Lipid metabolism in metastasis and therapy

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Abstract (100-120 words)

Alterations in lipid metabolism are being increasingly implicated in the initiation, aggressiveness, and progression to metastasis of cancers. Recent advances have shown that high levels of fat availability and altered lipid metabolism can promote the metastatic process by: i) providing energy for cancer cells, thereby supporting invasion and colonization; ii) promoting their survival by enhancing anti-oxidative, anti-apoptotic mechanisms and therapy resistance; and iii) inhibiting the immune surveillance from detecting/removing tumor cells. These findings are especially disturbing given the alarmingly high fat intake within our modern diet. However, the reprogramming of fat metabolism exhibited by cancer cells and intratumor immune cells promises to generate new pharmacological opportunities to treat metastasis.

Highlights (3-5 bullet points, 85 characters including spaces)

- Pro-metastatic cancer cells show avidity for lipids
- Tumor stromal adipocytes and fibroblasts can provide lipids to cancer cells
- Lipid accumulation favors cancer cell survival and provides energy to the metastatic process
- Enhanced lipid metabolism decreases the tumor immune surveillance and promotes therapy resistance
- Proteins involved in lipid metabolism are promising therapeutic targets

Introduction

Metastasis—the spread of cancer cells to other parts of the body—is the leading cause of cancer-associated deaths, rather than the primary cancers per se. Cancer progression was initially believed to primarily entail the progressive accumulation of mutations that eventually culminate in metastasis. However, epidemiologic studies have now indicated that metastatic tumour genomes can have similar mutational landscapes and driver genes as the primary tumours [1]. This suggests that tumor cells require non-mutational influences to metastasize. Indeed, metabolic alterations play a critical role in tumor progression and dissemination. Although glucose is considered the major metabolic substrate in rapidly proliferating tumours, other glycolytic metabolites (e.g., pyruvate and lactate), amino acids, and especially lipids can boost the metastatic process [2]. Lipid metabolism is commonly altered during the different steps of the metastatic cascade from tumorigenesis to dissemination, colonization of secondary organs and resistance to immune surveillance and clinical therapies. The increase of fatty acid (FA) uptake, synthesis and oxidation often observed in cancer cells at different steps of the metastatic cascade goes beyond energetically fueling this process, and triggers signaling events and membrane composition changes that favors metastasis [review Sarah]. In addition, metabolic alterations in the tumor microenvironment also generate a complex metabolic crosstalk between the tumor and surrounding cells promoting the tumor uptake of lipids released by stromal cells and affecting the immune cell compartment [review Sarah]. Furthermore, there is good evidence that obesity and the excessive consumption of high-fat food are associated with certain types of cancers and their aggressiveness, and that not having excess body fatness lowers the risk of cancer [3]. Thus, here we will review the state-of-the-art on what is known about the mechanisms behind how lipids affect the metastatic process.

Influence of the lipid metabolism in the metastatic process

Alterations in lipid metabolism are implicated in different stages of cancer progression. Tumor initiation seems to be promoted by an enhancement of lipid metabolism in normal tissues. For instance, key regulators of lipid metabolism (PPARα/γ) and FA transport (CD36) are upregulated in breast tissues even before cancer can be detected, suggesting that early activation of lipid metabolism in cancer-free tissues can favor tumor initiation and survival [4]. Excessive dietary fat consumption, even in the short term, can also promote tumorigenesis in liver by enhancing glucose metabolism and altering the lipid composition in non-transformed hepatocytes [5]. Furthermore, tumor initiating cells also have alterations linked to lipid metabolism to support cell growth, as observed in gliomas, where cancer stem cells (CSCs; i.e. those with tumorigenic capacity) epigenetically promote the synthesis of polyunsaturated FA required for plasma membrane formation via epidermal growth factor receptor (EGFR) oncogenic signaling [6]. Other

oncogenes, such as MYC, can increase FA uptake and oxidation based on the activation of calcium signaling to enhance early tumor cell proliferation in triple-negative breast cancer (TNBC) [13]. The expansion of CSCs in colorectal cancer can also be favored by high-fat diets through the activation of the peroxisome proliferator-activated receptor delta (PPARδ) transcriptional program [7].

