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REVIEW

Lipid metabolism and its implications in tumor cell plasticity and drug resistance: what we learned thus far?

Ravichandran Vishwa[1] · Bandari BharathwajChetty[1] · Sosmitha Girisa[1] · Babu Santha Aswani[1] · Mohammed S. Alqahtani[2] · Mohamed Abbas[3] · Mangala Hegde[1] · Ajaikumar B. Kunnumakkara[1]

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Abstract

Metabolic reprogramming, a hallmark of cancer, allows cancer cells to adapt to their specific energy needs. The Warburg effect benefits cancer cells in both hypoxic and normoxic conditions and is a well-studied reprogramming of metabolism in cancer. Interestingly, the alteration of other metabolic pathways, especially lipid metabolism has also grabbed the attention of scientists worldwide. Lipids, primarily consisting of fatty acids, phospholipids and cholesterol, play essential roles as structural component of cell membrane, signalling molecule and energy reserves. This reprogramming primarily involves aberrations in the uptake, synthesis and breakdown of lipids, thereby contributing to the survival, proliferation, invasion, migration and metastasis of cancer cells. The development of resistance to the existing treatment modalities poses a major challenge in the field of cancer therapy. Also, the plasticity of tumor cells was reported to be a contributing factor for the development of resistance. A number of studies implicated that dysregulated lipid metabolism contributes to tumor cell plasticity and associated drug resistance. Therefore, it is important to understand the intricate reprogramming of lipid metabolism in cancer cells. In this review, we mainly focused on the implication of disturbed lipid metabolic events on inducing tumor cell plasticity-mediated drug resistance. In addition, we also discussed the concept of lipid peroxidation and its crucial role in phenotypic switching and resistance to ferroptosis in cancer cells. Elucidating the relationship between lipid metabolism, tumor cell plasticity and emergence of resistance will open new opportunities to develop innovative strategies and combinatorial approaches for the treatment of cancer.

Abbreviations

27HC	27-Hydroxycholesterol
27HCR	27-Hydroxycholesterol resistance
27HCS	27-Hydroxycholesterol sensitive
ACACA	Acetyl-CoA carboxylase alpha
ACM	Adipocyte conditioned media
ACSLs	Acyl-CoA synthetase long-chain family proteins
ACOX1	Acyl-CoA oxidase 1
ANGPTL4	Angiopoietin-like 4
APC	Activated protein C
ASCs	Adipocyte stem cells
ASCM	Adipocyte-derived stem cell conditioned media
ATP	Adenosine triphosphate
BRAF	B-Raf proto-oncogene
CACT	Carnitine/acylcarnitine translocase
CaMK	Calcium/calmodulin-dependent protein kinase
CCL6	C-C motif ligand 6
CD133	Cluster of differentiation 133
cKO	Conditional knockout
CPT	Carnitine palmitoyltransferase
CRAT	Carnitine acetyltransferase
CS	Charcoal stripped
CSC	Cancer stem cell
CSS	Charcoal stripped serum
CYP51A1	Lanosterol 14α-demethylase
DHCR	Dehydrocholesterol reductase
DL-FBS	Delipidated fetal bovine serum
DNA	Deoxyribonucleic acid

✉ Ajaikumar B. Kunnumakkara
kunnumakkara@iitg.ac.in

[1] Cancer Biology Laboratory, Department of Biosciences and Bioengineering, Indian Institute of Technology Guwahati (IITG), Guwahati 781039, Assam, India

[2] Radiological Sciences Department, College of Applied Medical Sciences, King Khalid University, Abha 61421, Saudi Arabia

[3] Electrical Engineering Department, College of Engineering, King Khalid University, Abha 61421, Saudi Arabia

DNL	*De novo* Lipogenesis
ECM	Extracellular matrix
ECH1	Enoyl-CoA hydratase 1
EGFR	Epidermal growth factor receptor
EMT	Epithelial-mesenchymal transition
FA	Fatty acid
FABP	Fatty acid binding protein
FAK	Focal adhesion kinase
FAO	Fatty acid oxidation
FASN	Fatty acid synthase
FAT	Fatty acid translocase
FATP	Fatty acid transport protein family
FER	Ferrostatin
FFA	Free fatty acids
FN	Fibronectin
GOLM1	Golgi membrane protein 1
GPX4	Glutathione peroxidase 4
GSH	Glutathione
HIF-1α	Hypoxia inducible factor-1α
HILPDA	Hypoxia-inducible lipid droplet-associated protein
HMGCR	Hydroxymethylglutaryl-coenzyme A reductase
HPA	Human primary adipocytes
LDL	Low-density lipoprotein
LDLR	Low-density lipoprotein receptor
LIPA	Lipase A
LIPE	Lipase E
LPA	Lysophosphatidic acid
LPAR	Lysophosphatidic acid receptor
LRP	Low-density lipoprotein receptor-related protein
MARCO	Macrophage receptor with a collagenous structure
MEK	Mitogen-activated protein kinase
MUFA	Monounsaturated fatty acids
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NL	Neutral lipids
NPC	Nasopharyngeal carcinoma
OCT4	Octamer-binding transcription factor 4
PL	Phospholipids
pmCiC	Plasma membrane citrate transporter
PROCR	Protein C receptor
RNA	Ribonucleic acid
ROS	Reactive oxygen species
RTKs	Receptor tyrosine kinases
S1P	Sphingosine-1-phosphate
SCD	Stearoyl-CoA desaturase
SERPINE1	Serpin family E member 1
SGPL1	Sphingosine-1-phosphate lyase 1
shRNA	Short hairpin RNA
siRNA	Small interfering RNA
SLC	Solute carrier
SLC27	Solute carrier family 27
SL	Sphingolipids
SOX2	SRY-box transcription factor 2
SREBF	Sterol regulatory element binding transcription factor
SREBP	Sterol regulatory element binding protein
SSO	Sulfo-N-succinimidyl oleate
TAM	Tumor-associated macrophage
TCA	Tricarboxylic acid
TG	Triglyceride
TGF-β	Transforming growth factor-beta
TKI	Tyrosine kinase inhibitor
TME	Tumor microenvironment
ZEB1	Zinc finger E-box binding homeobox 1

1 Introduction

Cancer, with a worldwide death of nearly 10 million in 2020, remains one of the most lethal diseases of mankind [1]. The fundamental question of understanding cancer remains a difficult task because of the various challenges associated with the observation [2–4]. Diverse molecular pathways governing cellular processes such as survival, proliferation, phenotype transition, migration, aging, and death rely on the cascades of intracellular signalling [5–8]. Anomalies arising from errors in deoxyribonucleic acid (DNA) replication, chromosomal modifications, and epigenetic changes disrupt these processes [5–8, 9]. Consequently, these disruptions foster aberrant cell growth, ultimately contributing to tumorigenesis [5, 8]. Human cells acquire various functional attributes that are essential during their transition from normal state to neoplastic state and are termed as hallmarks of cancer, might be mapped to align with each step of tumorigenesis [5, 8]. The metabolic reprogramming observed in cancer cells, was identified as a hallmark by Hanahan and Weinberg in 2011, involves aberrations in bioenergetic processes encompassing carbohydrate metabolism, amino acid metabolism, nucleic acid metabolism, lipid metabolism, and other metabolism [8, 10]. This adaptive process allows cancer cells to finely tune their molecular machinery in response to the microenvironment during various stages of cancer progression [8, 10]. Until 1900s, lipolysis and/or proteolysis were considered to be the necessary energy-yielding reactions associated with cancer growth [11]. Lipids, including phospholipids (PL), sphingolipids (SL), triglycerides (TG), fatty acids (FA), and sterols, were not only involved in essential biological functions such as energy reserves, membrane components, and signalling molecules, but also reported to be involved in immunoediting, angiogenesis, invasion, and migration of cancer cells [12–14]. Cancer cells obtain lipids from the neighboring microenvironment through

direct uptake or by *de novo* synthesis [12]. *De novo* lipogenesis (DNL) is the process of synthesizing lipids from glucose, acetate, or glutamine [12]. This process is specifically restricted to adipocytes, hepatocytes, and lactating breast in normal physiological conditions, but cancer cells reactivate this process of lipid synthesis [12]. Other than activation of DNL, genes responsible for lipid uptake such as, FA translocase/cluster of differentiation 36 (FAT/CD36), solute carrier (SLC) family 27 (SLC27) also known as FA transport protein family (FATP), and plasma membrane FA-binding proteins (FABPs), were observed to be modulated in tumor [15–20]. In cancer cells, augmented FA synthesis is typically observed irrespective of extracellular lipid availability [21, 22]. However, under metabolically stressful conditions, cells scavenge lipids over synthesis to meet the need for energy [23–26]. Tumor cells increase lipid levels and disrupt homeostasis by altering various lipid metabolic processes such as DNL, lipid transport, and lipid oxidation to assist cell proliferation and movement and to meet the future energy demand of the cancer cells [12, 13, 18, 27–29]. These disruptions enable metabolic adaptation of cancer cells linked with the tumor microenvironment (TME) changes to assist the progression of the disease [10, 12, 30–33]. The drugs designed to target cancer cells impede their proliferation; however, metabolic reprogramming subsequently reinstates the survival and growth of cancer cells, contributing to therapeutic failure [30, 34–36]. Thus, metabolic reprogramming also plays a pivotal role in the development of resistance [35–38]. Chemoresistance, whether intrinsic or acquired, encompasses the mechanisms employed by TME to evade the therapeutic effect of chemotherapy [35, 39–41]. This phenomenon arises due to distorted regulation in signalling pathways, cancer stem cells (CSCs) adaptations, alterations in cancer metabolism, epithelial-mesenchymal transition (EMT), drug efflux, dodging apoptosis, mutations in relapsed tumor and mitochondrial alterations [35, 39–41]. Resistance often evolves as a result of clonal selection by promoting a metabolic rewiring suited to the stress due to the drug and exerts a greater difficulty in achieving the expected therapeutic outcome [35–37, 42]. Another driving force for the emergence of resistance is tumor cell plasticity [43–45]. The ability of cells to reversibly switch phenotypes, known as cellular plasticity, is an indispensable feature of liver cells and stem cells to adapt to numerous cellular constraints that occur during liver regeneration and embryonic development [46, 47]. EMT is often referred to as a binary process distinguished either as epithelial or mesenchymal phenotype; however, a more recent understanding suggested that the cells lie in a continuum, allowing cells to exist anywhere in the spectrum of EMT, expressing combined features of both epithelial and mesenchymal phenotypes [48, 49]. In addition, cells in the intermediate EMT state have shown to exhibit stem cells characteristics [49]. EMT inducers, including SNAIL1 and TWIST, have also been observed to increase the degree of stemness of cells [49]. These observations demonstrated that EMT might be linked to acquisition of stem cell properties [48, 49]. Interestingly, targeting tumor cell plasticity and reversal of EMT has demonstrated the potential to improve cancer therapeutics [43, 50, 51]. The involvement of lipids in diverse facets of cancer progression and the role of tumor cell plasticity in conferring therapeutic resistance has been extensively investigated [13, 14, 43, 45]. However, there is currently a dearth of research focused on addressing the interconnected relationship between lipid metabolism and drug resistance associated with the plasticity of the tumor cells. Therefore, in this review, we focused on the process of understanding the tumor cell plasticity and the consequent development of drug resistance in response to lipid metabolic reprogramming. Moreover, in our exploration of tumor cell plasticity, we focused on key factors such as CSC, transdifferentiation, EMT, and the processes of invasion, migration, and metastasis that result from EMT in cancer cells. Inclusively, this offers a different vantage to delineate the molecular interactions within cancer by embracing lipid remodeling as a vital regulator of the tumor plasticity associated with drug resistance.

2 Lipid uptake and tumor cell plasticity

The process of lipolysis, including the hydrolytic cleavage of both extracellular and intracellular complex lipid entities into free FA (FFA), subsequently accompanied by FFA uptake, plays a pivotal role in augmenting the cellular FA pool [21, 52, 53]. FAs are essential components in diverse cellular functions, contributing to the composition of the plasma membrane, serving as an energy reservoir, and participating in signalling pathways [54, 55]. The uptake of cholesterol, low-density lipoproteins (LDL), and FAs were mediated by several surface receptor proteins, including the LDL receptor (LDLR), LDLR-related family proteins (LRP), adenosine triphosphate (ATP) binding cassette (ABC) A subfamily proteins, scavenger receptor proteins, and SLC27 [15–17, 56]. Modulation of lipid uptake proteins has been demonstrated to influence tumor cell plasticity and the development of drug resistance. A detailed summary has been given in Table 1.

