreasing ROS production, or inhibiting extracellular DNA traps formation (McDowell et al., 2021).

HFDs and metastasis

Although the effect of HFDs and fat accumulation are relevant for the development of the primary tumor, they are particularly important for the latest stages of tumor progression as well as during tumor relapse. This idea is further supported by the fact that a diet low in fat improves survival in breast cancer patients (Chlebowski et al., 2006, 2018), but has no effect on breast cancer incidence (Martin et al., 2011). Our group and others have found that when tumor cells metastasize or become resistant to therapies, they enhance mechanisms for lipid uptake, lipid oxidation and synthesis, which can be promoted by excessive fat consumption (Broadfield et al., 2021a; Martin-Perez et al., 2021). For instance, we found that, in mice bearing an oral tumor and fed a HFD, the primary tumor contained more metastasis-initiating cells and expressed higher levels of the FA receptor CD36 and lipid metabolism genes, while the mice produced more and bigger lymph node and lung metastases in a CD36-dependent manner, as compared to the same type of mice but fed a control diet (Pascual et al., 2016; Pascual et al., 2021). In line with these results, a HFD activates a lipid catabolism transcriptional program mediated by PPAR-δ in a mouse model of colorectal cancer, which in turn enhances the expression of the stemness-promoting transcriptional factor Nanog and ultimately leads to the induction of liver metastasis formation due to the increase of metastasis-initiating cells within the primary tumor (Wang et al., 2019). Likewise, metastasis can be promoted in prostate cancer by the aberrant activation of sterol regulatory element–binding protein (SREBP) dependent lipogenic program, and this can be triggered by feeding mice a HFD, leading to increased lipid abundance in prostate tumors and favoring migration and invasion processes (Chen et al., 2018b). HFD-induced obesity also promotes peritoneal and lung metastasis in gastric cancer via the upregulation of diacylglycerol acyl transferase 2 (DGAT2), a lipogenic enzyme in charge of triacylglycerol (TAG) synthesis and lipid droplet expansion (Li et al., 2020). Importantly, targeting lipogenesis by silencing SREBP or DGAT2 reduces proliferation and activates apoptotic mechanisms, thereby decreasing metastasis formation (Chen et al., 2018b; Li et al., 2020). In addition, HFDs can also favor cancer invasion and metastasis by enhancing the expression of the inflammatory and pro-fibrotic adipokine PAI-1, as observed in Lewis lung carcinoma (Yan, L., and DeMars, 2014), or by altering the ECM composition as observed in breast cancer models (Wishart et al., 2020). Similarly, chronic consumption of a HFD alters the expression of genes involved in inflammation, angiogenesis, and cellular proliferation, promoting lung metastasis in mouse models of colon (Park et al., 2012a) and breast cancer (Bousquenaud et al., 2018). HFDs, especially when rich in saturated fats, can hyperactivate other transcriptional programs, such as oncogenic MYC, as observed in murine models of prostate cancer (Labbé et al., 2019). This is accomplished by altering the lipid composition of prostate tissue, which then favors epigenetic modifications in the promoter regions of MYC targets and promotes tumor burden and metastasis; of note, this process can be attenuated by switching to a low-fat diet (Labbé et al., 2019), possibly through suppression of the IGF-AKT pathway and reduced cell proliferation (Kobayashi et al., 2008). Thus, HFDs seem to favor cancer progression and metastasis burden by increasing the amount of circulating fats and their availability for use by tumor cells, which is directly associated with alterations in the lipid composition of tumor cells, tumor vascularization, and inflammatory signaling.

Interestingly, a short-term HFD can reduce the risk of metastasis by stimulating the activation of adipose tissue macrophages and the recruitment of CD4+ and CD8+ T cells to the visceral fat, which ultimately

prevents the metastatic seeding of colorectal cancer (Xiang et al., 2020). Although this finding seems in juxtaposition to the generally accepted view that a HFD leads to cancer promotion, the time window of HFD intervention could be important; in this specific study, the short-term intervention did not produce obesity, which reduced the possibility that disseminated colorectal cancer cells established in visceral fat, which presents a larger area in obese individuals. Supporting the idea that obesity is required for HFD-dependent tumor deterioration, the pro-tumorigenic effect of HFDs can be mitigated by restricting feeding in a mouse model of breast cancer (Sundaram and Yan, 2018). This agrees with the observations made in animal models fed on a fasting mimicking diet, which is low in calories, sugar, and protein and proportionally high in fat (Caffa et al., 2020). Also, short administration of ketogenic diets containing extreme proportions of fat-to-carbohydrate ratios reduced tumor burden in a mouse model of colorectal cancer, regardless on the plant or animal origin of fat (Dmitrieva-Posocco et al., 2022), although this is not the case for pancreatic and lung cancer models where low-calorie but not ketogenic diets impair tumor growth, and the addition of palm oil can prevent the low-calorie diet's effect on tumor progression (Lien et al., 2021). In this sense, transgenic mice that present difficulties in gaining weight or depositing fat fed on a HFD do not show the epigenetic reprogramming priming the initiation and progression of colon cancer (Li et al., 2014b). However, there is also compelling evidence showing that HFDs increase tumor growth and metastasis in obesity-resistant mice (without body weight gain) in colorectal cancer or breast cancer by inducing the expression of genes involved in the stimulation of inflammation, angiogenesis, cell migration, and proliferation (Kim et al., 2011; Lamas et al., 2015; Park et al., 2012a). Moreover, we have recently shown that feeding tumor-bearing mice a HFD rich in palmitic acid, even for a short period of time, increases the aggressiveness and metastatic capacity of oral cancer and melanoma cells, by imprinting an epigenetic memory that sustains metastasis progression (Pascual et al., 2016; Pascual et al., 2021).

Overall, HFDs can boost the metastatic capacity of cancer cells by increasing the availability of lipids and altering the systemic and intra-tumoral lipid homeostasis which reduces immune surveillance (**Table 1**). However, the presence of high amounts of fat in a diet per se is not the only relevant factor for inducing metastasis; rather, numerous factors should be considered, including body weight, changes in fat deposits, the type of fat, the proportion of other dietary ingredients, the food intake, and the timeframe of feeding. Cancer type is also relevant as observed in a recent meta-analysis of 203 studies and over 6.3 million individuals which suggests that cancer patients with obesity (BMI>30) have poor survival outcomes overall, except for some cancer types such as renal cell carcinoma, lung cancer and melanoma (Petrelli et al., 2021). These exceptions (i.e., "obesity paradox") could be related to a lower cachexia incidence, a promotion of the antitumor immune response by an increase of adipose tissue acting as a reservoir of activated immune cells, and a better immunotherapy predisposition and lower toxic effects of chemotherapy in obese patients (Wang et al., 2018b; Petrelli et al., 2021). This finding underlines the need to adapt dietary interventions according to specific cancer types and stages.

2. Effect of lipids in metastasis

Major lipid types include phospholipids, sphingolipids, triglycerides (fats and oils), fatty acids, and sterols. Phospholipids and sphingolipids are the major components of lipid bilayers of cell membranes but can also act as signaling molecules together with other lipid signaling molecules (e.g., prostaglandins, ceramides; addressed in Section 4). Fats and oils are stored as a form of energy in our bodies and are made up of fatty

acids and either a glycerol or sphingosine molecule. Of the sterols, cholesterol is the most important form in animals; besides being part of cell membranes, it also acts as a systemic signaling molecule and precursor of hormones and vitamins. Increased circulating levels of fatty acids (FAs) and cholesterol is a hallmark of obesity, and both have been linked to poorer outcomes in cancer patients (Carr et al., 2018; Madak-Erdogan et al., 2019; Ye et al., 2020). Therefore, it could be speculated that both FAs and cholesterol may mediate some of the pro-metastatic effects induced by obesity and HFDs (**Table 1**).