Apart from its role in tumor initiation, lipid metabolism is particularly relevant for the metastatic cascade. In fact, within the tumor heterogeneity, the small set of cells with metastatic capacity (i.e. those that can form secondary tumors) show increased lipid metabolism and expression of CD36, a FA transporter crucial for metastasis formation [8]–[12]. To colonize distant organs, metastatic initiating cells (MICs) in the primary tumor must undergo important phenotypic changes to exit the tumor, and then migrate and implant on the new niche. Lipid metabolism seems to play an important role in all these processes. For example, the invasion and migration processes triggered by the epithelial-to-mesenchymal (ETM) transition of MICs can be favored by an enhancement of the FA uptake and oxidation via CD36 and CPT1A (the key rate-limiting enzyme of FA oxidation (FAO)) overexpression, respectively [13]-[14]. Similarly, increased *de-novo* lipid biosynthesis through ATP-citrate lyase (ACLY) (a first-step, rate-controlling enzyme in lipid synthesis) and FA synthase (FASN) (a major lipogenic protein), also promote the migration and invasion abilities of cancer cells [15]- [16], which can be mediated by a switch to a 3D anchorage-independent growth [17] and an accumulation of lipids into lipid droplets to energetically support invasiveness [12], [19]–[21]. On the other hand, cell transformation into a more aggressive phenotype can be favored by modifications in their lipid composition, such as by having an elevated arachidonic acid vs. eicosapentaenoic acid ratio [25], increased glycerophospholipids [26] and diacylglycerols levels [27], especially those containing saturated FAs [28]. Imbalances in the cellular FA composition can also promote malignancy. For instance, melanoma cells can have an increased saturated-to-monounsaturated ratio due to the dysregulation of the stearoyl-CoA desaturase (SCD), the main cellular FA desaturase, switching cells to an inflammatory and invasive phenotype **[29]. 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 [30], underscoring the tremendous metabolic flexibility of malignant cells.

To endure the metabolic alterations occurring during metastatic dissemination and the exposure to new environments, cancer cells also elicit protective responses that can be triggered by the activation of lipid-metabolism and cell droplet accumulation. These responses can prevent anoikis-triggered cell death, and favor the production of NADPH, thereby overcoming oxidative stress in several cancer types [12], [19]–[21]. Interestingly, exposure of melanoma CSCs to environments with elevated FA concentrations (e.g.

lymph nodes) also potentiates an anti-oxidative stress response supported by GPX4 expression that protects them from ferroptotic cell death and favors their survival in the systemic circulation to colonize distant organs **[22]. Accumulation of the non-polar lipid squalene or alterations in cholesterol homeostasis also protects cancer cells from ferroptosis, providing a survival advantage in oxidative stress environments and favoring metastatic capacity [23]- [Liu et a. 2021], which highlights the relevant role of ferroptosis in metastasis. Lipids can also favor the extravasation of cancer cells from the blood to other organs: in obese mice on a high-fat diet, extravasation of circulating breast cancer cells to 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 **[24]. Finally, to proliferate in the new niche, metastatic cells require enhanced lipid biosynthesis, as observed in HER2-positive breast cancer cells which increases FASN expression when growing in the brain [18].

Of note, although most evidence suggests that the enhancement of lipid metabolism may favor the metastatic process, a recent study shows that FA degradation was downregulated in metastatic lesions as compared to primary tumors in colorectal cancer patients [31]. Other studies also report that lipid metabolic markers are inversely correlated with poor prognosis in pancreatic cancer [32], and that certain lipids can impair invasiveness and growth in liver and oral cancer by diminishing the β-catenin pathway or by reducing cell membrane fluidity [33], [34]. Some of these opposite findings could be attributed to the developmental grade of the metastatic lesion when the sample was taken (later stages may be energetically less dependent on lipid oxidation) or to lipo-toxicity thresholds (timing and proportions). However, how lipids influence the metastatic process appears to be more nuanced than expected, and more studies are needed to work out the details.