Exploring the effect of adipocyte conditioned media (ACM) on breast cancer cell lines, Zaoui and colleagues observed increased levels of palmitic acid and arachidonic acid, along with reduced oleic acid levels in ACM obtained after differentiation of adipocyte stem cells (ASCs) from breast cancer patients compared to ACM from ASCs of cancer-free women [57]. Culturing breast cancer cell lines with ACM, induced invasion and migration of SUM159 cells irrespective of whether ASCs originated from tumors

Table 1 Lipid uptake and its implications on tumor cell plasticity and drug resistance

Type of the study	Cell line/model/tissue	Condition/treatment	Effect on plasticity	Mechanism/experimental outcome	Reference
Breast cancer					
In vitro	SUM159	Tumor ACM, Normal ACM	↑Invasion and Migration	↑CD36	[57]
In vitro	MCF-7	ASCM	↑Migration	↑HIF-1α ↓Spheroid roundness	[58]
In vitro	MCF-7	CS-ASCM	↓Migration	↑Spheroid roundness ↓HIF-1α	[58]
In vitro	MCF-7	CS-ASCM + LM	↑Migration	↑HIF-1α ↓Spheroid roundness	[58]
In vitro	4T1-27HCR	FBS (regular)	↑Migration	↑Lipid droplets, FAU, VLDLR, FABP3, FABP4, FABP7, FABP9, ACSL6 ↓HMGCS, HMGCR, FASN, SCARA5, ACSL3, ACSL4, ACSL5, DBI	[18]
In vitro	4T1-27HCR	DL-FBS	↑Migration	No prominent increase in migration	[18]
In vitro	Py230-27HCR	FBS (regular)	↑Migration	↑Lipid droplets, HMGCS, HMGCR, SCARB1, VLDLR, SLC27A1, SLC27A3, FABP4, FABP5, ACSL3 ↓LDLR, DBI, ACSL1	[18]
In vitro	Py230-27HCR	DL-FBS	-	No prominent change in migration	[18]
In vivo	BALB/c mice xenograft (4T1-27HCR)	NT	↑Metastasis	↑Lung metastasis	[18]
In vivo	C57BL/6 mice xenograft (Py230-27HCR)	NT	↑Metastasis	↑Lung metastasis	[18]
In vitro	HCC1954-27HCR	FBS (regular)	↑Migration	↑Lipid droplets, total lipids, cholesterol, PL, NL, SL, FFA, sterol, FAU, ABCA1, CD36, LDLR, ACSL3, ACSL4, SLC27A1, SLC27A2, SLC27A3, SLC27A5 ↓ACC1, ACSL5	[18]
In vitro	HCC1954-27HCR	DL-FBS	-	No prominent change in migration	[18]
In vitro	rBT474	siCD36	-	↑Apoptosis	[59]
In vitro	rBT474	SSO + Lapatinib	-	Sensitized to lapatinib ↓Cell proliferation	[59]
In vivo	NSG mice xenograft (rBT474)	JC63.1 + Lapatinib	-	Sensitized to lapatinib ↓Tumor volume	[59]
Colon cancer					
In vitro	WiDr	ASCM	↑Migration	↑HIF-1α, N-cadherin, VIM, ZEB1, SLUG, β-catenin ↓Spheroid roundness, E-cadherin, ZO1	[58]
In vitro	WiDr	CS-ASCM	↓Migration	↑Spheroid roundness ↓HIF-1α	[58]
In vitro	WiDr	CS-ASCM + LM	↑Migration	↑HIF-1α ↓Spheroid roundness	[58]
In vivo	BALB/c nude mice xenograft (WiDr)	LM	↑Metastasis	-	[58]
In vivo	BALB/c nude mice xenograft (WiDr)	LM + siHIF-1α	↓Metastasis	-	[58]

Table 1 (continued)

Type of the study	Cell line/model/tissue	Condition/treatment	Effect on plasticity	Mechanism/experimental outcome	Reference
Ovarian cancer					
In silico	Omental metastasis tissue data from Oncomine dataset (Abid, Bittner, and Tothill)	NT	-	↑CD36	[19]
In vitro	SKOV3ip1	HPA co-culture	↑Invasion and Migration	↑CD36, total cholesterol, IL-8 ↓ACACA, SREBF1, SREBF2	[19]
In vitro	SKOV3ip1	HPA co-culture + shRNA-CD36	↓Invasion and Migration	↑p-AMPkα ↓Lipid droplet area, total cholesterol	[19]
In vivo	BALB/c nude mice xenograft (SKOV3ip1)	shRNA-CD36	↓Metastasis	↓CD36	[19]
In vivo	BALB/c nude mice xenograft (OVCAR-8)	anti-CD36 antibody	↓Metastasis	↓CD36 activity	[19]
Clinical	Omental metastasis tissues	NT	-	↑CD36	[19]
Prostate cancer					
In vivo	NOD-SCID mice xenograft ($Pten^{-/-}$; $Smad4^{-/-}$ PCa cells)	NT	↑Invasion	↑CD206, ADFP, lipid loaded TAMs, CCL6	[60]
In vivo	NOD-SCID mice xenograft ($Pten^{-/-}$; $Smad4^{-/-}$ PCa cells)	αMARCO	↓Invasion	↓Lipid droplets	[60]
In vivo	NOD-SCID mice xenograft ($Pten^{-/-}$; $Smad4^{-/-}$ PCa cells)	αMARCO + Docetaxel	↓Resistance	↓Tumor size, docetaxel resistance	[60]
In vitro	PC-3	ASCM	↑Migration	↑HIF-1α ↓Spheroid roundness	[58]
In vitro	PC-3	CS-ASCM	↓Migration	↑Spheroid roundness ↓HIF-1α	[58]
In vitro	PC-3	CS-ASCM + LM	↑Migration	↑HIF-1α ↓Spheroid roundness	[58]
In silico	Bone metastasis tissue data from Iglesias-Gato proteome dataset	NT	-	↑ABCA3, ABCB6, ABCB10, ABCF2, GOT2, LDLR, LRP1, LRP5, LRP8, LRPAP1, NPC1, SCARB1, SCARB2, SLC27A1, SLC27A2, SLC27A3 ↓ABCA2, SLC27A4	[20]
In silico	Metastasis tissue data from Oncomine dataset (Grasso, LaTulippe)	NT	-	↑LDLR	[20]
In silico	Metastasis tissue data from Oncomine dataset (Grasso, Varambally, LaTulippe)	NT	-	↑SCARB1	[20]
Skin cancer					
In vitro	BPD6-27HCR	FBS (regular)	↑Migration	↑Lipid droplets, FAU, ABCA1, ABCG1 HMGCS, LDLR, FASN, ACC1	[18]
In vitro	BPD6-27HCR	DL-FBS	-	No prominent change in migration	[18]

Table 1 (continued)

Type of the study	Cell line/model/tissue	Condition/treatment	Effect on plasticity	Mechanism/experimental outcome	Reference
In vitro	B16F10-27HCR	FBS (regular)	↑Migration	↑FAU, ABCA1, FASN, ACC1, SCARB1, SCARB2, LDLR, VLDLR, FABP4, FABP5, FABP7, FABP9, ACSL5, DBI, SLC27A1 ↓ABCG1, HMGCS, FABP3, ACSL1, ACSL6, SLC27A6	[18]
In vitro	B16F10-27HCR	DL-FBS	-	No prominent change in migration	[18]
In vivo	C57BL/6 mice xenograft (BPD6-27HCR)	NT	↑Metastasis	↑Lung metastasis	[18]

27HC 27-hydroxycholesterol, *27HCR* 27-hydroxycholesterol resistant, *27HCS* 27-hydroxycholesterol sensitive, *ABC* ATP-binding cassette family proteins, *ACACA* Acetyl-CoA carboxylase alpha, *ACC* Acetyl-CoA carboxylase, *ACM*, Adipocyte conditioned media, *ACSL* Acyl-CoA synthetase long-chain family proteins, *ACSL4* Acyl-CoA synthetase long-chain family member 4, *ADFP* Adipose differentiation-related protein, *AMPK* Adenosine monophosphate-activated protein kinase, *ASCM* Adipocyte derived stem cell conditioned media, *CCL6* C–C motif chemokine ligand 6, *CD206* Cluster of Differentiation 206, *CD36* Cluster of differentiation 36, *CS* Charcoal stripped, *DBI* Diazepam binding inhibitor, *DL-FBS* Delipidated fetal bovine serum, *FABP* Fatty acid binding protein, *FASN* Fatty acid synthase, *FAU* Fatty acid uptake, *GFP* Green fluorescent protein, *GOT2* Glutamic-oxaloacetic transaminase 2, *HIF-1α* Hypoxia inducible factor-1α, *HMGCR* Hydroxy-3-methylglutaryl-CoA reductase, *HMGCS* Hydroxy-3-methylglutaryl-CoA synthase, *HPA* Human primary adipocytes, *IL-8* Interleukin-8, *LDLR* Low-density lipoprotein receptor, *LM* Lipid mixture, *LRP* Low-density lipoprotein receptor-related proteins, *MARCO* Macrophage receptor with collagenous structure, *NL* Neutral lipid, *NT* No treatment, *PL* Phospholipids, *SCARA5* Scavenger receptor class A member 5, *SCARB* Scavenger receptor class B, *shRNA* Short harpin RNA, *SL* Sphingolipid, *SLC* Solute carrier family proteins, *SREBPF* Sterol regulatory element binding transcription factor, *SSO* Sulfo-N-succinimidyl oleate, *TAMs* Tumor-associated macrophages, *VIM* Vimentin, *VLDLR* Very low density lipoprotein receptor, *ZEB1* Zinc finger E-box binding homeobox 1, *ZO1* Zonula occludens-1

or normal tissues [57]. The ACM treatment also resulted in an increased expression of CD36, but no lipid accumulation was observed in SUM159 cells, irrespective of ACM origin [57]. Interestingly, a similar alteration in CD36 expression was observed in MCF-7 cell line upon ACM treatment, but with an increased lipid accumulation regardless of ACM origin [57]. This change in CD36 expression and lipid droplet levels did not significantly affect the invasion and migration of the MCF-7 cell line [57]. These observations showed that the ACM from ASCs of tumor and normal tissues were not fundamentally different [57]. In another study, co-culture with human primary adipocytes (HPA) increased CD36 expression in ovarian cancer cell lines and enhanced FA uptake and total cholesterol level [19]. In addition, ACM also increased FA uptake in the SKOV3ip1 cell line, and this effect was repressed by the CD36 inhibitor sulfo-N-succinimidyl oleate (SSO) [19]. HPA co-culture mediated increase in CD36 expression shifted lipid metabolism towards reliance on exogenous FAs and cholesterol, indicated by a decrease in the expression of acetyl-CoA carboxylase alpha (ACACA), sterol regulatory element-binding transcription factor (SREBF)1 and SREBF2, proteins and transcription factors involved in lipid synthesis [19]. HPA co-culture also upregulated interleukin-8, which is involved in omental metastasis, in SKOV3ip1 cells [19]. The enhanced CD36 expression facilitated the invasion and migration of SKOV3ip1 cells [19]. Moreover, the knockdown of CD36 with short hairpin ribonucleic acid (shRNA) reversed the HPA co-culture-induced invasion and migration of SKOV3ip1 cells along with a reduction in the total cholesterol level and lipid accumulation [19]. Further, inhibition of CD36 resulted in significant reduction of metastasis in SKOV3ip1 and OVCAR-8 xenograft models [19]. Furthermore, supporting the *in vitro* and *in vivo* results, CD36 expression was higher in omental metastasis tissues compared to paired primary tumor tissues in ovarian cancer patients, and consistent upregulation was observed in omental metastatic expression data from Oncomine datasets [19]. Another study showed that inhibition of CD36 with SSO sensitized the lapatinib-resistant breast cancer cells (rBT474) to lapatinib [59]. In addition, small interfering RNA (siRNA) mediated silencing of CD36 enhanced apoptosis in rBT474 cell line [59]. Moreover, the CD36 inhibitor, JC63.1, sensitized the lapatinib treatment in SCID mice bearing lapatinib-resistant breast cancer cells [59]. Breast, colon, and prostate cancer cells, upon exposure to adipocyte-derived stem cell conditioned media (ASCM), showed hypoxia-inducible factor-1α (HIF-1α) upregulation and enhanced cell migration [58]. The increased migratory capability of WiDr colorectal cancer cells upon ASCM treatment was attributed to increased expression of HIF-1α, subsequently led to the upregulation of vimentin, zinc finger E-box binding homeobox 1 (ZEB1), SLUG, and β-catenin and downregulation of E-cadherin

and zonula occludens-1 [58]. In addition, treatment with charcoal-stripped (CS)-ASCM, downregulated HIF-1α and reduced migration of MCF-7, PC-3, and WiDr cells [58]. Moreover, when these cell lines treated with lipid mixture and CS-ASCM, the HIF-1α expression and cell migration were increased [58]. Further, the involvement of HIF-1α in the metastatic transformation of cancer cells was substantiated through *in vivo* studies on WiDr cells xenografts, which showed reversal of lipid mixture induced metastasis by intraperitoneal injection of HIF-1α siRNA [58]. Thus, adipocyte-derived lipids enhanced the cancer cell migration by regulating EMT-related genes via the lipid/HIF-1α axis [58].