Cholesterol

Cholesterol levels in the body come from two sources: dietary intake and biosynthesis through the mevalonate pathway. Clinical and experimental studies indicate that cholesterol plays an important role in cancer development through the activation of oncogenic pathways such as Hedgehog and mTORC1 signaling (Ding et al., 2019; Kuzu et al., 2016), as well as by promoting epithelial-to-mesenchymal transition (EMT) and invasion (Beckwitt et al., 2018). Cholesterol may also facilitate metastasis, as observed in breast cancer models, by repressing the action of immune cells (Baek et al., 2017) or by enhancing resistance of metastatic cells to ferroptosis (Liu et al., 2021), a type of programmed cell death dependent on iron and characterized by the accumulation of lipid peroxides from membranes. These findings support the positive correlation between cholesterol levels and metastasis incidence observed in breast and prostate cancer (Hirano et al., 2020; Nelson et al., 2013). Interestingly, the pro-metastatic effects of cholesterol in breast cancer requires its conversion to 27-hydroxycholesterol, which functions as a ligand for the estrogen and liver X receptors, and blocking this conversion by the use cytochrome P450 oxidase CYP27A1 inhibitors attenuates the effects of cholesterol on tumor pathology (Nelson et al., 2013). On the other hand, other cholesterol derivates can suppress breast cancer (de Medina et al., 2013), and increasing cholesterol levels can prevent metastatic phenotypes in breast cancer cells by altering membrane fluidity (Zhao et al., 2016). Therefore, although the mechanisms by which cholesterol promotes metastasis are not fully understood, anti-cholesterol therapies preventing cholesterol synthesis (statins) or chelating membrane cholesterol from disrupting signaling in lipid rafts are being tested for preventing cancer progression and/or metastasis with some success (Chimento et al., 2019; Nielsen et al., 2012). Statins inhibit HMGCR, the rate-limiting enzyme for cholesterol synthesis (di Bello et al., 2020), and have shown promising results in pre-clinical studies in inhibiting both tumor growth and metastastatic capacity (Chou et al., 2019; Yin et al., 2018), as well as in re-sensitizing resistant cancer cells to different chemotherapy treatments (Yin et al., 2018; Heilos et al. 2018; Feng et al., 2020).

Non-essential FAs

Non-essential FAs constitute most FAs in our bodies and are commonly classified according to their saturation degree into saturated FAs (SFAs) and unsaturated FAs. FA biosynthesis occurs in the cytoplasm through the action of FA synthase (FASN), a multifunctional enzyme that catalyzes the conversion of acetyl-CoA to the 16-carbon SFA palmitic acid. Overexpression and hyperactivity of FASN is commonly associated with malignant cells and cancer progression (Fhu and Ali, 2020). Palmitic acid (16:0) can be elongated to stearic acid (18:0) and longer FAs through the action of FA elongases (ELOVLs), the overexpression of which is also associated with cancer progression (Su et al., 2018; Yamashita et al., 2017). SFAs usually account for 30% to 40% of total FA content in animal tissues (Legrand and Rioux, 2010), with palmitic acid the most abundant one (15–25%), followed by stearic acid (10–20%). Shorter SFAs, such as myristic acid (14:0) (0.5–1%) and lauric acid (12:0) (<0.5%), are produced in minor amounts through the usual FASN pathway but can also be derived by shortening palmitic acid, likely by peroxisomal

β-oxidation (Rioux et al., 2007). On the other hand, mono-unsaturated FAs (MUFAs) account for 47–50% of total FAs, with oleic acid (18:1) the main one (44–47%) (Resources N.R.C, 1976). MUFAs are generated from saturated FAs through the action of desaturases, such as FA desaturase (FADS) and the stearoyl-CoA desaturase (SCD) families. For instance, palmitic acid can be desaturated to palmitoleic acid (16:1 n-7) or sapienic acid (16:1 n-10) via SCD1 or FADS2, respectively, being both enzymes implicated in cancer progression as well (Li et al., 2017; Vriens et al., 2019; Vivas-García et al., 2020; Lien et al., 2021). Finally, polyunsaturated FAs (PUFAs; i.e., containing two or more double bonds between carbon atoms) synthesis requires elongation and desaturation of essential linoleic and alpha-linolenic acids, although the rate of generation in normal conditions is very low (Broadfield et al., 2021a). Synthesized FAs can be then catabolized to produce energy via the β-oxidation pathway or else incorporated into phospholipids and distributed to the cell membranes, or triglycerides and stored in lipid droplets as energetic fat depots.

The degree of unsaturation confers remarkably different biological properties to fatty acids (Listenberger et al., 2003; Ricchi et al., 2009; Henique et al., 2010; Peng et al., 2011; Nicholas et al., 2017; Palomer et al., 2018; Kakimoto et al., 2021). For instance, palmitic acid increases cellular levels of diacylglycerols and ceramides, and is known to be proinflammatory, lipotoxic, to produce insulin resistance, ER stress, and to stimulate mitochondrial oxidative respiration inducing more reactive oxygen species (ROS). In contrast, oleic acid is mostly stored as triacylglycerols in lipid droplets, is generally less toxic, has anti-inflammatory properties, and has lower binding affinity to fatty acid transporter CD36 (Jay et al., 2015). Moreover, FA composition of lipid membrane makes them more or less fluid, being areas with short or unsaturated and disordered lipids such as PUFAs more fluid whereas tightly packaged areas full of saturated phospholipids, sphingolipids and cholesterol are less fluid and allow the colocalization of different proteins being a hub for cellular signaling (lipid rafts) (Bi et al., 2019; Levental et al., 2020). Highly migratory cells tend to display more fluid membranes due to the lesser content of saturated fats and cholesterol which favors EMT and the intra- and extravasation from blood vessels (Zeisig et al., 2007; Zhao et al., 2016). On the contrary, cancer cells with a higher degree of membrane saturation and cholesterol, and therefore higher membrane rigidity, are less susceptible to oxidative stress induced by chemotherapeutic agents or ferroptotic mechanisms since they contain fewer double bonds that can be targeted for peroxidation (Rysman et al., 2010; Heilos et al., 2018; Liu et al., 2021). These differences influence the actions of the different FAs on cancer cells.

We have found that dietary palmitic acid, but not oleic acid or linoleic acid, promotes metastasis in different models of oral cancer and melanoma by inducing stable transcriptional and chromatin changes dependent on CD36 expression (Pascual et al., 2016; Pascual et al., 2021). Other studies also showed that palmitic acid potentiates the invasiveness and migration of pancreatic and gastric cancer cells through the activation of ROS-mediated inflammatory response or the nuclear localization of β-catenin via AKT signaling (Binker-Cosen et al., 2017; Pan et al., 2019). Long term exposure to palmitic acid increases colorectal cancer growth in a β2 adrenergic receptor–dependent manner (Fatima et al., 2019) and also promotes tumor formation and growth in breast and ovarian cancer cells (Liu et al., 2022; Yu et al., 2020). This process is governed epigenetically through increased chromatin occupancy of the transcription factor CCAAT/enhancer-binding protein beta (C/EBPB), which promotes tumor stemness (Liu et al., 2022). Similarly, cell transformation into a more aggressive phenotype is favored by increasing the levels of SFAs into diacylglycerols and membrane phospholipids (Nishida-Aoki et al., 2020; Roy et al., 2019; Rusu et al., 2019). This membrane remodeling is mediated in glioblastoma by LPCAT1, which favors EGFR oncogenic

signaling within a positive feedback loop (Bi et al., 2019). On the other hand, oleic acid can be toxic for certain cancer cells (Jung et al., 2016; Menendez et al., 2005) and reduces their migration and invasion capacities (Giulitti et al., 2021). In this sense, dietary intake of unsaturated FAs is related to the reduced risk of esophageal SCC (Tang et al., 2022), while SFA intake is associated with an enhanced MYC transcriptional signature and poorer outcome in prostate cancer patients (Labbé et al., 2019). Accordingly, different clinical studies also suggest that a Mediterranean diet, rich in oleic acid, provides a beneficial effect in the primary prevention of breast and prostate cancers and reduces their aggressiveness (Castelló et al., 2018; Toledo et al., 2015; Urquiza-Salvat et al., 2018).