Lipid-related alterations in the tumor microenvironment (TME) facilitate the metastatic process

The TME is the environment around a tumor, including the surrounding stromal cells and non-cellular components (extracellular matrix, signaling molecules and metabolites). Stromal cells can be classified into immune and non-immune cells which, among others, include fibroblasts, the main component of the connective tissue that secretes collagen and extracellular matrix, and adipocytes, a cell specialized in storing energy as fat. Recent results have underscored the important roles that metabolic interactions between tumor cells and the stroma can play in cancer progression. Some tumors and their metastases grow in adipose tissue–enriched environments, which provide both energy and stimuli to support invading surrounding tissues or colonizing distal organs. For instance, fatty environments such as the liver provide a protective niche for leukemic cells and, through the upregulation of endothelial lipase (LIPG) and polyunsaturated

FA-mediated processes, can induce growth and survival pathways **[35]. Further, stromal adipocytes can favor growth and invasion of neighboring cancer cells by transferring lipids to them through lipid transporters overexpressed on the tumor surface [9], [36]–[40], or by enhancing Wnt/β-catenin signaling via CPT1a-mediated FA-oxidation [41]. Cancer cells, in turn, can produce cytokines that activate stromal adipocytes to secrete FA in a paracrine signaling communication loop that promotes cancer progression [42]. Cancer-associated fibroblasts (CAFs) can also secrete lipids that 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 [43]. In the aged skin, fibroblasts secrete neutral lipids, especially ceramides, which can be uptaken and accumulated in melanoma cells via FATP2 *[44].

The immune compartment of the TME encompasses different cell types with very different functions. Macrophages and neutrophils are phagocytes belonging to the innate immune system with different activation modes that promote the secretion of multiple mediators regulating other immune cells. Natural killer (NK) cells are cytotoxic lymphocyte critical to the innate immune system. On the other hand, cytotoxic T-cells (CD8+ or CD4+) are part of the adaptative immune response that kills tumors, while regulatory T-cells (Tregs) are a specialized subpopulation of T-cells that act to suppress immune response, thereby maintaining homeostasis and self-tolerance. Lipids in the TME can impact the function and interactions of infiltrating immune cells, and a pan-cancer integrative analysis revealed a correlation between the immune response and lipid metabolic genes associated with poor prognosis [45]. The stromal immune cells include tumor-associated macrophages (TAMs), which promote tumor growth and metastasis by suppressing the immune surveillance. TAMs can be polarized towards a pro-tumor phenotype by enhanced FAO via the PPAR-γ transcriptional program [46], increased lipid accumulation and JAK/STAT activation [47], or mTOR signaling activation [48]. Stress-activated neutrophils, in turn, can reactivate dormant tumor cells by releasing oxidized lipids that upregulate the fibroblast growth factor pathway in lung and ovarian cancer cells, thereby promoting the formation of new tumor lesions [49]. The antitumor response of other components of the innate immune response, such as the NK cells, can be impaired by obesity or by FA-enriched diets, due to PPARα/δ signaling upregulation and inhibition of mTOR-mediated glycolysis [50]. Similarly, lipid accumulation in NK cells has been observed after surgical intervention, which reduces their cytotoxicity and promotes metastasis formation in colorectal cancer [51]. Accumulation of lipids in the TME can impair the anti-tumor function of CD8+ T-cells by increasing their intracellular lipid levels and inducing lipotoxicity via CD36 overexpression and peroxidation-mediated ferroptosis *[52], [53] or by downregulating the lipid catabolic enzyme VLCAD [54]. Cytotoxic CD4+ T-cell responses are also inhibited in diet-induced obese mice through the dysregulation of autophagy, which is

necessary to sustain their activation [55]. Intratumoral Tregs in breast cancer patients have increased lipid metabolism and CD36 expression as compared with circulating Treg cells, which promotes their accumulation in the TME and therefore their immunosuppressive function [56]. Finally, sterol regulatory element–binding proteins (SREBPs) are activated in intratumoral Treg cells, where they coordinate cellular programs for lipid synthesis and inhibitory receptor signaling via enhanced expression of FASN and PD-1 *[57].

Overall, the enhancement of lipid metabolism in the different cell compartments of tumor stroma favor metastasis formation either by proportioning lipids to fuel the aggressiveness of cancer cells (adipocytes and fibroblasts) and/or by enhancing the regulatory control of cytotoxic cells (TAMs, neutrophils, Tregs) and/or by directly attenuating them (CD8+ T-cells, CD4+ T-cells, NK cells). Thus, lipid metabolism not only enables the metastatic potential of tumor cells but also attenuates the organism response to control and kill them. This implies that targeting lipid metabolism can help prevent metastasis by directly challenging the tumoral cells and by boosting the immune response against them.