27-Hydroxycholesterol (27HC), an oxysterol, has been shown to attenuate the growth of estrogen receptor-negative breast cancer cells [18]. In addition, the ability of migration of 27HC resistant (27HCR) 4T1, Py230, and HCC1954 breast cancer cell lines and BPD6 and B16F10 melanoma cell lines was enhanced on normal culture condition with fetal bovine serum (FBS), when compared to its 27HC sensitive (27HCS) counterparts [18]. 27HCR cell lines showed increased lipid levels and FA uptake by altering the expression of VLDLR, SLC27, and FABPs [18]. Particularly in the HCC1954-27HCR cell line, increased levels of cholesterol, PL, neutral lipids (NL), SL, sterols, and FFA were observed [18]. Moreover, culturing with delipidated FBS (DL-FBS), the migrating ability of HCC1954-27HCR, Py230-27HCR, BPD6-27HCR, and B16F10-27HCR cell lines were not enhanced, and there was a reduction in 4T1-27HCR migrating index on comparing with 4T1-27HCR FBS culture [18]. Besides, the *in vivo* models bearing 4T1-27HCR, Py230-27HCR, and BPD6-27HCR cell lines displayed high metastatic potential [18]. In another study, *in silico* analysis performed using proteome datasets from the Iglesias-Gato database showed a remarkable upregulation of 16 lipid transporters in bone metastasis samples compared to primary tumor samples from prostate cancer patients [20]. In contrast, the expression of two other lipid transporters, ABCA2 and SLC27 member 4, was found to be decreased in the bone metastasis samples [20]. In addition, an elevated expression of LDLR was observed in metastatic samples compared to the primary tumor, in prostate cancer data from the Grasso and LaTulippe cohorts of the Oncomine dataset [20]. In metastatic samples from the Grasso, Varambally, and LaTulippe cohorts, the scavenger receptor class B type 1 gene was upregulated [20].

Further, single-cell analysis of prostate cancer tissues revealed the presence of increased numbers of lipid-loaded tumor-associated macrophages (TAMs) characterized by elevated expression of adipophilin [60]. This phenomenon is associated with prostate cancer progression, as these TAMs release the chemokine C–C motif ligand 6 (CCL6), thereby promoting the migration of prostate cancer cells [60]. These lipid-loaded TAMs also contributed to invasion of cancer cells and to development of resistance to docetaxel in prostate cancer, which was shown to be effectively reversed by treatment with macrophage receptor with a collagenous structure (MARCO) neutralizing antibody [60]. MARCO is a scavenger receptor involved in the uptake of LDLs into TAMs, thus contributing to the generation of lipid-loaded TAMs [60]. Collectively, increased expression of lipid transporters has demonstrated to enhance the uptake of FAs, consequently promoting cancer metastasis via inducing tumor cell plasticity (Fig. 1). Notably, the overexpression of CD36, a scavenger receptor, has been consistently linked to the invasion, migration, and metastatic potential of various cancers [19, 57, 59]. A recent study showed that the SUM159 and MCF-7 breast cancer cell lines responded differently to ACM treatment [57]. This observation indicates that cancer cells exhibit distinct responses to their microenvironment based on their specific energy requirements [57]. Not only in cancer cells but also increased uptake of LDL by the TAMs in TME conferred chemoresistance and also promoted the disease progression [60].

3 Lipid synthesis and tumor cell plasticity

Lipid synthesis, or lipogenesis, constitutes the intricate biochemical pathway responsible for the production of lipids from surplus cellular energy sources such as glucose and glutamine [12, 61]. The process involves a series of enzymatic reactions mainly involving ATP-citrate lyase, ACACA, FA synthase (FASN), stearoyl-CoA desaturase (SCD), glycerol phosphate acyltransferase, acylglycerolphosphate acyltransferase and hydroxymethylglutaryl-coenzyme A reductase (HMGCR), lanosterol 14α-demethylase (CYP51A1), that convert precursors, such as acetyl-CoA and malonyl-CoA, into different forms of lipids, including FA, TG, LPA and cholesterol [55, 62–64]. In the subsequent discussion, we will explore how lipid synthesis drives the plasticity of cancer cell, ultimately fostering therapeutic resistance and disease progression (Table 2).

The overexpression of the protein C receptor (PROCR) in nasopharyngeal carcinoma (NPC) significantly enhanced the stem cell properties of the cancer cells [67]. This enhancement was evidenced by the upregulation of SRY-box transcription factor 2 (SOX2) and NANOG when PROCR was activated by its specific ligand, activated protein C (APC) [67]. Apart from serving as a marker for NPC, PROCR also plays a crucial role in promoting invasion and migration [67]. Specifically, in the PROCR overexpressed 5-8F NPC cell line, upon APC treatment, there was a notable increase in the cells' ability to invade and migrate through the ECM, which was facilitated by the transition of cancer cells from an epithelial state to a mesenchymal state [67]. When PROCR is activated, it triggered signalling through

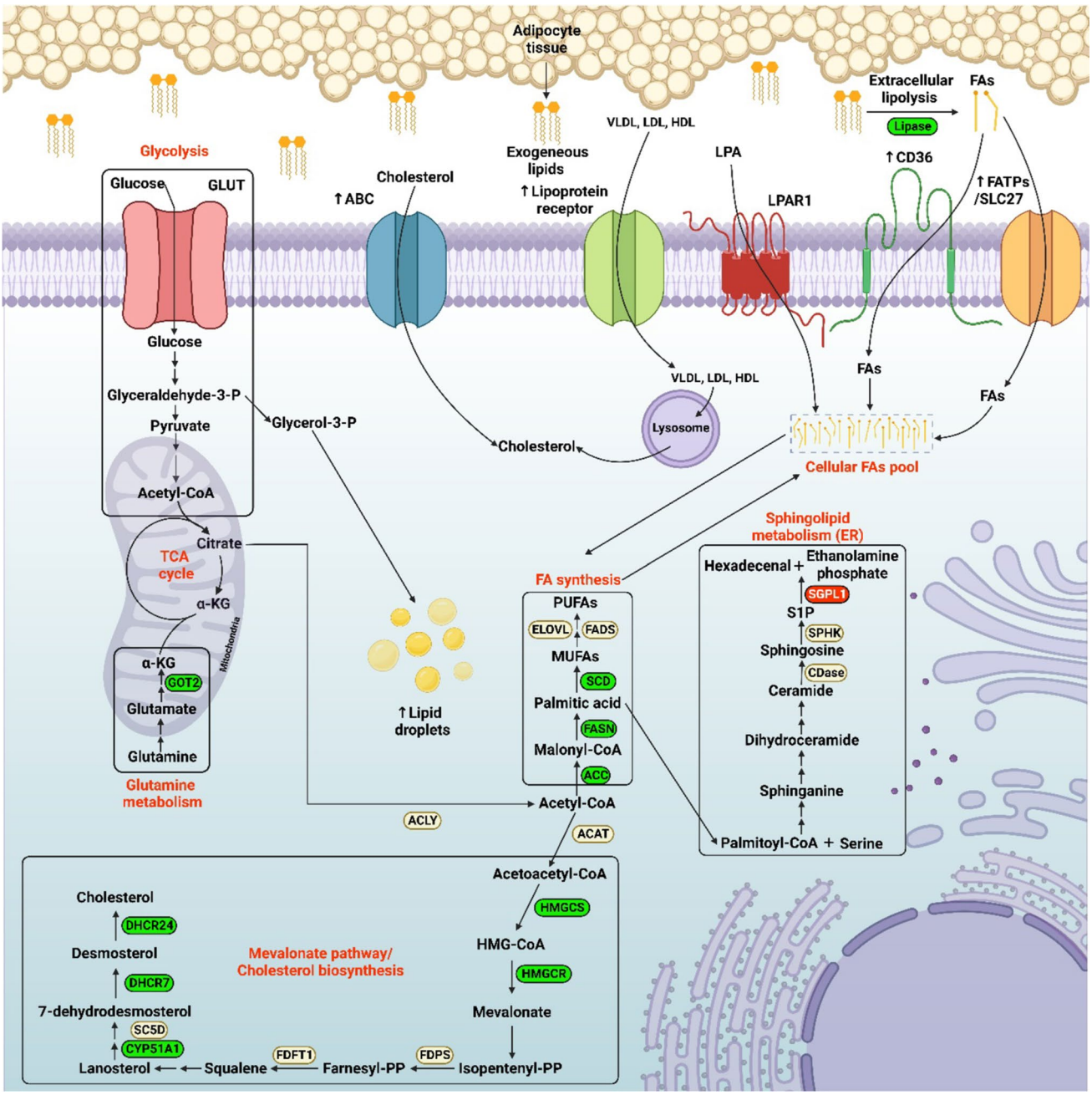


Fig. 1 This figure provides an overview of the involvement of lipid uptake and lipid synthesis in modulating tumor cell plasticity and drug resistance in cancer cells. It illustrates the fatty acid transporters, cholesterol receptors, and scavenger receptors, which mediate the transport of fatty acids resulting from extracellular lipolysis of exogenous lipids released from adipocyte tissues, circulating lipoproteins, and cholesterol. In addition, it depicts the biosynthesis pathways of cholesterol, fatty acids, and sphingolipids. Moreover, this figure majorly highlights the elevated expression (indicated either in green color or with "↑") and the diminished expression of proteins denoted in red color, thereby contributing to increased plasticity and drug resistance in cancer. 3P, 3 phosphate; ABC, ATP-binding cassette family proteins; ACC, Acetyl-CoA carboxylase; ACAT, Acetyl-CoA acetyltransferase; ACLY, ATP citrate synthase; AGPAT, 1-acylglycerol-3-phosphate O-acyltransferase; CD36, Cluster of differentiation 36; CDase, Ceramidase; ELOVL, Fatty acid elongase; ER, Endoplasmic reticulum; FA, Fatty acids; FADS, Fatty acid desaturase; FASN, Fatty acid synthase; FDFT1, Farnesyl diphosphate farnesyltransferase 1; FDPS, Farnesyl pyrophosphate synthase; GLUT, Glucose transporter; GOT2, Glutamic-oxaloacetic transaminase 2; HDL, High density lipoprotein; HMG-CoA, Hydroxy-3-methylglutaryl-coenzyme A; HMGCR, Hydroxy-3-methylglutaryl-coenzyme A reductase; HMGCS, Hydroxy-3-methylglutaryl-coenzyme A synthase; LDL, Low density lipoprotein; LPA, Lysophosphatidic acid; LPAR1, Lysophosphatidic acid receptor 1; MUFAs, Monounsaturated fatty acids; PUFAs, Polyunsaturated fatty acids; S1P, Sphingosine-1-phosphate; SCD, Stearoyl-CoA desaturase; SGPL1, Sphingosine-1-phosphate lyase 1; SLC27, Solute carrier family 27; SPHK, Sphingosine-1-kinase; TCA, Tricarboxylic acid; VLDL, Very low density lipoprotein; αKG, Alpha-ketoglutarate

Table 2 Lipid synthesis and its implications on tumor cell plasticity and drug resistance

Type of the study	Cell line/model/tissue	Condition/treatment	Effect on plasticity	Mechanism/experimental outcome	Reference
Brain cancer					
In vitro	Glioma stem-like cells	shSCD1	↓Stem cell phenotype	↓SCD1, SOX2, NANOG, OLIG2, OCT4, Nestin, cell viability	[65]
In vitro	Glioma stem-like cells	CAY + Temozolomide	↓Resistance	↑GADD34, CHOP, sXBP1, γ-H2AX, caspase-3/7 activity, ↓RAD51, cell viability, 2^{ary} spheroid formation	[65]
In vitro	Glioma stem-like cells	shSREBP1	↓Stem cell phenotype	↓SREBP1, ACSS2, ACC1, FASN, ELOVL6, SCD1, SOX2, OCT4, OLIG2, NANOG, Nestin	[65]
Breast cancer					
In vitro	MCF-7, BT-20, MDA-MB-231	NT	-	↓SGPL1	[66]
In vitro	MCF-7, BT-20	S1P	↑Migration	↓Gap area	[66]
In vitro	MCF-7, BT-20	S1P + SGPL1-cDNA-GFP	↓Migration	↑Gap area	[66]
Head and neck cancer					
In vitro	5–8 F	PROCR overexpression + APC	↑Stem cell properties, Invasion and Migration	↑PROCR, NF-κB, FASN, lipid droplets, SOX2, NANOG, DRP1, FIS1, Ca^{2+} flux, fragmented mitochondria, cAMP, total TG and cholesterol	[67]
In vitro	5–8 F	PROCR overexpression + APC + C75	↓Stem cell properties and Migration	↓SOX2, NANOG, DRP1, FIS1, fragmented mitochondria	[67]
In vitro	HONE1	PROCR KO-lentiCRISPRv2 vector	↓Stem cell properties and Migration	↓PROCR, Ca^{2+} flux	[67]
In vitro	$PROCR^+$ biopsy samples	APC	↑Stem cell properties	↑SOX2, NANOG	[67]
In vitro	$PROCR^+$ biopsy samples	C75	↓Stem cell properties	↑FASN inhibition ↓SOX2, NANOG	[67]
In vivo	B-NDG mice xenograft (Patient derived)	$PROCR^+$ cells	↑Metastasis	↑Lung nodules, peripheral blood $PROCR^+$ cells	[67]
In vivo	B-NDG mice xenograft (5-8F)	PROCR overexpression	↑Metastasis	↑Lung nodules, self-renewal	[67]
In vivo	B-NDG mice xenograft (5-8F)	PROCR overexpression + APC	↑Metastasis	↑Lung nodules	[67]
In vivo	B-NDG mice xenograft (5-8F)	PROCR overexpression + APC + C75	↓Metastasis	↑FASN inhibition	[67]
Lung cancer					
In vitro	H1299, H1650, H1975	Lapatinib/Gefitinib	-	↑CYPA5A1, SREBF2, SREBP2, DHCR24, DHCR7, mitochondrial cholesterol, total cholesterol	[68]
In vitro	H1650 DT	Lapatinib + Ketoconazole	-	↑Apoptosis, cleaved PARP-1, cleaved caspase-9, ↓Cell survival, total cholesterol, Survivin	[68]
In vitro	H1299 DT	Lapatinib + Ketoconazole	-	↑ Cleaved PARP-1, cleaved caspase-9, cytoplasmic cytochrome ↓Cell survival, Survivin, mitochondrial membrane potential	[68]
In vivo	C57BL/6 mice xenograft (LLC1)	Lapatinib	-	↑CYPA5A1, SREBP2, total cholesterol, LSS ↓Tumor growth	[68]
In vivo	Nude mice xenograft (H1650)	Lapatinib to Lapatinib + Ketoconazole	-	↓Tumor growth	[68]