In contrast, some studies support that palmitic acid impairs the invasiveness and tumor growth by inactivating mTOR and STAT3 signaling and reducing cell membrane fluidity (Lin et al., 2017; Sun et al., 2020), whereas oleic acid has an opposite effect by activating PIK3, PKC/Src/EGFR, or Src/ERK signaling in breast, prostate, and cervical cancer cells (Hardy et al., 2000; Soto-Guzman et al., 2010; Liotti et al., 2018; Yang et al., 2018b). Oleic acid can also favor survival and chemotherapy resistance in prostate and gastric cancer (Liotti et al., 2018; Li et al., 2020), probably by promoting lipid droplet formation and FAO-dependent NADPH production to overcome oxidative stress (Li et al., 2020). Similarly, exposure of melanoma cancer stem cells to environments with elevated concentrations of oleic acid (e.g., lymphatic system) potentiates an anti-oxidative stress response supported by glutathione peroxidase 4 (GPX4) expression, which protects them from ferroptotic cell death and favors their survival in the systemic circulation to colonize distant organs (Ubellacker et al., 2020). Interestingly, oleic acid can also induce ROS production in colorectal cancer cells via activation of NOX4, which ultimately favors extravasation and leads to increased metastasis (Shen et al., 2020).

Thus, there is no clear dogma on the pro- or anti-metastatic effects of SFAs and unsaturated FAs, in part because of the complex metabolism of cancer cells that can be rewired to allocate FAs to different fates according to cellular requirements. This discrepancy could be also related to the cancer cell type, the environment, the amount of FAs, the duration of FA exposure, and whether the FA needs to be metabolized to exert its effect. What does seem clear is that an increase in the systemic levels of FAs can produce deleterious consequences for cancer patients. Both SFAs and unsaturated FAs can be catabolized via beta-oxidation to produce energy as well as reduced NADPH, which are necessary to endure the metabolic alterations that occur during metastatic dissemination, while preventing oxidative stress–triggered cell death (i.e., anoikis due to loss of epithelial interactions, and ferroptosis due to circulation in an iron-rich environment). This is supported by the fact that in certain studies, both palmitic acid and oleic acid (individually or in combination) have been found to enhance cell migration and invasion (Chen et al., 2018b), promote lipid droplet formation (Corbet et al., 2020), or decrease the ability of NK cells to kill tumor cells (Michelet et al., 2018). Furthermore, our diet contains both saturated and unsaturated FA (although Western diets tend to contain increased proportions of SFAs), and experimental HFDs are mostly based on lard, which is enriched in saturated fats compared to other lipid sources such as most vegetable oils. Furthermore, part of the pro-metastatic effects of the excess dietary saturated fats may stem from their conversion to unsaturated fats via FA elongases and desaturases, which are overexpressed in many cancers, but the opposite process (i.e., hydrogenation of unsaturated fats into saturated fats) is impossible, at least in eukaryotic cells (Kemp et al., 1975). This is consistent with the view that cancer progression is influenced not only the type of FAs but also by their ratios in the diet and the total amount of fat intake. Thus, imbalances in the cellular FA composition can promote malignancy. FA imbalances can also come from

cellular rearrangements; for instance, pro-metastatic melanoma cells can show increased saturated-to-monounsaturated ratios due to the dysregulation of SCD, the main cellular FA desaturase, and this switches cells to an inflammatory and invasive phenotype (Vivas-García et al., 2020). On the other hand, the lipid imbalance generated by the inhibition of SCD activity also produces lipotoxicity and can slow cancer progression (Lien et al., 2021; Rudalska et al., 2021). Also, the increased expression of SCD observed in ovarian cancer stem cells produces higher unsaturated lipid profile that maintains stemness (Li et al., 2017). FA desaturation is therefore an essential process in cancer progression, and cancer cells can exploit alternative FA desaturation pathways to proliferate, such as by producing sapienate biosynthesis from palmitate via FADS2 (Vriens et al., 2019), underscoring the tremendous metabolic flexibility of malignant cells.

Essential FAs

Most fatty acids (FAs) can be synthesized in our bodies except for two that are essential for humans and must be obtained through the diet: alpha-linolenic acid (ALA, an omega-3 FA) and linoleic acid (an omega-6 FA). Both ALA and linoleic acid are PUFAs and act either directly as signaling molecules or as precursors to make other omega-3 and omega-6 PUFA that can also be involved in cellular signaling or be an integral part of cellular membranes. Omega-3 PUFAs are widely accepted to have anti-inflammatory properties, whereas omega-6 PUFAs are the precursors for pro-inflammatory molecules. These pro-inflammatory and anti-inflammatory mechanisms are mostly associated with tumor-promoting and antitumor effects, respectively, with some exceptions (Serhan 2005; Yang et al., 2014). Furthermore, the reduced cancer risk associated to omega-3 FAs consumption may not be limited to its ability in promoting resolution of inflammation, but they can also modulate the expression of genes linked to lipid metabolism control such as SREBP1 and PPAR-α (Howell et al., 2009; Bargut et al., 2014). In this regard, Western diets are significantly enriched in omega-6 PUFAs, which is associated with increased cancer progression, while omega-3 enriched diets have been associated with reduced risks of developing cancer (Koundouros and Poulogiannis, 2019). Accordingly, primary tumors from patients with metastatic colorectal cancer compared to those with non-metastatic cancer show significantly higher levels of omega-6 PUFAs and lower levels of omega-3 PUFAs (Notarnicola et al., 2018; Tutino et al., 2019). However, little information is available regarding the effects of essential FAs on tumor growth and metastasis, and the studies of associations between dietary PUFAs and cancer are inconsistent (Azrad et al., 2013; Liput et al., 2021). For instance, diets rich in ALA can inhibit tumor growth and metastasis in breast cancer mouse models by increasing T-lymphocyte infiltration and decreasing estrogen receptor expression and cell proliferation (Fritsche and Johnston, 1990; Vara-Messler et al., 2017). In contrast, ALA (alone or in combination with LA) has also been shown to increase liver metastases in pancreatic cancer, which is associated with an increase in hepatic lipid peroxidation (Wenger et al., 1999, 2000). Although dietary linoleic acid can stimulate invasion and peritoneal metastasis of gastric carcinoma cells through the activation of MAPK signaling and the generation of prostaglandins via cyclooxygenase metabolism (Matsuoka et al., 2010), we have observed that exposure of oral cancer cells to linoleic acid does not promote metastasis in oral cancer models (Pascual et al., 2021). Therefore, careful optimization of omega-3 to omega-6 ratios is necessary to use dietary interventions based on essential FAs to combat metastasis.

Odd-chain and short-chain FAs

Most FAs are made up of chains with an even number of carbon atoms. Odd-chain FA are very rare in animals and are most particularly found in ruminant fat and milk. They are generated when propionyl-CoA

rather than acetyl-CoA is used as the primer for the biosynthesis of fatty acids, but they are less preferred substrates for FAO than even-numbered FAs and therefore accumulates in the cell (Gotoh et al., 2008). Few studies have addressed the effect of these FAs in cancer progression, although they may bear anti-carcinogenic properties (Jenkins et al., 2015; Venn-Watson et al., 2020) and can suppress stemness in cancer cells by inhibiting proinflammatory signaling and inducing apoptosis (To et al., 2020).

On the other hand, short-chain FA (<5 carbons) such as acetate, are mostly produced by gut microbiota, and are known to have anti-inflammatory properties. Despite the little information available, they seem to be protective against tumorigenesis, especially in colorectal cancer (Casanova et al., 2018; Matthews et al., 2012; Nakkarach et al., 2021; Yang et al., 2020a), but they can also limit the immune response against cancer (Coutzac et al., 2020).