Lipid metabolism–mediated therapy resistance and metabolic vulnerabilities

Cancer cells that overcome conventional therapies frequently show alterations in their lipid metabolism that provide them survival advantages for resisting cellular stresses (see Box 1). For instance, castration-resistant prostate cancer cells frequently overexpress the beta-oxidation mitochondrial enzyme 2,4-dienoyl-CoA reductase (DECR1), which controls the balance between saturated and unsaturated phospholipids and induces a redox state that prevents ferroptosis [58]. Overexpression of the endothelial lipase LIPG by leukemic stem cells infiltrating the liver promotes anti-apoptotic pathways and interestingly also induces neighboring hepatocytes to release enzymes capable of degrading chemotherapy drugs **[35]. In HER2-positive breast cancer, chemotherapy resistance has been associated with increased FA metabolism and stemness due to CD36 overexpression and FA synthesis [59], or to CPT1-mediated FA oxidation [60]. Overexpression of FASN is also associated with poor prognosis and increased multidrug resistance in multiple cancers [61]. Melanoma cells, in turn, can evade the BRAF/MEK inhibition by incorporating lipids from the stroma, by upregulating the FATP2 lipid transporter *[44]. In addition, a small population of CD36+ melanoma cells is predominant in the remaining lesions after BRAF/MEKi chemotherapy treatment [62]. Overall, these studies reveal the tremendous metabolic plasticity of cancer cells that allow them to evade current chemotherapy and targeted treatments.

This reinforces the idea that targeting lipid metabolism might be a promising strategy for preventing cancer progression, as successfully shown in numerous preclinical studies (see Box 2). Additionally, given the avidity for FAs and the large number of membrane lipid transporters observed in cells with resistance to chemotherapy, the design of FA-like prodrugs could be a smart and effective strategy to facilitate drug entry into chemoresistant cells to target them [63]. Alternatively, anti-obesity drugs, such as orlistat and other FASN inhibitors, can also prevent tumor progression by restraining FA synthesis and are currently being tested in clinical trials [64], [65]. However, a recent study suggests that orlistat is only effective at high doses due to the availability of FA in plasma [66], and inhibition of FASN can upregulate CD36 expression as a compensatory mechanism for increasing FA uptake and sustaining cell proliferation [67]. Thus, the anti-tumor efficacy of FASN-targeted therapies could be improved if combined with FA uptake inhibitors [67], as observed in prostate cancer cells treated with CD36-inhibiting antibodies [68]. This adds to the growing body of evidence that suppressing FA uptake via CD36 inhibition has the potential to reduce cancer severity and prevent metastasis in several cancer models [8], [9], [11], [69]. Inhibition of other lipid transporters, such as FABP4, also prevents chemoresistance and metastasis formation in ovarian cancer [40]. Moreover, cancer progression can be restrained through chemical inhibition of key regulators of lipid metabolism, such as CPT1a [12], [14], [70], SCD desaturase **[29], [30], [71], and the lipogenic enzymes DGAT1 [20], [72], acetyl-CoA carboxylase 1/2 (ACC1/2) [73], and acetyl-CoA synthetase 2 (ACSS2) [74]. Similarly, repurposing of the antiparasitic drug pyrvinium pamoate has shown promising effects in killing CSCs and reducing metastasis through inhibition of lipid anabolism in TNBC [75]. On the other hand, drugs enhancing lipid peroxidation in cancer cells to promote ferroptosis have also shown potential as a therapeutic strategy [76], which agrees with recent findings describing FA oxidation–induced ferroptosis as a mechanism by which radiotherapy and immunotherapy control tumor growth [77]. Finally, inhibition of protein lipidation can boost the immune response against tumors if proteins involved in immunosuppressive mechanisms, such as PD-L1, are targeted **[57], [78], [79], and can prevent migration and growth of cancer cells if proteins involved in the metastatic process, such as TEAD, are targeted [80]–[83].