Table 2 (continued)

Type of the study	Cell line/model/tissue	Condition/treatment	Effect on plasticity	Mechanism/experimental outcome	Reference
Pancreatic cancer					
In vivo	Athymic nude mice xenograft (L3.6pl)	Gluconate	↓Metastasis	↑Apoptosis ↓VIM, CD31, α-SMA	[69]
Prostate cancer					
In vitro	PC-3 M	Citrate preincubation-48 h	↑Invasion and Migration	↑PC, PI, SM, SNAIL, VIM, single cells, ameboid cells, filopodia ↓pmCiC	[69]
In vitro	PC-3 M	Citrate preincubation-2 weeks	↑Metastatic colonization	↑GLUT1, flattened cells ↓SNAIL, SLUG, VIM, filopodia	[69]
In silico	Bone metastasis tissue data from Iglesias-Gato proteome data set	NT	-	↑FASN, HMGCR	[20]
In vitro	PC-3	CSS	↑Invasion and Migration	↑BM disintegration ↓Spheroid roundness	[70]
In vitro	LNCaP	CSS	↑Invasion	↓Spheroid roundness	[70]
In vitro	PC-3	CSS + LPA, CSS + S1P	↓Invasion and Migration	↑Spheroid roundness ↓BM disintegration	[70]
In vitro	PC-3	CSS + LPA + siLPAR1, Medium (10% FBS) + Ki16425	↑Invasion	↓Spheroid roundness	[70]
Skin cancer					
In vitro	3D melanoma cells	NT	↑Stemness	↑SCD1, OCT4, NANOG, CD133, SOX2, MUFA percentage	[71]
In vitro	3D melanoma cells	BRAFi + MEKi + MF-438	↓Stemness and Resistance	↓Spheroid-forming efficiency, MUFA percentage, BRAF/MEK resistance, IC_{50}, OCT4, NANOG, JARID1B, YAP, TAZ, BIRC5, TEAD4	[71]
In vitro	3D melanoma cells	BRAFi + MEKi + siSCD1	↓Stemness and Resistance	↓SCD1, NANOG, CD133, JARID1B, OCT4, YAP, TAZ, BIRC5, TEAD4	[71]

α-SMA Alpha-smooth muscle actin, *γ-H2AX* H2A histone family member X, *APC* Activated protein C, *BIRC5* Baculoviral IAP repeat containing 5, *BRAF* B-Raf proto-oncogene, *BRAFi* BRAF inhibitor, *BM* Basement membrane, *cAMP* Cyclic adenosine monophosphate, *cDNA* Complementary deoxyribonucleic acid, *CD* Cluster of differentiation, *CHOP* C/EBP homologous protein, *CSS* Charcoal stripped serum, *CYP51A1* Lanosterol 14α-demethylase, *DHCR* Dehydrocholesterol reductase, *DNA* Deoxyribonucleic acid, *DRP1* Dynamin-related protein 1, *DT* Drug-tolerant, *ELOVL6* Fatty acid elongase 6, *FASN* Fatty acid synthase, *FBS* Fetal bovine serum, *FIS1* Mitochondiral fission 1 protein, *GADD34* Growth arrest and DNA damage-inducible protein, *GLUT1* Glucose transporter 1, *GFP* Green fluorescent protein, *HMGCR* Hydroxy-3-methylglutaryl-coenzyme A reductase, IC_{50} Half-maximal inhibitory concentration, *JARID1B* Lysine-specific demethylase 5B, *LPA* Lysophosphatidic acid, *LPAR1* Lysophosphatidic acid receptor 1, *LSS* Lanosterol synthase, *MEK* Mitogen-activated protein kinase, *MEKi* MEK inhibitor, *MUFA* Monounsaturated fatty acid, *NF-κB*, Nuclear factor kappa-light-chain-enhancer of activated B cells, *NT* No treatment, *OCT4* Octamer-binding transcription factor 4, *OLIG2* Oligodendrocyte transcription factor 2, *PARP-1* Poly (ADP-ribose) polymerase 1, *PC* Phosphatidylcholine, *PI*, Phosphatidylinositol, *pmCiC* Plasma membrane citrate transporter, *PROCR* Protein C receptor, *S1P* Sphingosine-1-phosphate, *SCD1* Stearoyl-CoA desaturase 1, *SM* Sphingomyelin, *SGPL1* Sphingosine-1-phosphate lyase 1, *SOX2* SRY-box transcription factor 2, *SREBF1* Sterol regulatory element binding transcription factor 1, *SREBP* Sterol regulatory element binding protein, *sXBP1* Syntaxin-binding protein 1, *TAZ* Transcriptional co-activator with PDZ-binding motif, *TEAD4* TEA domain transcription factor 4, *VIM* Vimentin, *YAP* Yes-associated protein

the cAMP-protein kinase A pathway, resulting in the release of calcium from the endoplasmic reticulum [67]. Subsequently, calcium activated calcium/calmodulin-dependent protein kinase, which further activated Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) [67]. The activated NF-κB then initiated the transcription of FASN, which is a rate-limiting enzyme involved in DNL [67]. By inhibiting the enzymatic activity of FASN with C75, the abnormal lipid synthesis was disrupted, leading to the reversal of the enhanced invasive and migratory properties of NPC cancer cells [67]. This suggests that the elevated lipid production facilitated by FASN is directly involved in promoting the invasive and migratory behavior of NPC cancer cells [67]. Similarly, in prostate-to-bone metastasis samples of prostate cancer patients from the Iglesias-Gato proteome dataset, the expression of FASN and HMGCR mRNA was found to be upregulated, suggesting increased lipid synthesis in these metastatic samples [20]. Another study showed that SCD1 inhibition in glioblastoma stem-like cells with shSCD1 resulted in reduced unsaturated FA levels along with downregulation of pluripotency markers such as octamer-binding transcription factor 4 (OCT4), SOX2, NANOG, Nestin, and oligodendrocyte transcription factor 2 [65]. A similar reduction in the stem cell phenotype was observed when a master regulator of lipid synthesis, sterol regulatory element binding protein (SREBP) 1, was silenced with shRNA [65]. In addition, inhibition of SCD1 with CAY (SCD1 inhibitor) sensitized the glioblastoma stem-like cells to temozolomide by increasing the level of apoptotic proteins, namely caspase-3/7 along with DNA repair proteins such as C/EBP homologous protein, syntaxin-binding protein 1, and γ-H2AX as well as decreasing the expression of RAD51 [65]. Similarly in another study, SCD1 was shown to regulate the stemness in the 3D spheroids of melanoma cancer cell lines by increasing the level of monounsaturated FA (MUFA) as well as stem cell markers, including OCT4, NANOG, cluster of differentiation 133 (CD133), and SOX2 [71]. They have also showed that the increased expression of SCD1 sustained resistance to BRAF inhibitors [71]. Moreover, treatment with MF-438 (SCD1 inhibitor) sensitized melanoma cells to B-Raf proto-oncogene (BRAF)/mitogen-activated protein kinase kinase (MEK) inhibitors by decreasing the IC_{50} value, MUFA levels, YAP/TAZ activity and reducing the expression of baculoviral IAP repeat containing 5, TEA domain transcription factor 4 and stem cell markers such as OCT4, NANOG, JARID1B and CD133 [71]. Further, similar reversal of resistance to BRAF/MEK inhibitors was observed when treated along with SCD1 siRNA [71]. Therefore, lipogenesis has shown to be a significant contributor to the promotion of invasion and migration in cancer cells while also playing a crucial role in maintaining the CSC phenotype.

Citrate is an important metabolite of cells that provides energy through the TCA cycle [72]. Besides that, the transport of citrate through membrane transporters plays a crucial role in lipid biosynthesis [73–75]. Similarly, prostate cancer cell line pre-incubated with citrate showed enhanced lipid synthesis, particularly the levels of phosphatidylcholine, phosphatidylinositol, and sphingomyelin were elevated [69]. This alteration in lipid composition affects membrane fluidity, facilitating disease progression [69]. Following 48 h of incubation with citrate, the cells undergo EMT, characterized by an increase in SNAIL and vimentin expression, as well as an increase in the number of single cells, ameboid cells, and filopodia, indicating enhanced migration of prostate cancer cells [69]. Furthermore, long-term (2 weeks) exposure to citrate is associated with metastatic colonization, as evidenced by the downregulation of SNAIL, SLUG, and vimentin, along with a reduction in filopodia and increased GLUT1 expression and flattened cells [69]. Surprisingly, despite the significant downregulation of the plasma membrane citrate transporter (pmCiC) after 48 h of citrate incubation, the lipid synthesis was increased in PC-3 M cells [69]. However, significant pmCiC downregulation was not observed after 2 weeks of incubation of PC-3 M with citrate [69]. It is worth noting that, in the case of pancreatic cancer *in vivo* model, the inhibition of pmCiC with gluconate leads to increased apoptosis and reduced metastasis [69]. These findings further support the notion that citrate-induced alterations in lipogenesis promote plasticity of cancer cells and contribute to the progression of the disease [69].

Lipids are also involved in signal transduction that supports the development of cancer and promotes survival, proliferation, and metastasis [76]. Lysophosphatidic acid (LPA) and sphingosine-1-phosphate (S1P) are intermediates of lipid metabolism, which can also act as signalling molecules to regulate cellular processes such as lipid synthesis, differentiation, survival, adhesion, and migration [77–79]. In addition, the expression of S1P lyase 1 (SGPL1) was observed to be downregulated in MCF-7, BT-20, and MDA-MB-231 breast cancer cell lines when compared to normal breast epithelial cell lines MCF-10A and MCF-12A [66]. This downregulation of SGPL1 promoted the migration of breast cancer cell lines when treated with S1P [66]. Conversely, overexpressing SGPL1 reduced the migrating capacity of MCF-7 and BT-20 cell lines [66]. Another study showed contradicting results with charcoal-stripped serum (CSS) and S1P [70]. Supplementing the prostate cancer cell lines with CSS, deprived of LPA and S1P, increased the invasiveness and migrating ability of PC-3 and LNCaP cell lines [70]. This was characterized by a decrease in spheroid roundness and an increase in basement membrane disintegration [70]. However, the CSS-induced migration and invasion were inhibited by the addition of LPA or S1P [70]. Moreover, specifically inhibiting the activity of LPA

receptor (LPAR) 1, but not LPAR2 and S1P receptors 1–4, increased the invasiveness of the PC-3 cell line [70]. Subsequent molecular-level analyses and *in vivo* validations were warranted for a robust interpretation of these findings. Despite Harma and colleagues reported the involvement of LPAR1 in modulating the invasiveness of a prostate cancer cell line, these results present contradictions when compared to recent studies conducted using DL-FBS and charcoal-stripped media, wherein the increase in lipid content was associated with enhanced cellular plasticity [18, 58, 70].