3. Lipid metabolism in metastasis and targetable vulnerabilities

Cancer cells can exploit lipid metabolism to favor the different steps of the metastatic cascade, ranging from the generation of metastasis-initiating cells to metastatic outgrowth. Next, we discuss recent findings linking the metastatic process with alterations in major pathways of lipid metabolism and potential therapeutic targets (**Figure 1** and **Table 2**).

Lipid uptake

Induction of FA uptake seems to be a general mechanism used by cancer cells to fuel their dissemination and resistance to therapy, and CD36 is one of the main receptors implicated. CD36 is a scavenger receptor that can bind and internalize long-chain FAs, oxo-LDLs, thrombospondin-1, and pathogen-associated molecules, among others (Li et al., 2020). CD36 expression in patient samples is generally associated with poor prognosis and metastatic progression (Feng et al., 2019; Nath and Chan, 2016; Yang et al., 2020b) with some exceptions (Jia et al., 2018). We and others have found that metastatic-initiating cells are characterized by the presence of CD44-stem cell marker and CD36 receptor in their plasma membrane. In the context of metastatic-initiating cells, CD36's main function consists of internalizing long-chain FAs that boost the metastatic capacity of the cell (Pascual et al., 2016; Pascual et al., 2021). In fact, CD36 can promote the nuclear localization of MYC and activate the EMT program through the GSK-3β/ β-catenin pathway (Wang et al., 2020c), which in turn maintains CD36 expression in a positive feedback loop (Casciano et al., 2020). On the other hand, chemical inhibition of CD36, as well as its genetic silencing or depletion, reverses the mesenchymal and invasive phenotype of tumor cells (Nath et al., 2015; Yoshida et al., 2020) and also reduces oncogenic signaling lipids and tumor progression in mouse models of prostate cancer (Watt et al., 2019). In addition, blockage of lipid entrance through CD36 with neutralizing antibodies can inhibit metastasis formation or decrease the metastatic burden in immunocompromised models of oral squamous cell carcinoma (Pascual et al., 2016) or colorectal cancer (Gong et al., 2020). CD36 overexpression in cancer cells can protect against therapy, as observed in hepatocellular carcinoma (Bort et al., 2020), breast cancer (Feng et al., 2019), melanoma (Rambow et al., 2018; Aloia et al., 2019), and leukemias (Farge et al., 2017; Landberg et al., 2018). Therefore, combinations of an anti-cancer treatment with CD36 inhibition could constitute a novel therapeutic strategy to boost the efficiency of front-line chemotherapy. Indeed, targeting CD36 re-sensitizes resistant cells to immune- and chemo-therapies (Landberg et al., 2018; Feng et al., 2019).

Tumor cells can also augment other lipid transporters on their surface, such as FATP1 (Zhang et al., 2018a) or FATP2 (Alicea et al., 2020), to increase intracellular lipid availability and support cancer progression and therapy resistance. Similarly, tumor cells can overexpress FA-binding proteins involved in intracellular and extracellular lipid transport, such as FABP4, to fuel growth and promote metastasis as well as chemoresistance (Nieman et al., 2011; Hao et al., 2018; Mukherjee et al., 2020; Yu et al., 2020). Overall, considering the importance of FA uptake and lipid transporters in cancer progression and therapy resistance, they should be considered as promising therapeutic targets; in addition, the design of FA-like prodrugs could be an effective strategy to facilitate drug entry specifically in the cells of interest, decreasing drug toxicity (Jayawardhana et al., 2020), although they should be used with caution since some tissues such as heart are mainly fueled by FAs.

Lipid catabolism

Cells that upregulate lipid uptake usually present an enhanced FAO. This mostly occurs in the mitochondria, where FAs are catabolized via beta-oxidation pathway, which not only fuels cancer cells but also generates reducing power required for combating oxidative stress during cancer dissemination (Carracedo et al., 2012; Qiao et al., 2020; Sawyer et al., 2020; Zhao et al., 2020). CPT1A is the rate limiting enzyme of beta-oxidation, regulating the entrance of FAs to the mitochondria, and its activation can enhance the expression of EMT and stemness markers and promote invasion and boost the metastatic capacity of gastric cancer and hepatocellular carcinoma cells (Wang et al., 2020b; Zhao et al., 2020). FAO activation via CPT1A upregulation downstream of the PPAR-α transcriptional program, can also favor chemotherapy resistance (Aloia et al., 2019; Han et al., 2020), probably through stemness induction (He et al., 2019; Wang et al., 2018a; Han et al., 2020). Furthermore, cancer cells that metastasize to lymph nodes shift their metabolism towards FAO to adapt to the node fatty environment through the activation of a signaling pathway driven by the yes1-associated protein (YAP1) transcription factor (Lee et al., 2019). Thus, FAO could be targeted to hamper cancer progression by inhibiting CPT1A, which decreases EMT and invasion (Wang et al., 2020b), induces anoikis (Sawyer et al., 2020), dampens energy production (Camarda et al., 2016), reduces metastasis (Lee et al., 2019), or re-sensitizes resistant cells to chemotherapy by reversing their stem phenotype (He et al., 2019; Wang et al., 2018a; Han et al., 2020) .Moreover, silencing of ACSL enzymes, responsible for converting FAs to their acyl-CoA active form before being metabolized, also decreases the tumorigenesis and metastatic capacity of cancer cells, as observed for ACSL1 (Pascual et al., 2016) and ACSL3 (Padanad et al., 2016; Ubellacker et al., 2020). Nevertheless, targeting FAO may not be enough to halt cancer progression, as tumor cells could overcome FAO inhibition by upregulating glycolysis (Aloia et al., 2019).

Lipid uptake and catabolism genes are mostly regulated by the PPAR family of transcription factors (and especially the alpha and gamma forms) whose overexpression is a negative prognostic factor and is pro-metastatic (Zhu et al., 2015; Wang et al., 2019; Zou et al., 2019; Galbraith et al., 2021), although some exceptions exist (Shen et al., 2012). Thus, PPAR modulators are attractive candidates for treating metastatic cancer (Chi et al., 2021).

Lipid biosynthesis

Exacerbation of FA synthesis has been widely described in aggressive cancers as a mechanism to produce membranes for cell proliferation, as well as to modulate membrane composition and generate fat storage.

For instance, induction of *de novo* lipogenesis via FASN in cervical cancer cells is associated with lymph node metastasis and can induce migration and invasion *in vitro* (Guo et al., 2019; Xu et al., 2020). Upregulation of FASN and lipid metabolism also correlates with intrahepatic cholangiocarcinoma aggressiveness (Zhang et al., 2020). Interestingly, to proliferate in the new niche, metastatic cells may require enhanced lipid biosynthesis, as observed in human epithelial growth factor receptor 2 (HER2)–positive breast cancer cells, which increase FASN expression when growing in brain but not in other organs, allowing them to compensate for the decreased availability of lipid nutrients (Ferraro et al., 2021). Some cells also upregulate FASN to produce the reductive power necessary to quench the excess of ROS via IDH (isocitrate dehydrogenase) dependent reductive carboxylation and allow a three-dimensional anchorage-independent growth (Bueno et al., 2019; Seguin et al., 2012). Overexpression of FASN is also associated with poor prognosis and increased multidrug resistance in multiple cancers (Papaevangelou et al., 2018), and metastatic cells epigenetically favor the expression of lipogenic regulators such as FASN to promote cell motility and metastasis (Lu et al., 2022). Thus, anti-obesity drugs, such as orlistat and other FASN inhibitors, could prevent tumor progression by restraining FA synthesis and are currently being tested in clinical trials (Falchook et al., 2021; Fhu and Ali, 2020). Pre-clinical studies with orlistat have already shown promising results, decreasing the metastatic burden of melanoma (Seguin et al., 2012) and oral cancer (Agostini et al., 2014) by reducing their angiogenic and invasive capacities. Also, orlistat in combination with cisplatin delays tumor growth in cisplatin-resistant ovarian cancer cells (Papaevangelou et al., 2018). Of note, FASN inhibition can lead to CD36 upregulation as a compensatory mechanism, or vice versa, therefore combined FASN and CD36 inhibition might be required to overcome this resistance (Watt et al., 2019; Drury et al., 2020). In fact, dual targeting of lipid uptake and synthesis pathways can inhibit proliferation of prostate cancer-derived organoids to a greater degree than a single treatment (Watt et al., 2019).