Finally, it should be considered that, as previously stated, interventions targeting lipid metabolism would also impact on the activation/inactivation of stromal cells altering the metabolic crosstalk and the immune response. Also, the metabolic plasticity observed among different tumor types and sometimes within the same tumor can impede the efficacy of therapeutical interventions. This tumor heterogeneity in terms of metabolic phenotype highlights the relevance of designing tailored interventions targeting cancer metabolism to specific tumors.

Conclusions

Metastasis is a systemic process that requires metabolic adaptations in cancer cells to evade the primary tumor and to survive and proliferate in new environments. Increasing evidence indicates that cancer cells rely on lipid metabolism to metastasize, and that lipid accumulation in the TME can fuel this process and prevent immune surveillance. Metastatic cells can also escape current anti-cancer therapies, which mostly target the primary tumor, by switching their lipid metabolism. This raises an alarm about the potential impact that both fat-rich diets and the increasing percentage of obesity could have in promoting metastasis and therapy resistance—especially since both are very prevalent in today's world. On the flip side, artificial modulation of lipid metabolism could be also devised as a therapeutic strategy to exacerbate the targetable vulnerabilities of metastatic cells *[72] or to enhance immunotherapy [84]. Thus, strategies combining metabolic interventions and targeted therapies will probably be required to prevent metastasis but could also be hijacked in therapies to boost antitumor immunity and chemotherapy efficacy.

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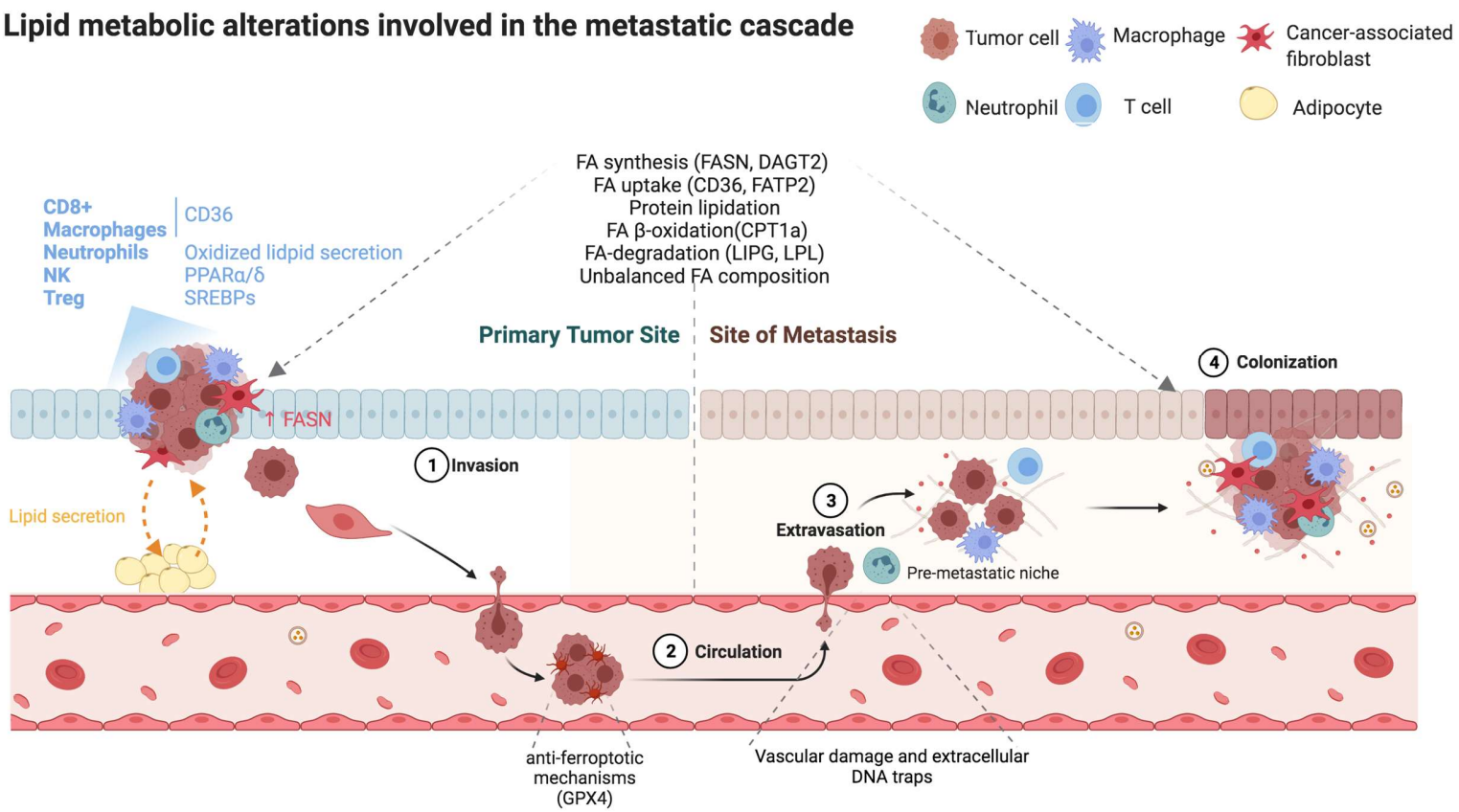