Many studies have highlighted the role of cholesterol in the progression of cancer and the development of therapeutic resistance [68, 80–82]. In the context of prostate cancer, it has been observed that cholesterol facilitated the interaction between adipocyte plasma membrane-associated proteins and epidermal growth factor receptor (EGFR) substrate 15-related protein (ESP15R) [80]. This interaction resulted in a decrease in EGFR endocytosis, subsequently promoting EMT in prostate cancer [80]. In another study, Shao et al. have elucidated a mechanism in which cholesterol plays a regulatory role in the selective autophagic degradation of receptor tyrosine kinases (RTKs) mediated by Golgi membrane protein 1 (GOLM1) through the mammalian target of rapamycin complex-1 axis [81]. In hepatocellular carcinoma, cholesterol impeded the degradation of RTKs such as EGFR and MET, consequently enhancing the recycling of these receptors [81]. Interestingly, the combination of the cholesterol inhibitor, lovastatin with tyrosine kinase inhibitor (TKI) enhanced the effectiveness of TKI, resulting in a reduction of pathways associated with tumor formation [81]. Additionally, another study demonstrated an increase in the synthesis of cholesterol in lung cancer cell lines treated with lapatinib or gefitinib, both of which are inhibitors of the EGFR tyrosine kinase [68]. The research uncovered that the administration of these drugs induced resistance in the cell lines by activating specific genes associated with cholesterol synthesis, namely CYP51A1, SREBP2, dehydrocholesterol reductase (DHCR) 7, and DHCR24 [68]. Intriguingly, co-treatment with ketoconazole, an inhibitor of CYP51A1, reversed this resistance and triggered apoptosis [68]. Corresponding outcomes were observed in a xenograft mice model where the combined treatment resulted in diminished tumor growth [68]. Notably, in nude mice H1650 xenograft model, transitioning from lapatinib monotherapy to a combination with ketoconazole led to a reduction in tumor growth compared to the group with only lapatinib treatment [68].

In essence, lipid synthesis has been shown to be a key factor in the metastatic progression of cancer, the generation of CSCs, and the development of drug resistance which is commonly associated with stem cells [41]. Figure 1 summarizes the process of lipid synthesis and highlights the major genes that are involved in enhancing cell invasion and migration and in maintaining the CSC phenotype. As discussed previously, Drexler et al. showed that citrate treatment increased the aggressiveness of prostate cancer cells [69]. Contrastingly, a recent study by Zhao et al. demonstrated that treatment with citrate promotes senescence in tumor cells and inhibits the growth of various cancers, such as breast, colorectal, and lung, by stimulating excessive lipid synthesis [72]. These conflicting results suggest that the role of lipid synthesis may vary across different types of cancer. Further investigation is necessary to elucidate the precise contribution of metabolites and genes involved in lipogenesis and their impact on tumor cell plasticity and drug resistance.

4 Lipid catabolism and tumor cell plasticity

Lipid catabolism is an integral aspect of lipid metabolism, serving as the process through which the body breaks down fats mainly to generate energy [55, 83]. It plays a crucial role in maintaining energy homeostasis, ensuring a continuous fuel supply to meet the energy requirements of various cellular processes [83]. The degradation of FAs forms a central part of lipid catabolism [55, 83]. FAs are the building blocks of simple and complex lipids [55]. The initial step, lipolysis, entails the hydrolysis of lipids, resulting in the generation of FFAs [53]. Before being transported into the mitochondrion for oxidation, FFAs are activated to form fatty acyl-CoA by the acyl-CoA synthetase long-chain family proteins (ACSLs) [84]. On the outer mitochondrial membrane, an enzyme called carnitine palmitoyltransferase I (CPT1) converts fatty acyl-CoA to fatty acylcarnitine [55, 84]. The acylcarnitine is then shuttled into the mitochondrial matrix by the carnitine/acylcarnitine translocase (CACT) located on the inner mitochondrial membrane [55, 84]. Once entered inside the matrix, carnitine palmitoyltransferase II (CPT2), positioned on the matrix side of the inner membrane, converts acylcarnitine back to acyl-CoA for further metabolism and production of ATP [55, 84]. Interestingly, cancer cells have developed intricate alterations to modify this energy-generating process, to support their progression by undergoing molecular and phenotypic changes [85–88]. In this session, we will discuss the modifications in lipid catabolic pathway in cancer cells to facilitate their progression. Table 3 summarizes the role of lipid catabolism and associated proteins in tumor cell plasticity and drug resistance.

In a study conducted by Blucher and group, treating the breast cells with ACM derived from adipose tissue of morbidly obese patients, upregulated angiopoietin-like 4 (ANGPTL4), cAMP responsive element binding protein 3 like 3, and FA β-oxidation genes such as CPT1A, SLC family 25 member 20 and acetyl-CoA acyltransferase 2 [85]. These alteration in expression of genes resulted in increased invasion and migration of MDA-MB-231, HCC38, and E0771

Table 3 Lipid catabolism and its implications on tumor cell plasticity and drug resistance

Type of the study	Cell line/model/tissue	Condition/treatment	Effect on plasticity	Mechanism/Experimental outcome	Reference
Breast cancer					
In vitro	SUM159	Bexarotene	↓Mesenchymal state	↑Lipid droplets, E-cadherin ↓Tumor sphere formation, ZEB1, FN, SERPINE1, SLUG, CD44, FAO	[87]
In vitro	SUM159-PACR	Bexarotene	↓Mesenchymal state	↑E-cadherin ↓ZEB1, SLUG, KRT5	[87]
In vitro	SUM159-PACR	Bexarotene + 5FU	↓Resistance	↓Cell viability	[87]
In vitro	MCF-7-Slug + Sox9	Doxycycline	↑Mesenchymal state	↑SLUG, SNAIL, SERPINE1, N-cadherin, FN1, ZEB1, VIM, MGLL ↓Lipid droplets, E-cadherin, GPAM, DGAT1	[87]
In vitro	MCF-7-Slug + Sox9	Doxycycline + Etomoxir	↓Mesenchymal state	↑E-cadherin, GPAM, DGAT1 ↓SLUG, SNAIL, SERPINE1, N-cadherin, VIM, FN1, ZEB1, MGLL	[87]
In vitro	MCF-7-Slug + Sox9	Doxycycline + shCPT1A	↓Mesenchymal state	↑E-cadherin ↓Reduction in lipid droplets, N-cadherin, SNAIL, SERPINE1, ZEB1, FN1	[87]
In vitro	Patient-derived cell line (BC2.2)	Bexarotene	↓Mesenchymal state	↑E-cadherin, ACSL1, ACSL5, AGPAT4, DGAT2, PLIN1, LIPE, Lipid droplets ↓SLUG, FAO	[87]
In vitro	Patient-derived cell line (BC2.2)	Bexarotene + 5FU	-	↓Cell viability	[87]
In vitro	Patient-derived cell line (BC29.1)	Bexarotene	↓Mesenchymal state	↑Lipid droplets, E-cadherin ↓SLUG	[87]
In vivo	NSG mice xenograft (BC2.2)	Bexarotene	↓Mesenchymal state	↑ACSL5, E-cadherin ↓FN	[87]
In vivo	NSG mice xenograft (MCF-7-Slug + Sox9)	Doxycycline	↑Metastasis	↑FN, SLUG, ZEB1	[87]
In vivo	NSG mice xenograft (MCF-7-Slug + Sox9)	Doxycycline + Etomoxir	↓Metastasis	↓FN, SLUG, ZEB1	[87]
In vitro	MDA-MB-231	$ACM_{>40}$	↑Invasion and migration	↑ANGPTL4, MMP2, MMP9, CREB3L3, PDK4, CPT1A, SLC25A20, ACAA2, FAO enzymatic activity, FFA, pFAK (Tyr567/77), pFAK (Tyr397) ↓SCD1, FASN, pSREBP, nSREBP, palmitic acid synthesis	[85]
In vitro	MDA-MB-231	$ACM_{>40}$ + siANGPTL4	↓Invasion and migration	↓ANGPTL4	[85]
In vitro	MDA-MB-231	$ACM_{>40}$ + shANGPTL4	↓Invasion and migration	↓ANGPTL4, pFAK (Tyr567/77)	[85]

Table 3 (continued)

Type of the study	Cell line/model/tissue	Condition/treatment	Effect on plasticity	Mechanism/Experimental outcome	Reference
In vitro	HCC38	$ACM_{>40}$	↑Invasion and migration	↑ANGPTL4, CPT1A, SLC25A20, ACAA2, PLIN2 ↓SCD1, FASN, pSREBP, nSREBP, Palmitic acid synthesis	[85]
In vitro	E0771	$ACM_{>40}$	↑Migration	↑ANGPTL4, CREB3L3, PLIN2, CPT1A, SLC25A20, ACAA2 ↓SCD1, FASN, pSREBP, nSREBP, Palmitic acid synthesis	[85]
In vitro	4T1	Lung neutrophils co-culture	-	↑Lipid droplets, OCR, LIPA, LIPE, ATGL, CPT1B, CPT2, ECH1, ACOX1	[88]
In vitro	4T1	Lung neutrophils co-culture + Cerulenin/C75	-	↑Cell survival	[88]
In vitro	Neutrophils from lung of 4T1 tumor-bearing BALB/cJ mice (Premetastatic)	NT	-	↑Lipid droplets, TG, HILPDA, CIDEC, G0S2 ↓TG hydrolase activity, lipase activity	[88]
In vivo	4T1 cells bearing mice	4T1 cells co-cultured with lung neutrophils	↑Metastasis	-	[88]
In vivo	AT3 cells bearing mice	AT3 cells co-cultured with ATGL-cKO mice-lung neutrophils	↑Metastasis	-	[88]
In vivo	AT3-g-csf-bearing ATGL-cKO mice	NT	↑Metastasis	↑Lung metastatic nodules, lipid droplets in neutrophils	[88]
In vivo	AT3-g-csf-bearing HILPDA-cKO mice	NT	↓Metastasis	↓Lung metastatic nodules	[88]
Lung cancer					
In vitro	A549	TGF-β	↑Mesenchymal state	↑N-cadherin, VIM, SLUG ↓Lipid droplets, E-cadherin	[87]
In vitro	A549	TGF-β + Etomoxir	↓Mesenchymal state	↑E-cadherin ↓N-cadherin, VIM, SLUG	[87]
Liver cancer					
In vitro	Hep3B	TGF-β	↑Mesenchymal state	↑N-cadherin, VIM, FN ↓Lipid droplets, E-cadherin	[87]
In vitro	Hep3B	TGF-β + Etomoxir	↓Mesenchymal state	↑E-cadherin ↓N-cadherin, VIM, FN	[87]
Prostate cancer					

Table 3 (continued)

Type of the study	Cell line/model/tissue	Condition/treatment	Effect on plasticity	Mechanism/Experimental outcome	Reference
In vitro	PC-3, LNCaP	NT	-	↑Palmitate oxidation, CPT1A, CACT, CRAT, activity of CPT1A, CACT and CRAT ↓Malonyl-CoA, miR-124, miR-129, miR-378	[86]
In vitro	PC-3	miR-124	↓Invasion and Migration	↓CPT1A, AIAC	[86]
In vitro	PC-3	miR-124 + UTR less CPT1A vector	↑Invasion and Migration	-	[86]
In vitro	PC-3	miR-129	↓Invasion and Migration	↑AIAC ↓CACT	[86]
In vitro	PC-3	miR-129 + UTR less CACT vector	↑Invasion and Migration	-	[86]
In vitro	PC-3	miR-378	↓Invasion and Migration	↑AIAC ↓CRAT, ASAC	[86]
In vitro	PC-3	miR-378 + UTR less CRAT vector	↑Invasion and Migration	-	[86]
In vitro	LNCaP	miR-124	↓Invasion and Migration	↓CPT1A, AIAC	[86]
In vitro	LNCaP	miR-124 + UTR less CPT1A vector	↑Invasion and Migration	-	[86]
In vitro	LNCaP	miR-129	↓Invasion and Migration	↑AIAC ↓CACT	[86]
In vitro	LNCaP	miR-129 + UTR less CACT vector	↑Invasion and Migration	-	[86]
In vitro	LNCaP	miR-378	↓Invasion and Migration	↑AIAC ↓CRAT, ASAC	[86]
In vitro	LNCaP	miR-378 + UTR less CRAT vector	↑Invasion and Migration	-	[86]

5FU 5-fluorouracil, *ACAA2* Acetyl-CoA acyltransferase 2, *ACM* Adipocyte conditioned media, *ACOX1* Acyl-CoA oxidase 1, *ACSL* Acyl-CoA synthetase long-chain family proteins, *AGPAT4* 1-acylglycerol-3-phosphate-O-acyltransferase 4, *AIAC* Acid-insoluble acylcarnitine, *ANGPTL4* Angiopoietin-like protein 4, *ASAC* Acid-soluble acylcarnitine, *ATGL* Adipose triglycerides lipase, *CACT* Carnitine-acylcarnitine translocase, *CD44* Cluster of differentiation 44, *CIDEC* Cell death inducing DFFA like effector C, *cKO* Conditional knockout, *CPT1A* Carnitine palmitoyltransferase 1A, *CPT2* Carnitine palmitoyltransferase 2, *CRAT* Carnitine O-acetyltransferase, *CREB* cAMP-response element binding protein 3 like 3, *DGAT1* Diacylglycerol acyltransferase-1, *DGAT2* Diacylglycerol acyltransferase 2, *ECH1* Enoyl-CoA hydratase 1, *FAK* Focal adhesion kinase, *FAO* Fatty acid oxidation, *FASN* Fatty acid synthase, *FFA* Free fatty acid, *FN* Fibronectin, *G0S2* G0/G1 switch gene 2, *GPAM* Glycerol-3-phosphate acyltransferase, mitochondrial, *HILPDA* Hypoxia-inducible lipid droplet-associated protein, *LIPA* Lipase A, *LIPE* Lipase E, *miR* micro RNA, *MGLL* Monoglyceride lipase, *MMPs* Matrix metalloproteinases, *nSREBP* Active SREBP, *NT* No treatment, *OCR* Oxygen consumption rates, *PACR* Paclitaxel-resistant, *PDK4* Pyruvate dehydrogenase kinase 4, *PLIN1* Perilipin 1, *pSREBP* Precursor SREBP, *SCD1* Stearoyl-CoA desaturase 1, *SERPINE1* Serpin Family E Member 1, *SLC* Solute carrier family proteins, *SREBP* Sterol regulatory element-binding proteins, *TG* Triglyceride, *TGF-β* Transforming growth factor beta, *UTR* Untranslated region, *VIM* Vimentin, *ZEB1* Zinc finger E-box binding homeobox 1