The activities of ACLY and ACC, the rate-limiting enzymes in lipid synthesis that respectively generates acetyl-CoA and malonyl-CoA from TCA cycle intermediates, have also been linked to the metastatic capacity of cancer cells. ACLY is a key enzyme for redirecting the excess of glycolytic flux toward lipid synthesis for tumor growth and differentiation (Hatzivassiliou et al., 2005), and ACLY overexpression downstream of integrin ITGA2, IGF-1 and beta-catenin signaling pathways also favors stemness and metastasis in several cancer models (Adorno-Cruz et al., 2021; Han et al., 2021; Qiao et al., 2021; Wen et al., 2019). Aggressive prostate tumor cells also show a lipogenic phenotype mediated by ACC and FASN that increases cellular levels of saturated lipids and results in an overall decrease of the proportion of PUFA phospholipids in the plasma membrane, thus making cancer cells less sensitive to lipid peroxidation and ferroptosis (Rysman et al., 2010). However, care must be taken with using ACC as a therapeutic target, as phosphorylation-mediated inactivation of ACC1 can prime breast cancer cells to an invasive phenotype by increasing the intracellular levels of acetyl Co-A and protein acetylation of EMT activators, which promote metastasis induction and tumor recurrence (Rios Garcia et al., 2017).

The excess of newly synthesized or internalized saturated FAs, if not catabolized, needs to be desaturated by cancer cells to prevent lipotoxicity and ER stress-induced apoptosis (Pinkham et al., 2019; Rudalska et al., 2021) or ferroptosis (Tesfay et al., 2019). SCD1 expression has also been linked to EMT, promoting migration and invasion of colorectal cancer cells (Ran et al., 2018), and increased lipid desaturation via SCD1 is essential to favor a stemness phenotype in ovarian cancer cells (Li et al., 2017) and to promote metastasis in gastric cancer via the hippo/YAP pathway (Gao et al., 2020). In fact, inhibition of SCD1 alone

or in combination with lipogenic induction could be used as a therapeutic target to enhance lipotoxicity and death of cancer cells (Li et al., 2017; Rudalska et al., 2021; Luis et al., 2021). However, targeting SCD1 can produce self-defeating results, as observed in melanoma, where SCD1 downregulation causes an increase in the ratio SFA/MUFA that decreases cancer cell proliferation yet also induces a pro-inflammatory phenotype and metastasis formation (Vivas-García et al., 2020). Moreover, SCD1 chemical inhibition can be bypassed by the cells through an alternative FA desaturation pathway involving FADS2 (Vriens et al., 2019). Further studies are needed to clarify the concrete cancer types and circumstances in which SCD1 inhibition can be beneficial.

Cancer cells also promote the storage of newly synthesized lipids into lipid droplets that serve as energy depots to fuel cancer cell spreading (Rozeveld et al., 2020) but also to support anoikis resistance (Corbet et al., 2020), probably by providing oxidative stress resistance (Bailey et al., 2015). In fact, upregulation of diacylglycerol acyltransferases (DGATs), which catalyze the final reaction in the synthesis of triglycerides and promote lipid droplet expansion, can induce peritoneal and lung metastases in gastric cancer (Li et al., 2020), whereas silencing DGATs prevents the formation of lipid droplets and can inhibit metastasis by killing cancer through anoikis (Li et al., 2020) or ferroptosis (Dierge et al., 2021). Other mechanisms enhancing lipid droplet formation, such as LPCAT2 overexpression, can also support colorectal cancer chemoresistance (Cotte et al., 2018).

SREBP1, a master transcriptional regulator of lipogenesis, is overexpressed in many cancer types (Shimano et al., 2017), and its activation increases the expression of main lipogenic genes (e.g., FASN, ACLY, ACC, and SCD1) and also promotes cell proliferation, migration, invasion, and metastasis (Bao et al., 2016; Chen et al., 2018b; Gao et al., 2019; Heo et al., 2020; Li et al., 2014a; Sun et al., 2020); as well as chemotherapy resistance (Shen et al., 2019; Yin et al., 2019; Xu et al., 2021a). Therefore, apart from being used as a prognostic marker (Heo et al., 2020; Li et al., 2014a; Sun et al., 2020), it could also become a potential therapeutic target for treating cancer as a metabolic disease (Guo et al., 2014; Xiao and Song, 2013).

Lipid-mediated cell death

Lipid metabolism can promote apoptotic cell death by modulating membrane permeability and activating different enzymes, including caspases (Huang and Freter, 2015), but it is especially relevant in other mechanisms of programed cell death, such as ferroptosis (Magtanong et al., 2016). Ferroptosis is driven by iron-dependent peroxidation of membrane lipids (Dixon et al., 2012), especially PUFAs since SFAs and MUFAs are not subjected to lipid peroxidation (Jiang et al., 2021). Ferroptosis-associated lipid peroxidation starts in the cell, with removal of a hydrogen atom between two carbon-carbon double bonds in a PUFA moiety of a phospholipid (PLH). This generates a phospholipid radical (PL●) that, under oxygen presence, it is readily converted into a phospholipid peroxyl radical (PLOO●). The lipid peroxyl radical can abstract a hydrogen atom from another PUFA, generating the phospholipid hydroperoxide (PLOOH) and thus propagating lipid peroxidation. If not converted to an alcohol (PLOH) by GPX4, PLOOH and lipid free radicals can react with other PUFAs in the membrane and generate a chain reaction that results in a breakdown of membrane integrity (Jiang et al., 2021). This type of death is triggered in iron-enriched environments, such as blood, and cancer cells need to regulate their membrane lipid composition to survive hematogenous dissemination. Interestingly, melanoma cells that disseminate through the lymphatic system prior to accessing blood are less sensitive to ferroptosis (Ubellacker et al., 2020), thanks to the uptake of MUFAs from the lymph environment and incorporation of them in membranes (Ubellacker et al., 2020),

as observed in different cancer cells exposed to MUFAs (Magtanong et al., 2019). On the other hand, certain lymphomas acquire protection from ferroptosis by accumulation of squalene, an intermediate metabolite of the cholesterol synthesis. The accumulation of this polyunsaturated lipid seems to protect membrane PUFAs from lipid peroxidation, although the concrete mechanism remains to be elucidated (Garcia-Bermudez et al., 2019).

Altogether makes ferroptosis a highly interesting therapeutic target. Indeed, GPX4 genetic depletion leads to tumor regression (Viswanathan et al., 2017) and significantly reduces the metastatic incidence in preclinical models of melanoma (Ubellacker et al., 2020). Furthermore, mesenchymal therapy resistant cells can upregulate GPX4 as a mechanism to deal with an increased proportion of PUFAs in the plasma membrane as a consequence of their EMT transition (Viswanathan et al., 2017). This excess of PUFAs creates a dependency of those cells on targetable-GPX4 to avoid ferroptosis. Thus, sensitization of cancer cells to ferroptosis by increasing the amount of dietary PUFAs (Dierge et al., 2021) can be exploited to overcome certain therapy resistances, although they could use alternative mechanisms to cope with lipid peroxidation upon GPX4 inhibition (Blomme et al., 2020; Garcia-Bermudez et al., 2019; Jiang et al., 2021).

