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The central role of mitochondria in the relationship between dietary lipids and cancer progression

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ABSTRACT

Evidence demonstrates the importance of lipid metabolism and signaling in cancer cell biology. *De novo* lipogenesis is an important source of lipids for cancer cells, but exogenous lipid uptake remains essential for many cancer cells. Dietary lipids can modify lipids present in tumor microenvironment affecting cancer cell metabolism. Clinical trials have shown that diets rich in polyunsaturated fatty acids (PUFA) can negatively affect tumor growth. However, certain n-6 PUFAs can also contribute to cancer progression. Identifying the molecular mechanisms through which lipids affect cancer progression will provide an opportunity for focused dietary interventions that could translate into the development of personalized diets for cancer control. However, the effective mechanisms of action of PUFAs have not been fully clarified yet. Mitochondria controls ATP generation, redox homeostasis, metabolic signaling, apoptotic pathways and many aspects of autophagy, and it has been recognized to play a key role in cancer. The purpose of this review is to summarize the current evidence linking dietary lipids effects on mitochondrial aspects with consequences for cancer progression and the molecular mechanisms that underlie this association.

Abbreviations: 2D-HG, D-2-hydroxyglutarate; ACC, acetyl CoA carboxylase; ACLY, ATP-citrate lyase; AMPK, AMP-activated protein kinase; COX, cyclooxygenase; CPT-I, carnitine palmitoyltransferase I; DAG, diacylglycerols; DHA, docosahexaenoic acid; DMH, N,N-Dimethylhydrazine dihydrochloride; ECAR, Extracellular acidification rate; EGF, epidermal growth factor; EPA, eicosapentaenoic acid; ER, endoplasmic reticulum; ERRα, estrogen-related receptor α; FABPs, Fatty acid binding proteins; FAO, fatty acid oxidation; FAs, fatty acids; FASD2, fatty acid desaturase 2; FASN, fatty acid synthase; GFRs, growth factor receptors; GPX, glutathione peroxidase; GSH, glutathione; LXR, liver X receptors; mETC, mitochondrial electron transport chain; MMP, mitochondrial membrane potential; MOMP, mitochondrial outer membrane permeabilization; MS, mass spectrometry; mTOR, mammalian target of rapamycin; MUFA, monounsaturated fatty acids; NMR, nuclear magnetic resonance; OA, oleic acid; OCR, oxygen consumption rate; OXPHOS, oxidative phosphorylation; PLs, Phospholipids; PPARs, peroxisome proliferator-activated receptors; PTEN, phosphatase and tensin homolog; PUFA, polyunsaturated fatty acids; RAR, retinoic acid receptor; Redoxome, redox metabolome; ROS, reactive oxygen species; SaGA, spatiotemporal cellular and genomic analysis; SCD1, Stearoyl-CoA desaturase-1; SFA, saturated fatty acid; SOD, superoxide dismutase; SREBP, sterol regulatory element binding proteins; TBARS, thiobarbituric acid reactive substances; TCA, tricarboxylic acid; UFA, unsaturated FAs; UPR, unfolded protein response; VEGF, vascular endothelial growth factor.

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1. Introduction

Lipid levels in an organism are the result of the interplay between the nutritional intake and the lipogenic biosynthetic pathways existing in the cell [1]. In this line, the diet and the impact of the lipidic profile in the onset and progression of oncogenic pathologies is well known [2]. Mitochondria are involved in cancer progression from many different aspects [3]. There is a deep relationship between dietary lipids, mitochondria and cancer (e.g [4].) in which mitochondria might be considered as the conductor who decides the future of the cancer cell. This review addresses some of the issues that make the mitochondria this central element, paying attention to aspects such as bioenergetics, redox biology, cell signaling, cell death, autophagy and *de novo* lipogenesis. For reasons of space, it will not be possible to treat some aspects that are also very interesting but that could be the subject of complete reviews such as the role that the immune system or the tumor microenvironment plays in this relationship.

2. Mitochondria and cancer

The mitochondrion is an important organelle that mediates several critical processes in a eukaryotic cell, including cancer cells. From the bioenergetic point of view, since Warburg observed that tumor cells favored the glycolytic process as a source of ATP, increasing glucose uptake and diminishing oxidative phosphorylation (OXPHOS) even under aerobic conditions, subsequent studies have revealed that mitochondria in tumors are able to operate OXPHOS at lower capacities along with glycolysis [3].

Mitochondria are critical for providing intermediates required for biomass synthesis, which includes fatty acids, amino acids, and nucleotides that are required as building blocks for cell growth. In cancer cells, activity of several mitochondria enzymes or proteins involved in the synthesis of fatty acids, aminoacids, and nucleotides is upregulated in multiple different tumors [5]. Certain metabolites produced in tricarboxylic acid (TCA) cycle and fatty acid oxidation (FAO) pathways have been reported to be increased in tumors due to certain mutations being referred as oncometabolites. To date, only D-2-hydroxyglutarate (2D-HG), succinate, and fumarate are considered as oncometabolites [3].