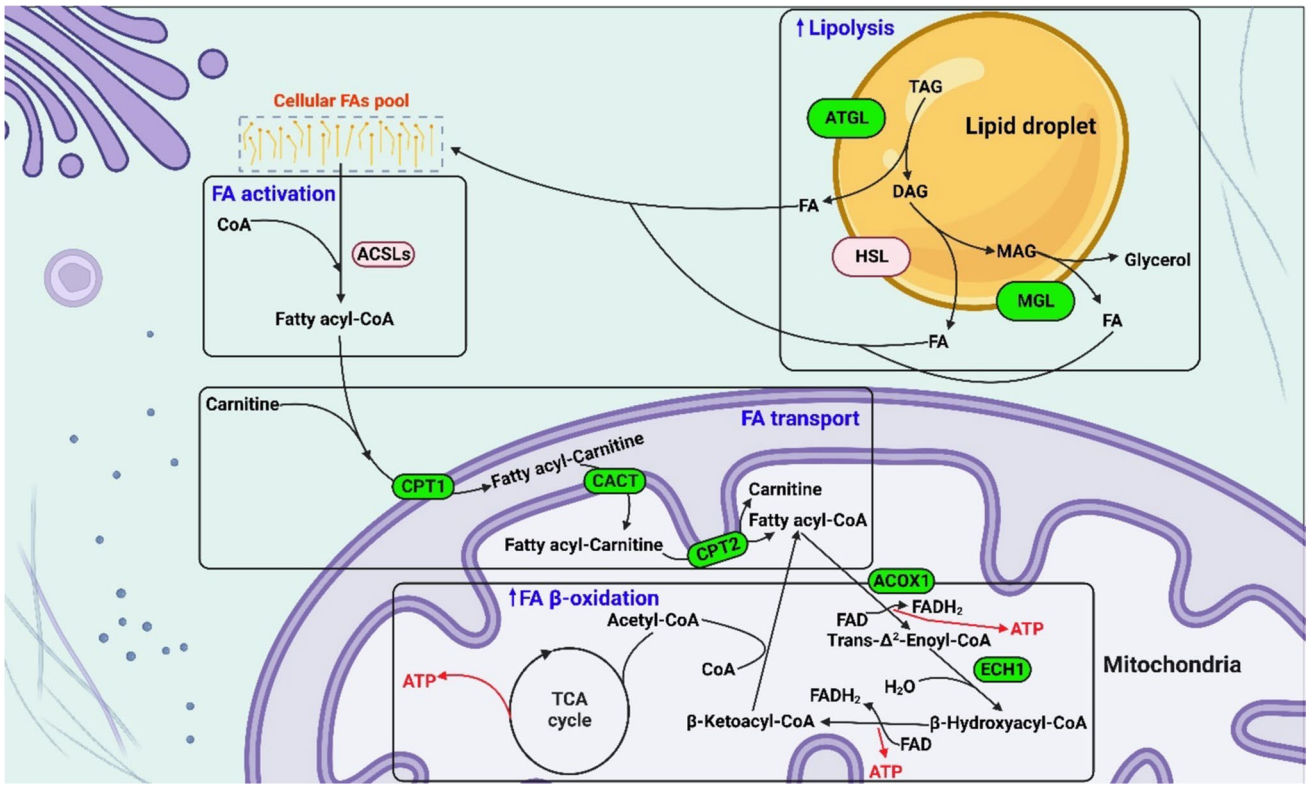


Fig. 2 This illustration depicts the accelerated lipid catabolism (indicated by "↑") in cancer cells, achieved by increasing the expression of the proteins (represented in green) that regulate this process. These modifications culminate in the increase of plasticity and promote cancer cell invasion and migration. Moreover, the figure elucidates the process of cytosolic lipolysis from the intracellular lipid storage and activation of fatty acid to assist the transportation into mitochondria to undergo β-oxidation for energy production. ACOX1, Acyl-CoA oxidase 1; ACSLs, Acyl-CoA synthetase long-chain family proteins; ATGL, Adipose triglyceride lipase; ATP, Adenosine triphosphate; CACT, Carnitine-acylcarnitine translocase; CoA, Coenzyme A; CPT1, Carnitine palmitoyltransferase 1; CPT2, Carnitine palmitoyltransferase 2; DAG, Diacylglycerol; ECH1, Enoyl-CoA hydratase 1; FA, Fatty acids; FAD, Flavin adenine dinucleotide; HSL, Hormone-sensitive lipase; MAG, Monoacylglycerol; MGL, Monoacylglycerol lipase; TAG, Triacylglycerol; TCA, Tricarboxylic acid

breast cancer cell lines [85]. Notably, the upregulation was more pronounced when cells were treated with ACM derived from adipose tissues of morbidly obese patients compared to tissues from overweight patients [85]. Additionally, inhibiting ANGPTL4 using siRNA or shRNA reduced the invasiveness and migration potential of MDA-MB-231 cells [85]. Moreover, the inactivation of focal adhesion kinase (FAK) signalling was also observed during ANGPTL4 inhibition, which was activated upon ACM treatment [85]. Therefore, the upregulation of ANGPTL4 by ACM, enhanced FAK signalling, consequently regulating tumor cell plasticity and increased the invasion and migration capabilities of breast cancer cells [85]. In another study, prostate cancer cell lines with a highly malignant phenotype exhibited enhanced utilization of FAs, as indicated by increased palmitate oxidation, elevated expression, and activity of key enzymes such as CPT1A, CACT, and carnitine acetyltransferase (CRAT), as well as reduction in malonyl-CoA levels [86]. Interestingly, the downregulation of miR-124, miR-129, and miR-378, which have the potential to target these three enzymes, respectively, was observed in PC-3 and LNCaP cell lines [86]. In addition, transfection of PC-3 and LNCaP cell lines with miR-124, miR-129, and miR-378 mimics downregulated CPT1A, CACT, and CRAT expression respectively, and resulted in decreased invasion and migration of these cell lines [86]. Bexarotene, a third-generation retinoid, treatment induced transition from mesenchymal to epithelial state (mesenchymal-epithelial transition) by decreasing the expression of ZEB1, fibronectin (FN), serpin family E member 1 (SERPINE1), SLUG, and CD44 [87]. This shift in phenotype is driven by reducing FA oxidation (FAO) and promoting lipid accumulation [87]. In addition, bexarotene exposure conferred susceptibility to 5-fluorouracil treatment in both mesenchymal state paclitaxel-resistant SUM159 cell line and patient-derived cell line [87]. Moreover, inducing expression of SLUG in the MCF-7 cell line exhibited an increase in stored lipids along with upregulation of mesenchymal markers such as SNAIL, vimentin, FN, ZEB1, and N-cadherin, as well as a reduction in E-cadherin [87]. Interestingly, inhibiting FAO with etomoxir (CPT1 inhibitor) or

by knocking down CPT1A led to a shift towards the epithelial state, and decrease in metastasis of MCF-7-Slug+Sox9 cells in *in vitro* and *in vivo* mice xenograft models [87]. Consistent findings were observed in A549 and Hep3B cell lines, where EMT was induced by transforming growth factor-beta (TGF-β), and etomoxir treatment resulted in the reversal of EMT in both lung and liver cancer cell lines [87]. Hence, lipid catabolism plays a crucial role in regulating plasticity and modulating cancer metastasis.

Li and team studied the role of lipid catabolic remodeling in neutrophils present in the lung microenvironment in facilitating breast cancer metastasis to the lungs [88]. The study showed that neutrophils were reported to promote lung metastasis of breast cancer by fueling the metastasizing breast cancer cells in lung microenvironment [88]. This is mainly achieved through the lipid-laden phenotype acquired by neutrophils through its interaction with lung mesenchymal cells [88]. The lung mesenchymal cells initiate this process by suppressing adipose triglyceride lipase (ATGL) activity in neutrophils, which then promotes the storage of accumulated lipids in the form of TG in neutrophils [88]. The lipid-laden neutrophils then serve as a form of fuel or energy for the disseminated tumor cells in the secondary tumor site at the lung through extracellular vesicle-mediated transport of TG, thus promoting proliferation and metastatic ability of breast cancer cells [88]. This neutrophil-mediated lipid-driven energy utilization by tumor cells was confirmed both *in vitro* and *in vivo* [88]. The 4T1 tumor cells when co-cultured with lung neutrophils, showed increased expression of various lipolysis and FAO genes such as lipase E (LIPE), ATGL, lipase A (LIPA), CPT1B, CPT2, enoyl-CoA hydratase 1 (ECH1) and acyl-CoA oxidase 1 (ACOX1) [88]. The upregulation of these genes was also correlated with high oxidative phosphorylation, leading to high oxygen consumption by the tumor cells, thus indicating metabolic shift and consumption of lipids as a source of energy for their proliferation and metastatic colonization in the lungs [88]. They have also observed an increase in the viability of 4T1 cells upon its co-culture with lung neutrophil, even when the DNL was inhibited with cerulenin or C75 [88]. This indicated that there was no involvement of DNL in this lipid-driven disease progression and supported that the 4T1 cells are dependent on transported TGs from neutrophils for energy [88]. In addition, analyzing the lung neutrophils of 4T1 tumor-bearing mice in the premetastatic stage showed that the level of lipid droplets was increased, and the lipase activity and TG hydrolase activity were decreased [88]. This was due to the increased expression of ATGL inhibitors such as hypoxia-inducible lipid droplet-associated protein (HILPDA), G0/G1 switch gene 2 and cell death-inducing DFFA-like effector c in lung neutrophils of 4T1 tumor-bearing mice at premetastatic stage [88]. Moreover, 4T1 cells co-cultured with lung neutrophils displayed increased metastasis in BALB/cJ mouse xenografts [88]. Furthermore, increased lipid droplets in neutrophils and enhanced metastasis were observed in AT3-bearing ATGL-conditional knockout (cKO) mice [88]. However, in AT3-bearing HILPDA-cKO mice, the metastatic colonization was inhibited [88]. These *in vivo* results showed that the tumor cells in the presence of lipid-laden neutrophils become more progressive, thereby increasing the colonization of breast cancer cells in the lungs [88]. Hence, regulating lipid metabolism might be beneficial in managing breast cancer metastasis in the lung microenvironment [88].

In summary, the FAO appears to be one of the main contributors to metastatic capabilities of cancer, as previously stated (Fig. 2). Inhibition of FAO through targeted interventions towards key enzymes involved in the process has been shown to reduce the invasion, migration and metastasis of cancer cells. Moreover, when FAO is upregulated and shown to be the cause of metastatic transition, a decrease in FA synthesis is coupled. As shown in the study conducted by Blucher et al. where the treatment with ACM from obese individuals increased the expression of ANGPTL4 and FAO, thereby increasing invasion and migration of breast cancer cells and, at the same time, genes involved in lipid synthesis such as SCD1, FASN, and SREBP were downregulated [85]. It was further supported by Valentino and colleagues, who observed a reduction in the level of malonyl-CoA and an increase in palmitate oxidation in metastatic prostate cancer cell lines [86]. Malonyl-CoA is an intermediate of FA synthesis that also acts as a direct inhibitor of CPT1, a rate-limiting enzyme in the β-oxidation pathway [84]. This indicates that cancer cells, while fulfilling their requisites for metastatic progression, consistently maintain a balance between lipid synthesis and catabolism.