4. Lipid signaling in metastasis

Apart from their metabolic and structural functions, lipids also serve as intracellular and intercellular signaling molecules. For instance, membrane phospholipids are broken into lipid mediators (e.g., diacylglycerol, phosphatidic acid, lysophosphatidic acid, and arachidonic acid) through the action of phospholipases and some of them (e.g., arachidonic acid) are then further converted into prostaglandins and leukotrienes through the cyclooxygenase pathway and the lipoxygenase pathway, respectively (**Figure 2A**). These bioactive lipids can be secreted from cancer cells and act as autocrine or paracrine mediators regulating multiple cellular processes that can favor tumorigenesis and metastasis, including proliferation, migration, invasion, and angiogenesis (Hisano and Hla, 2019; Luo et al., 2018; Magkrioti et al., 2018; Park et al., 2012b). For instance, lysophosphatidic acid and prostaglandins potentiate the secretion of angiogenic cytokines and the vascular endothelial growth factor (VEGF) to promote angiogenesis (Hisano and Hla, 2019). These bioactive lipid mediators, especially prostaglandins, can also promote chronic inflammation that stimulate tumor progression and can influence stromal cells (Chiurchiù et al., 2018), especially affecting the immune cell compartment and allowing cancer cells to escape from the immune system (Zelenay et al., 2015). On the other hand, cancer-associated fibroblasts can secrete lysophosphatidylcholines which are transformed into lysophosphatidic acid by cancer cells to promote proliferation and migration by activating AKT signaling (Auciello et al., 2019). On the other hand, membrane sphingolipids can also act as bioactive compounds with major implications in cancer regulation, such as ceramides and sphingosine-1-phosphate with mostly anti-proliferative and pro-survival signaling effects respectively (Ogretmen 2018).

Lipids can also act as modulators of intracellular signaling by being post-translationally bound to proteins and modifying their function. Proteins are most commonly modified by lipids via palmitoylation, which is a covalent modification with a palmitate moiety, but can also be modified by other long-chain SFAs (such as myristate), shorter or unsaturated FAs, and prenyl groups (farnesylation and geranylgeranylation). Protein palmitoylation mostly occurs in the form of S-palmitoylation on cysteine residues through a

thioester bond in a reaction catalyzed by the DHHC acyltransferase family of proteins (which contain a DHHC [aspartate-histidine-histidine-cysteine] domain). Importantly, S-palmitoylation is the only known lipid modification of proteins that is reversible, by the action of acyl thioesterases, and therefore regulatable, although there is some evidence of other enzyme-dependent delipidation mechanisms (Jing et al., 2017; Kakugawa et al., 2015; Komaniecki and Lin, 2021). Around 25% of 299 validated cancer driver proteins can be S-palmitoylated, according to a recent study (Ko and Dixon, 2018), and many S-palmitoylation–dependent processes have also been related to cancer progression (Anderson and Ragan, 2016; Chen et al., 2017; Draper and Smith, 2010; Ducker et al., 2004; Ko and Dixon, 2018; Yamamoto et al., 2007; Yuan et al., 2020).

Palmitoylation plays a relevant role in well-known oncogenic signaling pathways, like the Ras, epidermal growth factor (EGF), Wnt, and Hippo signaling pathways. For instance, the Ras family of GTPases can be S-palmitoylated (Busquets-Hernández and Triola, 2021) and inhibition of S-palmitoylation of oncogenic NRASG12D mutant at Cys181 induces mislocalization of mutant NRAS and inhibits downstream signaling, impeding disease development, and extending the life-expectancy of leukemia-bearing animals (Cuiffo and Ren, 2010) (**Figure 2B**). S-palmitoylation of the EGF receptor (EGFR), in turn, can enhance its ligand-independent homodimerization and activation in a process that seems to be dependent on FASN activity (Bollu et al., 2015) and that can relocate EGFR to the nucleus of the cell and confer chemotherapy resistance (Ali et al., 2018). However, there is also evidence suggesting that S-palmitoylation of EGFR prevents its autophosphorylation, thereby provoking its internalization and termination of the signaling cascade (Runkle et al., 2016). In Wnt signaling, Wnt5a signaling can control cell polarity through APT1 thioesterase and depalmitoylation of specific cell adhesion molecules in melanoma cells (Wang et al., 2015). Upon Wnt5a binding to its receptor, the inhibitory interaction of APT1 with DVL2 is inhibited, enhancing therefore the activity of APT1 thioesterase. This triggers the specific depalmitoylation of melanoma cell adhesion molecule (MCAM) but not of other palmitoylated proteins like caveolins. Depalmitoylated MCAM loses its location at the plasma membrane, inducing cell invasion (Wang et al., 2015). Finally, recent work has shown that S-palmitoylation is required for the transcriptional activation of Transcriptional Enhanced Associate Domain (TEAD) activation (Chan et al., 2016; Noland et al., 2016), and that this palmitoylation is required: i) for upregulation of multiple genes involved in cellular proliferation and survival, ii) downstream of the effectors of the Hippo pathway YAP and TAZ, and iii) for tumor growth (Holden et al., 2020).

On the other hand, S-palmitoylation can also regulate the activity of tumor suppressors, including SCRIB and p53. For its proper localization and function at the cell junctions, SCRIB must be S-palmitoylated by DHHC7 at two different cysteines (Chen et al., 2016). Unless both sites are palmitoylated, SCRIB will mislocalize to the cytoplasm, which leads to loss of cell polarity and overactivation of pathways like PI3K/AKT, MAPK or YAP, thereby increasing the malignancy of the cell (Chen et al., 2016; Feigin et al., 2014; Mohseni et al., 2014). The palmitoylation state of SCRIB is particularly relevant in breast cancer, in which the expression of ZDHHC7 is usually lost and APT2 (a specific thioesterase for SCRIB) tends to be upregulated (Hernandez et al., 2017), which underlines the antitumor function of SCRIB S-palmitoylation. Likewise, S-palmitoylation of p53 at several Cys residues by DHHC1 is fundamental for the subsequent phosphorylation of p53 and its nuclear translocation and is therefore fundamental for its function and its inhibition of tumor growth (**Figure 2B**). Furthermore, in cancer cells harboring wild-type p53, the palmitoylated tumor suppressor recruits DNMT3A to the ZDHHC1 promoter for hypermethylation,

generating a negative feed-back loop (Tang et al., 2021). Finally, the depalmitoylating enzyme ABHD17A has been identified as one of the main tumor suppressor mechanisms in the microenvironment of lung metastasis in mice (van der Weyden et al., 2017). ABHD17A has been recently implicated in the regulation of the N-Ras palmitoylation cycle which is required for N-Ras signalling and cancer progression (Remsberg et al., 2021).

Protein lipidation is therefore an important post-translational modification for cell signaling and cancer progression, and it can link the output of cellular metabolism to the regulation of protein function (Chen et al., 2018a). In this sense, changes in the intracellular concentration of lipid metabolites can have a strong impact on the protein lipidation mechanism. For instance, an excess of palmitic acid *in vivo* (through a HFD) or *in vitro* (through addition to cell culture media) can boost the S-palmitoylation of certain proteins (Spinelli et al., 2017; Tang et al., 2021). However, if the cells do not have enough palmitic acid, they can still synthesize it through FASN upregulation. Thus, the inhibition of S-palmitoylation, either by blocking palmitate synthesis or by transference of the moiety to the protein, can synergize with current therapies to treat cancer. Combination of tyrosine kinase inhibitors and broad inhibition of DHHCs with 2-bromopalmitate or inhibition of FA and steroid synthesis with cerulenin can synergize enhancing EGFR inhibition and doubling the percentage of dead cells as compared to tyrosine kinase inhibitors alone in certain types of cancer (Bollu et al., 2015; Runkle et al., 2016). Lastly, inhibition of protein S-palmitoylation can boost the immune response against tumors if proteins involved in immunosuppressive mechanisms, such as PD-L1, are targeted (Yang et al., 2018a; Yao et al., 2019). However, further studies are required to elucidate the extent to which protein S-palmitoylation plays a role in cancer, and whether it can be therapeutically modulated.