Figure 1. Diagram of the metastatic cascade. The main lipid-mediated processes and genes involved at each stage are shown. Adapted from "Overview of Metastatic Cascade", by BioRender.com (2021). Retrieved from https://app.biorender.com/biorender-templates

BOX 1 Summary of lipid metabolic genes and processes involved in chemotherapy resistance

Metabolic process	Genes	Cancer type	References
Lipid catabolism / FA oxidation	**LIPG**	Leukemia	**[35]**
	DECR1	Prostate cancer (castration-resistant)	**[58]**
	CPT1a	Breast cancer (HER2+)	**[60]**
Lipid anabolism	**FASN**	Ovarian cancer	**[61]**
Lipid uptake	**FATP2**	Skin cancer	**[44]**
	CD36	Breast cancer (HER2+)	**[59]**

BOX 2 Summary of potential pharmacological therapeutic targets involved in lipid metabolism

Metabolic process	Genes	Cancer type	References
Lipid catabolism / FA oxidation	**CPT1a**	Colorectal and Oral cancer	**[12]**
		Gastric cancer	**[14]**
		Ovarian cancer	**[70]**
FA desaturation	**SCD1**	Skin cancer	**[29]**
		Liver and Lung cancer	**[30]**
		Glioblastoma	**[71]**
Lipid anabolism	**FASN**	Breast cancer	**[17], [18]**
		Multiple cancers	**[65]**
		Colorectal cancer	**[66], [67]**
		Prostate cancer	**[68]**
	DGAT1	Gastric cancer	**[20]**
		Cervix, colorectal, oral cancer	**[72]**
	ACC1/2	Liver cancer	**[73]**
	ACSS2	Breast cancer (TNBC)	**[74]**
Lipid uptake	**CD36**	Oral, breast, skin cancer	**[8]**
		Ovarian cancer	**[9]**
		Gastric cancer, Colorectal cancer	**[11]**

	FABP4	Colorectal cancer Prostate cancer Ovarian cancer	**[67]** **[68], [69]** **[40]**

ABBREVIATIONS

AA: arachidonic acid

ACADVL: acyl-CoA dehydrogenase enzyme very long chain

ACC1/2: acetyl-CoA carboxylase ½

ACSS2: acyl-CoA synthetase short chain family member 2

CAF: cancer-associated fibroblast

CPT1A: carnitine palmitoyltransferase 1A

CSC: cancer stem cells

DAGT2: diacylglycerol O-acyltransferase 2

DECR1: 2,4-dienoyl-CoA reductase 1

EGFR: epidermal growth factor receptor

EPA: eicosapentaenoic acid

FA: fatty acid

FASN: fatty acid synthase

FATP2: fatty acid transport protein 2

HER2: human epithelial growth factor receptor 2

JAK: Janus kinase

LIPG: lipase G

mTOR: mammalian target of Rapamycin

NK cell: natural killer cell

PD-1: programmed cell death protein 1

PPARα/δ: peroxisome proliferator activated receptor alfa/delta

SCD: stearoyl-CoA desaturase

SREBP: sterol regulatory element binding protein

STAT: signal transducer and activator of transcription

TAM: tumor-associated macrophages

TEAD: TEA domain transcription factor

THEM6: Thioesterase superfamily member 6

TME: tumor microenvironment

TNBC: triple-negative breast cancer

Treg: regulatory T cells (which are immunosuppressive)