5 Lipid peroxidation and tumor cell plasticity

Lipid peroxidation is a biological process that occurs when free radicals interact with lipids, resulting in the production of lipid peroxyl radicals and hydroperoxides [89]. Typically, lipid peroxidation is linked to cellular damage and aging [90]. However, emerging research has revealed its intriguing potential in impeding cancer progression through a specific type of programmed cell death known as ferroptosis [91, 92]. Ferroptosis is a regulated mechanism characterized by the accumulation of lipid peroxides, which involves alteration in iron metabolism and the depletion of intracellular antioxidants, particularly glutathione (GSH) [91, 92]. GSH peroxidase 4 (GPX4), an essential selenoenzyme, utilizes GSH as a co-factor to prevent lipid peroxidation of cell membranes, particularly during times of increased oxidative

Table 4 Lipid peroxidation and its implications on tumor cell plasticity and drug resistance

Type of the study	Cell line/model/tissue	Condition/treatment	Effect on plasticity	Mechanism/Experimental outcome	Reference
Breast cancer					
In vitro	4T1-27HCR	NT	↑Migration	↑LPCAT3, SLC7A11, TFRC, IREB2, HSPA5, CHAC1, COX2, MT1 ↓SLC3A2, FDFT1, HSPB1	[18]
In vitro	Py230-27HCR	NT	↑Migration	↑SLC7A11, CHAC1 ↓GPX4, LPCAT3, PEBP1, FDFT1, GCLC, GCLM, GSS, CARS, CBS, NOX4, NQO1, MT1, TFRC, IREB2, NCOA4, FTH1, HSPA5, HSPB1, COX2	[18]
In vitro	HCC1954-27HCR	NT	↑Migration	↑ACSL4, FSP1, COX2 ↓GPX4, LPCAT3, PEBP1, SLC7A11, SLC3A2, GCLM, CARS, CBS, NRF2, NQO1, NCOA4, FTH1, HSPB1, FANCD2	[18]
In vitro	MDA-MB-436-27HCR	NT	-	↑PTGS2 ↓ACSL4, LPCAT3, FDFT1, CARS, CBS, TFRC, IREB2, NCOA4, HSPB1, FANCD2	[18]
In vitro	4T1-27HCS, Py230-27HCS, HCC1954-27HCS, MDA-MB-436-27HCS	27HC	-	↓GPX4	[18]
In vitro	4T1-27HCR	27HC	-	↓GPX4 reduction	[18]
In vitro	Py230-27HCR, MDA-MB-436-27HCR	27HC	-	↑GPX4	[18]
In vitro	HCC1954-27HCR	27HC	-	No prominent alteration of GPX4 expression	[18]
In vitro	4T1-27HCR, Py230-27HCR, Py230-27HCS, HCC1954-27HCR, HCC1954-27HCS, MDA-MB-436-27HCR, MDA-MB-436-27HCS	RSL3, ML210, Erastin	-	↓Growth	[18]
In vitro	4T1-27HCR, Py230-27HCR, HCC1954-27HCR, MDA-MB-436-27HCR	RSL3 + Fer	-	↑Growth	[18]
In vitro	Py230-27HCR	RSL3 + shGPX4-2, RSL3 + shGPX4-4	-	↓Growth	[18]
In vitro	Micro.Met1, Micro.Met2	RSL3, ML210	↑Resistance	No prominent decrease in growth	[18]
In vitro	Macro.Met1, Macro.Met2	RSL3, ML210	↑Resistance	No prominent decrease in growth	[18]
In vivo	C57BL/6 mice xenograft (Py230-27HCR)	NT	↑Metastasis	↑Overt macro metastasis	[18]
In vivo	C57BL/6 mice xenograft (Py230-27HCR)	shGPX4-2, shGPX4-4	↓Metastasis	↓No. of metastatic nodules	[18]
In vitro	BT474-PER	RSL3	-	↑ROS ↓Cell viability	[94]
In vitro	BT474-PER	ML210	-	↓Cell viability	[94]
In vitro	BT474-PER	RSL3 + Fer1/Lip1/PD146176/NDGA/SCPI-2/SCPI-4	-	↑Cell viability	[94]
Leiomyosarcoma					
In vitro	RKN	ML210	-	↓GPX4 mediated ferroptosis inhibition, cell viability	[95]

Table 4 (continued)

Type of the study	Cell line/model/tissue	Condition/treatment	Effect on plasticity	Mechanism/Experimental outcome	Reference
In vitro	RKN	sgRNA-GPX4 + Fer1 withdrawal	-	↓Cell viability	[95]
Lung cancer					
In vitro	HCC4006-GEFR	ML210	-	↓GPX4 mediated ferroptosis inhibition, cell viability	[95]
In vitro	PC9-PER	RSL3, ML210	-	↓Cell viability	[94]
In vitro	PC9-PER	RSL3/ML210 + Fer	-	↑Cell viability	[94]
Ovarian cancer					
In vitro	Kuramochi-PER	RSL3, ML210	-	↓Cell viability	[94]
Pancreatic cancer					
In vitro	KP4	ML210	-	↓Cell viability	[95]
In vitro	KP4	ML210 + PD146176/zileuton/sgRNA-ACSL4/sgRNA-LPCAT3/ sgRNA-ZEB1	-	↑Cell viability	[95]
In vitro	KP4	sgRNA-GPX4 + Fer1 withdrawal	-	↓Cell viability	[95]
In vitro	Patient-derived cell line (AA01)	Erlotinib	↑Resistance	No prominent reduction in cell viability	[95]
In vitro	Patient-derived cell line (AA01)	ML210	-	↓Cell viability	[95]
In vitro	Patient-derived cell line (AA01)	ML210 + Fer1	-	↑Cell viability	[95]
Prostate cancer					
In vitro	Patient-derived cell line (MSK-PCa4)	RSL3	-	↓Cell viability	[95]
Skin cancer					
In vitro	B16F10-27HCR	NT	-	↑LPCAT3, SLC7A11, SLC3A2, FDFT1, GCLC, GCLM, CARS, NQO1, MT1, TFRC, NCOA4, FTH1, HSPA5, CHAC1, FANCD2 ↓NOX4, NRF2	[18]
In vitro	B16F10-27HCS	27HC	-	↓GPX4	[18]
In vitro	B16F10-27HCR	27HC	-	↓GPX4 reduction	[18]
In vitro	B16F10-27HCR	RSL3, ML210, Erastin	-	↓Growth	[18]
In vitro	B16F10-27HCR	RSL3 + Fer	-	↑Growth	[18]
In vitro	B16F10-27HCR	RSL3 + shGPX4-2, RSL3 + shGPX4-4	-	↓Growth	[18]
In vivo	C57BL/6 mice xenograft (B16F10-27HCR)	shGPX4-2, shGPX4-4	↓Metastasis	↓Metastasis grade, tumor growth	[18]
In vitro	LOXIMVI	sgRNA-GPX4 + Fer1 withdrawal	-	↓Cell viability	[95]
In vitro	Patient-derived cell line (M000921, M980513)	TGF-β + PLX-4032	↑Mesenchymal state, PLX-4032 resistance	No prominent reduction in cell viability	[95]

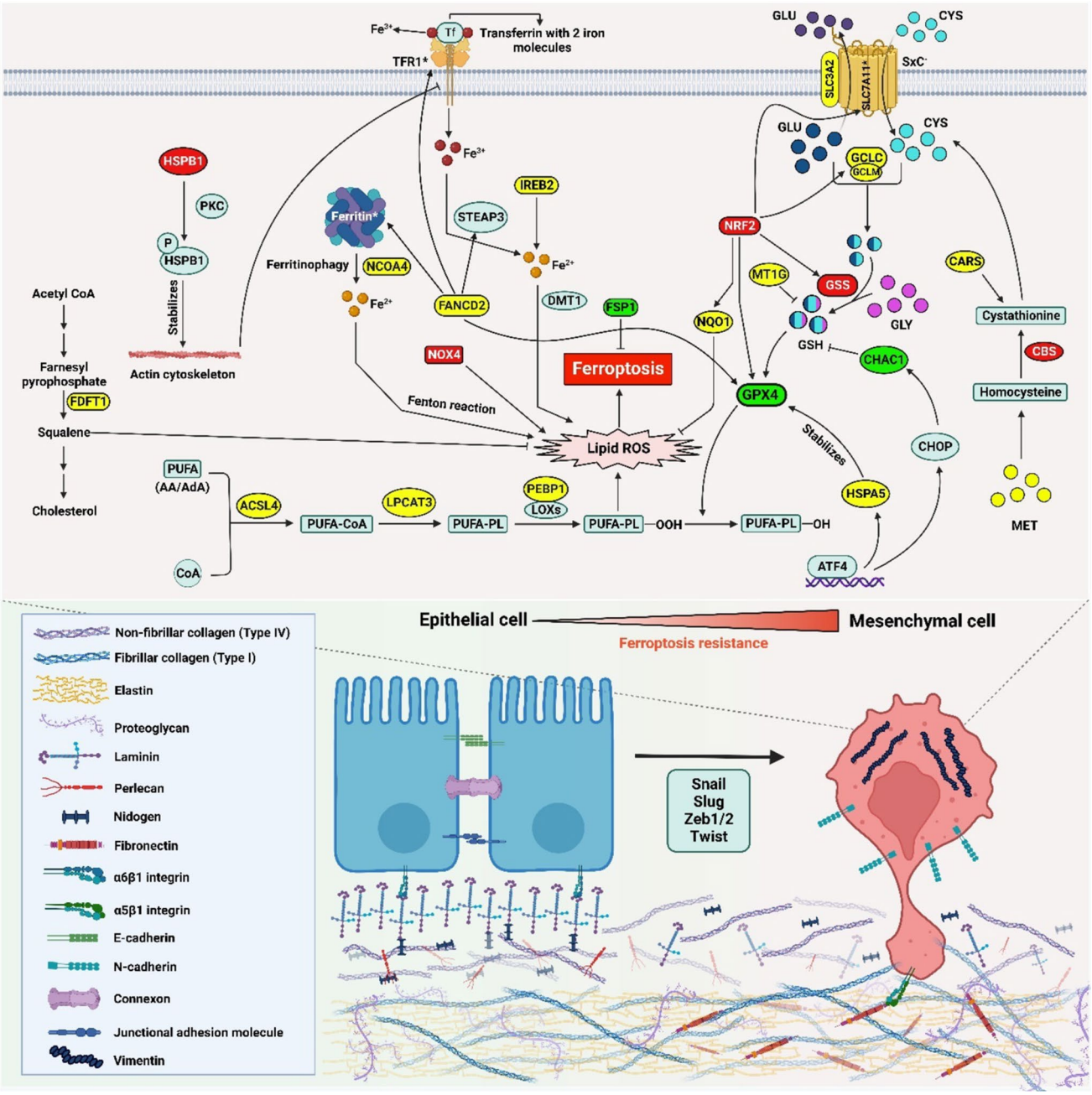
Table 4 (continued)

Type of the study	Cell line/model/tissue	Condition/treatment	Effect on plasticity	Mechanism/Experimental outcome	Reference
In vitro	Patient-derived cell line (M000921, M980513)	TGF-β + RSL3	-	↓Cell viability	[95]
In vivo	Athymic mice xenograft (LOXIMVI)	GPX4-WT + Fer1 withdrawal	-	↑Tumor growth	[95]
In vivo	Athymic mice xenograft (LOXIMVI)	sgRNA-GPX4 + Fer1 withdrawal	-	↓Tumor growth	[95]
In vitro	A375-PER	RSL3, ML210	-	↓Cell viability	[94]
In vitro	A375-PER	sgRNA-GPX4 + Fer1/PD146176/SCPI	-	↑Cell viability	[94]
In vitro	A375-PER	sgRNA-GPX4 + Fer1 withdrawal	-	↓Cell viability	[94]
In vitro	A375-PER	RSL3/ML210 + Fer/Lip/PD146176/NDGA/ SCPI-2/SCPI-4	-	↑Cell viability	[94]
In vivo	Athymic NCr nude mice xenograft (A375)	sgRNA-GPX4 + Fer1 withdrawal	-	↓Tumor volume	[94]

27HC 27-hydroxycholesterol, *27HCR* 27-hydroxycholesterol resistant, *27HCS* 27-hydroxycholesterol sensitive, *ACSL4* Acyl-CoA synthetase long-chain family member 4, *CARS* Cysteinyl-tRNA synthetase, *CBS* Cystathionine-beta-synthase, *CHAC1* ChaC glutathione specific gamma-glutamylcyclotransferase 1, *COX2* Cyclooxygenase 2, *FANCD2* Fanconi anemia complementation group D2, *FDFT1* Farnesyl-diphosphate farnesyltransferase 1, *Fer* Ferrostatin, *FSP1* Ferroptosis suppressor protein 1, *FTH1* Ferritin heavy chain 1, *GCLC* Glutamate cysteine ligase, *GCLM* Glutamate cysteine ligase modifier, *GEFR* Gefitinib-resistant, *GPX4* Glutathione peroxidase 4, *GSS* Glutathione synthetase, *HSPA5* Heat shock protein family A member 5, *HSPB1* Heat shock protein beta-1, *IREB2* Iron responsive element binding protein 2, *Lip1* Liproxstatin-1, *LPCAT3* Lysophosphatidylcholine acyltransferase 3, *MT1* Metallothionein 1, *NCOA4* Nuclear receptor coactivator 4, *NOX4* NADPH oxidase 4, *NQO1* NAD(P)H quinone dehydrogenase 1, *NRF2* Nuclear factor erythroid 2-related factor 2, *NT* No treatment, *PEBP1* Phosphatidylethanolamine binding protein 1, *PER* Persister cells *PTGS2* Prostaglandin-endoperoxide synthase 2, *ROS* Reactive oxygen species, *RSL3* RAS-selective lethal 3, *SLC* Solute carrier family proteins, *TFRC* Transferrin receptor, *TGF-β* Transforming growth factor beta, *ZEB1* Zinc finger E-box binding homeobox

stress [93]. In subsequent discussions, we aim to elucidate the significance of lipid peroxidation in the plasticity of tumors and the associated resistance (Table 4).