5. TME lipid metabolic alterations in metastasis

We discussed above how HFDs can increase the systemic and intra-tumor levels of lipids, which can affect the function of stromal cells. However, cancer cells themselves can also alter the metabolic composition of the tumor microenvironment (TME) and hijack the function of stromal cells. Apart from the signaling molecules that tumor cells can secrete, the metabolism of cancer cells may generate specific conditions (e.g., acidosis, anoxia, dyslipidemia) within the TME, switching the physiological activity of stromal cells towards a pro-tumorigenic phenotype, as discussed below (**Figure 3**).

Adipocytes

Certain tumor cells disseminate preferentially in fat-enriched tissues. For instance, leukemic stem cells can invade the liver and promote lipolysis as well as the release of chemotherapy-degrading enzymes in hepatocytes by upregulating LIPG lipase and PUFA metabolism (Ye et al., 2021). They can also invade gonadal adipose tissue and induce lipolysis in adipocytes to increase FA uptake via CD36 and acquire chemoresistance (Ye et al., 2016). Adipocytes in contact with ovarian or breast tumors also activate lipolysis and secrete FAs that cancer cells uptake (Balaban et al., 2017) through CD36 (Ladanyi et al., 2018; Zaoui et al., 2019) or FABP4 (Nieman et al., 2011; Yu et al., 2020; Kim et al., 2020) to boost metastasis by promoting FA catabolism and lipid droplet formation. This suggests that adipocytes act as an energy source for the cancer cells to promote rapid tumor growth and increase their invasive capacity. Similarly, melanoma cells can directly take FAs from subcutaneous adipocytes via FATP lipid transporters, which supports tumor growth and invasion (Zhang et al., 2018a), while cholangiocarcinoma associated adipocytes

can also promote metastasis through FABP4 overexpression (Nie et al., 2017). Bone-marrow adipocytes also supply lipids and adipokine factors to myeloma cells (Morris et al., 2020) and metastatic cancer cells colonizing the bone (Herroon et al., 2013), which promotes cell migration and invasiveness together with tumor growth and survival. In turn, cancer cells can produce cytokines that activate stromal adipocytes to secrete FAs, in a paracrine signaling communication loop that promotes cancer progression (Corn et al., 2020).

Cancer-associated fibroblasts (CAFs)

Cancer-associated fibroblasts (CAFs) are characterized by lipid storage (Nardi et al., 2018) and secretion of abundant lipids (Auciello et al., 2019; Gong et al., 2020), which can activate mitogenic and migratory pathways in cancer cells. In colorectal cancer, CAFs reprogram their metabolism by upregulating FASN, thereby increasing their secretion of lipids that cancer cells absorb through CD36 (Gong et al., 2020). Similarly, in pancreatic ductal carcinomas, CAFs derived from stellate cells secrete abundant lipids that support tumor growth (Auciello et al., 2019). Specifically, the secretion of lysophosphatidylcholines signaling lipids by CAFs promotes cancer cell proliferation, migration and AKT activation (Auciello et al., 2019). Worryingly, normal fibroblasts can undergo a lipogenic state during aging (Salzer et al., 2018). In the aged skin, fibroblasts secrete neutral lipids, especially ceramides, which can be uptaken and accumulated in melanoma cells via fatty acid transport protein 2 (FATP2), enhancing their resistance to therapy (Alicea et al., 2020).

Immune cells

In normal conditions, immune cell activity is governed by distinct metabolic programs. Most immune cells with antitumor activity rely on glycolysis and OXPHOS for proper maturation and functioning, including effector T cells (Cong, 2020; Howie et al., 2017), natural killer cells (NKs) (Cong, 2020; Mehla and Singh, 2019), M1 macrophages (Mehla and Singh, 2019), and N1 neutrophils (Injarabian et al., 2019). On the other hand, immunomodulatory cells, like Tregs (Kouidhi et al., 2017), M2 macrophages (Mehla and Singh, 2019), and MDSCs (Hossain et al., 2015), are characterized by enhanced FAO. Thus, the immune compartment of the TME is particularly sensitive to changes in the lipid metabolism.

The metabolic activity of cancer cells within a tumor generates a low-glucose and high-lipid environment that dampens immune surveillance and favors accumulation of immunomodulatory cells. This fatty environment induces CD36 overexpression and lipid uptake in CD8+ T cells, which leads to lipid peroxidation and T-cell dysfunction or even ferroptosis (Ma et al., 2021; Manzo et al., 2020; Xu et al., 2021b), although overexpression of GPX4 upon lipid accumulation in CD8+ T cells can prevent the ferroptosis death and restore their antitumour immunity (Xu et al., 2021b). Dendritic cells (DCs) within the TME accumulate lipid peroxidation byproducts that induce ER stress response and TAG biosynthesis. This lipid accumulation leads to DC dysfunction, decreased antigen cross-presentation, and lack of antitumor T cell activation (Cao et al., 2014; Cubillos-Ruiz et al., 2015; Veglia et al., 2017). Lipid accumulation via CD36 in NK cells upon tumor resection also decreases their cytotoxic capacity and can favor metastases formation after surgical stress (Niavarani et al., 2019; Tai et al., 2013). Interestingly, NK cell dysfunction in the TME due to suppression of glucose metabolism via lipid peroxidation-associated oxidative stress can be overcome by reprogramming cells to use lipids for energy production by activating the antioxidant pathway mediated by NRF2 (Poznanski et al., 2021).

Among immunomodulators, intratumoral Tregs upregulate CD36 and the transcription factor PPAR-β to enhance lipid uptake and FAO (Wang et al., 2020a). These cells can also upregulate SREBPs transcriptional program to increase FASN dependent lipid synthesis and PD-1 (programmed cell death protein 1)–mediated inhibitory receptor signaling (Lim et al., 2021). Tumor-associated macrophages (TAMs) also potentiate lipid metabolism by enhancing CD36 expression (Su et al., 2020), lipid droplet accumulation (Wu et al., 2019), and FAO (Su et al., 2020; Zhang et al., 2018b). Similarly, intratumor MDSCs overexpress FATP1/2 or CD36, which allows them to use and accumulate lipids and to synthesize prostaglandin E2, which ultimately boosts their immunosuppressive function and favors tumor growth (Al-Khami et al., 2017; Veglia et al., 2019).

Therefore, in addition to harnessing tumor development, targeting the lipid metabolism can enhance the immune response against tumors by repressing immunomodulator cells; for instance, inhibiting FAO in MDSCs delays tumor growth in a T cell–dependent manner (Hossain et al., 2015). Also, blocking lipid uptake via CD36 repression in cytotoxic CD8+ T cells (Ma et al., 2021) or Tregs (Wang et al., 2020a) increases the immune surveillance against tumors, which can be further enhanced by combining with anti-PD-1 therapy (Ma et al., 2021; Wang et al., 2020a). Importantly, CD36 expression is relevant for tumor-infiltrating Treg cells but not for the circulating Treg cells; thus, CD36 inhibition should not lead to autoimmune diseases (Wang et al., 2020a). Interestingly, even if it seems counterproductive, the use of PPAR agonists can improve cancer vaccine efficacy by promoting tumor cells to use TME lipids, which increases access of vaccine-induced, tumor-infiltrating CD8+ T cells to glucose and improves their antitumor function (Chekaoui and Ertl, 2021).

Other TME cells

As previously discussed, tumor cells can secrete lipid mediators (e.g., prostaglandins) within the TME that potentiate angiogenesis (i.e., the growth of endothelial vascular cells), which are essential for the growth and spread of cancers and provide a conduit for distant metastasis (Hisano and Hla, 2019). Dietary lipids could also promote tumor innervation; for instance, oral cancer tumors exposed to palmitic acid stimulate intratumor Schwann cells to secrete a specialized, pro-regenerative extracellular matrix that favors metastatic initiation (Pascual et al., 2021). Interestingly, metastatic cells also crosstalk with other cells from the neural system, as is the case of astrocytes, which act as PUFA donors to potentiate PPAR-γ signaling in brain metastasis (Zou et al., 2019).