Viswanathan et al. have conducted extensive research on understanding the relationship between therapy-resistant mesenchymal states of various types of cancer cell lines and ferroptosis [95]. They showed that the gefitinib-resistant lung cancer cell line with a high mesenchymal phenotype is sensitive to ML210, a GPX4 inhibitor known to induce ferroptosis [95]. Also, the high mesenchymal state pancreatic cancer cell line, KP4, was found to be sensitive to ML210 treatment [95]. However, the knockdown of ZEB1 led to the development of resistance to ML210 in KP4 [95]. This showed that ZEB1 plays an important role in GPX4 dependency of the mesenchymal state cells [95]. It was also demonstrated that ML210 sensitivity was negatively correlated with erlotinib sensitivity, along with the positive correlation of mesenchymal markers expression in patient-derived pancreatic cancer cell lines [95]. The supplementation of ferrostatin (FER) 1, a lipophilic antioxidant, facilitated the survival of GPX4-KO cancer cell lines by protecting them from ferroptosis-mediated cell death [95]. Nonetheless, upon withdrawal of FER1 supplementation, the GPX4-KO KP4 cell line exhibited increased cell death due to ferroptosis, whereas the epithelial state GPX4-KO cell lines remained unaffected [95]. The lipid peroxidation mediated ferroptosis was depended on the metabolism of long-chain polyunsaturated FA, such as arachidonic acid, which becomes reactive lipid peroxides upon lipoxygenase enzyme action [95]. Supporting their findings, KO of polyunsaturated FA metabolism genes ACSL4 and lysophosphatidylcholine acyltransferase 3 abolished the sensitivity of KP4 to ML210 treatment [95]. Similar results were observed when arachidonic acid lipoxygenases were inhibited with PD146176 and zileuton in the KP4 cell line [95]. In prostate cancer, the patient-derived organoid showed high expression of ZEB1, and mesenchymal genes, representing the therapy-induced neuroendocrine transition, were sensitive to treatment with RSL3, a direct inhibitor of GPX4 [95]. In addition, the TGF-β treatment changed the phenotype of patient-derived melanoma cell lines into a mesenchymal state [95]. These mesenchymal state cell lines were resistant to vemurafenib (PLX-4032), a BRAF inhibitor, and sensitive to RSL3 treatment [95]. Moreover, the mesenchymal state LOXIMVI melanoma cell line was found to be susceptible to GPX4 inhibition, demonstrating antitumor activity in both *in vitro* and *in vivo* models [95]. Leiomyosarcoma cell line, RKN, a rare type of smooth muscle cancer, was also shown to rely on GPX4 expression to maintain a highly mesenchymal state [95]. Similar to KP4 and LOXIMVI mesenchymal state cell lines, cessation of FER1 supplementation reduced the cell viability of the GPX4-KO mesenchymal state RKN cell line [95]. In another study conducted by Hangauer and team, they studied the susceptibility of persister cancer cells to GPX4 inhibition [94]. The breast, lung, ovarian, and skin cancer persister cell lines, generated from long-term treatment of standard anticancer drugs, showed a reversible resistance to the anticancer drugs [94]. They have showed upregulation of mesenchymal markers such as vimentin, N-cadherin, FN, TWIST1, and SNAI2 as well as downregulation of epithelial markers such as E-cadherin, claudin 4 and 7 only in BT474 persister cells [94]. In addition, all the breast, lung, ovarian, and skin cancer persister cells showed a reduction in cell viability upon treatment of RSL3 and ML210 [94]. Moreover, this GPX4 inhibitor susceptibility was reversed by treatment with lipophilic antioxidants Fer1 and liproxstatin-1, lipoxygenase inhibitors PD146176 and NDGA, and lipid transporter SCP2 inhibitors SCPI-2 and SCPI-4 in breast, lung, and skin cancer persister cells [94]. Further, the GPX4-KO A375 persister cells showed a reduction in cell viability upon Fer1 withdrawal [94]. Furthermore, cessation of FER1 supplementation reduced tumor relapse in GPX4-KO A375 mice xenografts [94]. In another study, 27HCR cell lines showing high migratory potential displayed altered expression of genes involved in lipid peroxidation, antioxidant-mediated defense, and iron metabolism, as shown in Table 4 [18]. In addition, they displayed a differential expression of amino acid transporter SLC family 7 member 11 and its associated protein SLC family 3 member 2 and ferroptosis markers such as CHAC1, FANCD2, and PTGS2 [18]. Moreover, on treating 4T1, Py230, HCC1954, MDA-MB-436 and B16F10, 27HCS cell lines with 27HC showed a consistent downregulation of GPX4 [18]. On the other hand, treating the 27HCR counterpart of these cancer cell lines with 27HC either showed an increase or no prominent reduction in the expression of GPX4 [18]. This showed the importance of GPX4 in mediating the ferroptosis inhibition in resistant cell types [18]. Further, RSL3 treatment reduced the growth of 4T1-27HCR, Py230-27HCR, HCC1954-27HCR, MDA-MB-436-27HCR, and B16F10-27HCR cell lines, and FER treatment reversed the effect of RSL3 treatment [18]. Furthermore, RSL3 treatment along with GPX4 knockdown, effectively reduced the growth of Py230-27HCR and B16F10-27HCR cell lines [18]. A similar reduction in the tumor growth along with a reduction in metastasis was observed in the *in vivo* mice xenografts of GPX4 knockdown Py230-27HCR and B16F10-27HCR cell lines [18]. The micro and macro lung metastasis cell lines derived from Py230-27HCS and Py230-27HCR xenografts, respectively, exhibited remarkable resistance to the treatment of RSL3 and ML210 [18]. This observed resistance of cell lines derived from metastasized cancer cells to GPX4 inhibitors strengthens the finding that ferroptosis inhibition was a specific feature of mesenchymal phenotypic cells, which was involved in the progression of cancer [18, 94, 95]. These findings collectively provide insights into the intricate relationship between GPX4, ferroptosis resistance, and mesenchymal



state in cancer cells (Fig. 3). Despite the alteration in the expression level of several proteins in such a way to support ferroptosis, blocking GPX4 displayed a significant reduction in growth and progression of cancer in both *in vitro* and *in vivo* models [18, 94, 95].

6 Conclusion

In recent years, there has been a growing emphasis on investigating lipid metabolism as a potential target for the development of innovative therapeutics against cancer [96–101]. Cancer cells have been shown to enhance their FA uptake to meet the energy requirements for their phenotypic transition and progression. Particularly, CD36 overexpression was shown to play a substantial role in promoting tumor cell plasticity and drug resistance [19, 57, 59]. It is crucial to highlight that co-treatment with CD36 inhibitors has demonstrated the ability to sensitize resistant cancer cells to anticancer drugs in both *in vitro* and *in vivo* models [59]. In addition, cancer cells have also been shown to enhance their lipid synthesis to develop and maintain stemness and to support metastasis. Similar to inhibition of FA uptake, suppression of lipid synthesis has shown efficacy in sensitizing

◂**Fig. 3** The transformation of cell phenotype (plasticity) from epithelial to mesenchymal state increases the resistance to ferroptosis. The figure comprises the complex interplay of various proteins that alters the crosstalk between iron metabolism, antioxidant defense, and proteins that directly or indirectly affect the generation of lipid reactive oxygen species. Importantly, the major proteins that assist the inhibition of ferroptosis in transformed mesenchymal cells were highlighted with different colors and symbols: green color and "↑" represents either an increase in the expression or activity of the protein, red color, and "↓" represents the reduction in the expression or activity of the protein and yellow color and "*" denotes the differential expression of the protein. AA, Arachidonic acid; ACSL4, Acyl-CoA synthetase long chain family member 4; AdA, Adrenic acid; ATF4, Activating transcription factor 4; CARS, Cysteinyl-tRNA synthetase; CBS, Cysteinyl-tRNA synthetase; CHAC1, ChaC glutathione specific gamma-glutamylcyclotransferase 1; CHOP, C/EBP homologous protein; CoA, Coenzyme A; CYS, Cysteine; DMT1, Divalent metal transporter 1; FANCD2, Fanconi anemia complementation group D2; FDFT1, Farnesyl-diphosphate farnesyltransferase 1; GCLC, Glutamate cysteine ligase; GCLM, Glutamate cysteine ligase modifier; GLU, Glutamate; GLY, Glycine; GPX4, Glutathione peroxidase 4; GSH, Glutathione; GSS, Glutathione synthetase; HSPA5, Heat shock protein family A member 5; HSPB1, Heat shock protein beta-1; IREB2, Iron responsive element binding protein 2; LOXs, Lipoxygenase; LPCAT3, Lysophosphatidylcholine acyltransferase 3; MT1G, Metallothionein 1 G; NCOA4, Nuclear receptor coactivator 4; NOX4, NADPH oxidase 4; NQO1, NAD(P)H quinone dehydrogenase 1; NRF2, Nuclear factor erythroid 2-related factor 2; MET, Methionine; PEBP1, Phosphatidylethanolamine binding protein 1; PKC, Protein kinase C; PL, Phospholipid; PUFA, Polyunsaturated fatty acid; ROS, Reactive oxygen species; RSL3, RAS-selective lethal 3; SLC3A2, Solute carrier family 3 member 2; SLC7A11, Solute carrier family 7 member 11; STEAP3, Six-transmembrane epithelial antigen of prostate 3; SxC-, System Xc-; TFR1, Transferrin receptor 1; ZEB, Zinc finger E-box binding homeobox

drug-tolerant and resistant cancer cells to drug treatment [65, 68, 71]. Ladanyi and group have demonstrated that there was an inhibition of lipid synthesis when adipocyte-induced CD36 expression propels ovarian cancer progression and metastasis [19]. However, 27HCR breast cancer and skin cancer cell lines concurrently exhibited an upregulation in the expression of both lipid uptake and lipid synthesis genes, accompanied by a simultaneous enhancement of cancer cell migration and metastasis [18]. The presented evidence substantiates the notion that diverse malignancies undergo discernible metabolic reprogramming processes conducive to their progression. Consequently, a compelling imperative for extended inquiry arises to comprehensively elucidate the role of lipid uptake and synthesis across diverse types of cancer and at various stages of their progression. Moreover, inhibition of lipid catabolism was shown to induce mesenchymal-epithelial transition and reduce the invasion and migration of cancer cells [85–87]. Unlike lipid uptake and lipid synthesis, β-oxidation of lipids and lipogenesis have not been reported to be enhanced simultaneously during the progression of cancer. These studies indicate that cancer cells modulate different aspects of lipid metabolism in a peculiar manner to support its progression and to develop resistant phenotypes. Notably, the reprogramming of lipid metabolism is evident not solely within cancer cells but extends to immune cells within the TME, particularly macrophages and neutrophils [60, 88, 102, 103]. This phenomenon induces malfunction in these immune cells, consequently promoting tumor growth, survival, and progression [60, 88]. As previously discussed, cancer cells undergoing metastatic colonization exhibited a reversal of EMT, favoring glucose uptake over citrate uptake mediated enhancement of lipid synthesis [69]. Additionally, cell lines derived from metastasized cancer cells showed resistance to GPX4 inhibitor treatment, while cells in a mesenchymal state were susceptible [18]. This highlighted the specificity of reprogrammed lipid metabolism and GPX4-mediated inhibition of ferroptosis in metastasizing cells. However, in-depth preclinical studies and clinical trials are warranted to completely understand the aspects of lipid metabolic shift during cancer metastasis. Moreover, GPX4 presents a promising therapeutic target, given its capacity to autonomously inhibit lipid peroxidation-induced ferroptosis and thereby assist the progression of cancer in preclinical studies [18, 94, 95]. In recent years, researchers have started exploring GPX4 inhibitors as therapeutic candidates for various cancers [104–108]. Furthermore, exploring the efficiency of GPX4 inhibitors to regulate the metastatic progression and as chemosensitizers will open new treatment strategies for cancer. Most importantly, clinical trials have to be conducted in order to validate the potential of GPX4 inhibition to control cancer metastasis and to reverse of resistance.

A notable lacuna exists in the integration of information pertaining to alterations in distinct lipid metabolism domains and the strategic selection by cancer cells between relying on lipid anabolism or exogenous FA to propel the progression of the disease and to develop resistant phenotypes. To bridge this research gap, investigations must simultaneously scrutinize modifications in various lipid metabolism domains, particularly as cancer cells undergo adaptations to modulate plasticity throughout the course of disease progression. The subtle alterations in lipid metabolism necessitate intricate examination in a spatiotemporal manner at each stage of cancer progression concomitant with the acquisition of plasticity. Despite the perturbations in the cellular lipid metabolism in tumors, an optimal balance between synthesis and catabolism appears to exist. In summary, we have elucidated the role of metabolic remodeling of lipids in facilitating tumor plasticity, thereby conferring drug resistance. However, additional studies are imperative to leverage these potentially targetable lipid metabolic pathways for controlling cancer progression and combating drug resistance. The proposition of innovative combinatorial therapeutics involving modulators across diverse lipid metabolism domains promises to unveil a novel therapeutic avenue for cancer.

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Declarations

Competing interests The authors declare no competing interests.

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