Conclusions

Cancer cells exploit the lipid metabolism to overcome the different challenges faced during the metastatic cascade. Lipid uptake and storage provide energy to support the journey and building blocks for membrane biosynthesis during secondary outgrowth. By regulating their lipid metabolism, metastatic cells also adapt their lipid membrane composition and generate metabolic intermediates to better tolerate the oxidative environment when detaching from the tumor matrix and during dissemination. Importantly, lipid alterations in the primary tumor and in the pre-metastatic niche can favor the evasion and seeding of cancer cells as well as their escape from the immune surveillance. Worryingly, these lipid-mediated mechanisms seem to be potentiated when diets are enriched in fat, and specially saturated ones. Thus, the exacerbation of different parts of lipid metabolism during the metastatic cascade offers distinct metabolic vulnerabilities that can be exploited to treat metastasis. Besides, some fundamental questions are yet to be fully elucidated

such as what stages of cancer development are more sensitive to fat-enriched diets and what is the required exposure for producing malignant effects. One may speculate that initial tumor formation can be promoted by a "chronic" rather than "sporadic" high fat ingestion since obesity is associated with increased risk of cancer; however, once the tumor is already established, lower exposures to high-fat diets may also result detrimental and increase cancer aggressiveness even in non-obese patients. Given the interconnection of different metabolic pathways, experimental strategies with specific dietary formulations, combined with metabolic tracers and the use of animal models or compounds modulating metabolic pathways may be necessary to detangle the metabolic complexity of the metastatic process. Furthermore, dietary interventions modulating feeding regime or the use of dissociated diets with distinct dietary formulation at different day times may be interesting strategies to prevent the metastatic spread and improve the life-quality of cancer patients. However, despite being a promising therapy, the extreme heterogeneity and metabolic flexibility of cancer cells may complicate the success of metabolic interventions, and combinatorial treatments with cancer-specific targeted therapies may be necessary to eliminate metastatic cells and prevent relapse.

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Conflict of interest statement

S.A.B is the co-founder of ONA Therapeutics

FIGURE LEGENDS

Graphical Abstract. Simplistic view of the lipid metabolism in the metastatic cascade.
Changes in tumor extrinsic factors such as diet composition, systemic lipid homeostasis (including the systemic lipid absorption and transport) and niche environment (including tumor surrounding cells) alter the lipid metabolism of cancer cells which can favor processes of tumor initiation, metastasis and therapy resistance or tumor relapse. Created with BioRender.com

Figure 1. Overview of the major lipid metabolism pathways involved in metastasis.
Fatty acids (FAs) can enter the cell through lipid translocases like CD36, FATPs and FABPs, or via passive diffusion. Once inside the cell FAs are esterified to acyl-CoAs (represented by blue circles) by ACSLs enzymes to be metabolized. Acyl-CoAs, if catabolized, are transported into the mitochondria through CPT1 where they enter fatty acid oxidation (FAO). Acetyl-CoAs generated upon FAO are transferred to the TCA cycle. Electrons from NADH and $FADH_2$ dinucleotides are used in OXPHOS for ATP generation and O_2 respiration. Citrate generated during the TCA cycle can exit the mitochondria and be transformed into acetyl-CoA by ACLY as the first step in de novo lipogenesis. Acetyl-CoA is then used by HMGCR to produce mevalonate in the rate-limiting step of cholesterol synthesis or by FASN, together with malonyl-CoA, to generate palmitate which is then activated to palmitoyl-CoA by ACSLs. Activated palmitate and other saturated fatty acids (SFas) such as stearate can be desaturated by SCDs and FADSs generating monounsaturated FAs (MUFAs). Both SFAs and MUFAs can be elongated by ELOVLs. As for essential FAs (LA and ALA), they are elongated by ELOVLs and desaturated by FADSs for the generation of different polyunsaturated FAs (PUFAs). Fatty acyl-CoAs are then fused with glyderol and converted first into monoacylglycerols (MAGs) and then by the addition of a second FA into diacylglycerols (DAGs). DAGs are used to produce membrane phospholipids or for storage. DGAT is the enzyme responsible for the addition of the last FA to the DAG and generate triacylglycerols (TAGs) which are then stored in lipid droplets. Realease of lipids from lipid droplest is acomplished by lipases that liberate FAs from TAGs, DAGs and MAGs by hydrolisis. The main transcriptional programs governing lipid catabolism (PPARs) and anabolism (SREBPs) processes are depicted on the bottom of the figure. Created with BioRender.com

Figure 2. Lipid signaling in tumor progression.
Tumor cells can use lipid mediators and lipid modifications of proteins to favor tumor progression. **A)** Membrane phospholipases (PLA2, PLC, PLD) generate distinct lipid intermediates that can signal intracelullarly or be secreted by the cell. PLA2 cleaves fatty acyl ester bonds on the glycerol backbone of membrane phospholipids liberating arachidonic acid (AA) and a lysophosphatidic acid (LPA). AA can be further metabolized at the cyclooxygenase (COX-1/2) or lipoxygenase (LOX) pathways for the generation of prostaglandins (PGs) or leukotrienes (LTs), respectively. PLC targets the bond between the glycerol and phosphate moieties generating inositol-1,4,5-trisphosphate (IP3) and diacylglycerol (DAG). PLD breaks the phosphodiester bond of phosphatidylcholine molecules producing choline and a phosphatidic acid (PPA). PGs and LTs are secreted by tumor cells and can trigger autocrine and paracrine signaling cascades, whereas IP3, DAG and PPA activate different intracellular signalings. IP3 is involved in Ca2+ signaling while DAG signals to PKC signaling cascade which is also affected by Ca2+ intracellular levels. On the other hand, PPA modulates mTOR activity and can be interconverted to DAG. **B)** Protein palmitoylation modulates the function different tumor suppressor or oncogene proteins: 1) S-palmitoylation of p53 by DHHC1 at three different cysteines is required for its subsequent phosphorylation upon stress signals and

intranuclear localization to activate different cellular programs; 2) NRAS is S-palmitoylated at the Golgi by DHHC9, what favors its trafficking to the plasma membrane through the endomembrane system. Once at the membrane, NRAS gets activated by different guanine nucleotide exchange factor proteins (GEFs) which triggers its signaling. Created with BioRender.com

Figure 3. Influence of lipids in the tumor microenvironment.
Cellular interactions in the tumor microenvironment mediated by lipids may provide survival advantages for cancer cells and favor metastasis. Stromal cells in red and blue color palettes have pro- and anti-tumoral effects, respectively. Activation of adipocytes, potentially by pro-inflammatory cytokines secreted by tumoral or stromal cells, induces lipolysis of stored triglycerides and secretion of fatty acids that cancer cells can uptake and use or store. Fatty acids secreted by adipocytes and other tumor-associated stromal cells, such as cancer-associated fibroblasts (CAFs), can have a tumor-promoting effect by enhancing growth and invasive/migration process directly in tumor cells but also by impairing or enhancing the functions of the immune cells that are recruited to the TME. For example, lipids in the TME impair the function of natural killer (NK) and T-cells, decreasing the secretion of apoptosis-inducing enzymes and cytokines. Lipids in the TME also decrease the activity of dendritic cells (DC) and promote myeloid derived suppressor cells (MDSC) infiltration and T-reg activity in TME which impair cytotoxic T cell function. Lipids can also induce tumor associated macrophages (TAM) function with pro-tumoral activity. Finally, lipids could also promote the crosstalk with the cells from neural system such as Schwann cells, promoting the secretion of a specialized extracellular matrix (ECM) that favors metastasis. Created with BioRender.com

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