Mitochondria are major organelles for reactive oxygen species (ROS) and redox molecules generation. At physiological levels, ROS functions as “redox messengers” in intracellular signaling but high levels of ROS can exceed antioxidant defense systems capacity to maintain a steady state and react with DNA, proteins, and lipids [6]. Cancer cells often contain high levels of ROS, arising due to oncogenic transformation, altered metabolism, deregulated redox homeostasis and hypoxia [3]. Moreover, an excess of reduction equivalents can lead to reductive stress which in turn can also produce more oxidative stress, although this aspect could be eventually used to fight cancer [7].

Mitochondria are also organelles that function as a regulator for multiple related signaling, which is essential for tumor cells to cope with surrounding environment [8]. Mitochondria play a key role in this issue since they are the main source for ROS and redox molecules generation. They are also the main sites of calcium storage, which control intracellular Ca^{2+} concentration that mediate in signaling for modulation of cell metabolism and survival [8].

Mitochondria are very relevant in the complex programmed cell death mechanisms triggering this process through several mechanisms [9]. Mitochondrion mediates the intrinsic apoptosis program characterized by cytochrome c release, which is regulated by Bcl-2 family proteins governing MOMP. Bcl-2 family proteins can be divided into members that function preventing apoptosis (the anti-apoptotic or pro-survival proteins Bcl-2, Mcl-1 and Bcl-xL) and those that induce apoptosis (the pro-apoptotic proteins Bax and Bak) operating as a core to integrate stress-signaling networks [10].

Autophagy is an evolutionary complex process used by cells to selectively eliminate aged and/or damaged cytoplasmic materials, such as misfolded proteins and organelles, through the delivery to lysosomes and digestion by hydrolytic enzymes [11,12]. A selective form of autophagy is mitophagy, that occurs both in yeast and mammalian cells and involves exclusively mitochondria [13]. Damaged or defective mitochondria are indeed recognized by some protein and lipid receptors, engulfed by the mitophagophore membrane and then transported and degraded inside lysosomes. Defective autophagy and mitophagy are involved in the onset of cancer where they seem to exert a paradoxical role: according to the nature, the rate and the duration of stress, as well as to the cellular genetic background and the surrounding microenvironment, they can promote the suppression or the progression of cancer [14] (Figs. 1 and 2).

3. Dietary lipids and cancer

Lipids play many roles in cell biology ranging from membrane formation and lipid storage to cell signaling. Despite the strong evidence for *de novo* lipogenesis as an important source of lipids for cancer cells, there is also abundant literature showing that exogenous lipid uptake remains an important source of lipids for cancer cells. Tables 1 and 2 summarizes main findings *in vitro* and *in vivo* on the role of fatty acids in cancer cells.

3.1. Dietary lipids and mitochondrial bioenergetics in cancer

Despite the focus on the so-called Warburg effect, the maintaining of a functional OXPHOS is also required for tumor progress. The OXPHOS pathway couples with TCA, but also with FAO that, in fact, is an important bioenergetic pathway in many cancers and promotes proliferation, metastasis, stemness and treatment resistance [15]. Lipids can provide a large quantity of energy and reductive equivalents for proliferating healthy cells [16]. In the FAO process, fatty acids (FAs) are degraded to acetyl-CoAs that are used in the TCA cycle for anabolic processes and the production of reducing equivalents. Despite cancer cells largely rely on glucose for energy production [17] as well as carbon source for anabolic processes [18], in hypoxic conditions or in response to treatment, tumor cells appear to favor FAO to rapidly generate ATP and NADPH promoting survival [19].

Dietary lipids can exert modulatory effects in cancer cell bioenergetics. N-3 PUFA have shown deleterious effects on mitochondrial metabolism the human acute myeloid leukemia cell lines U937, MOLM-13 and HL-60 [20]. Extracellular acidification rate (ECAR) and oxygen consumption rate (OCR) values found in treated cells suggested that docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) or the n-3 polyunsaturated fatty acids (PUFA)-rich fish oil, but not the n-6 PUFA-rich sunflower oil caused shift in mitochondrial energy metabolism from OXPHOS to glycolytic metabolism in the mentioned cell lines along with dose-dependent decrease in cell viability [20]. Alterations in mitochondrial ultrastructure and cellular metabolism in parallel to growth inhibition of Walker 256 carcinosarcoma xenograft tumors has been reported in rats fed gamma-linolenic acid and EPA. At a concentration of 150 μM, both FAs diminished cell proliferation and altered energy metabolism as indicated the decrease in mitochondrial respiratory chain complexes I + III and IV activities and the increased in deposition triacylglycerol in the form of lipid droplets. In addition, intracellular ATP concentrations that presumably would resulted from increased utilization of glucose for ATP generation [21]. In a similar model, the n-6 PUFA gamma-linoleic acid also decreased hexokinase and carnitine palmitoyltransferase I (CPT-I) activities, which would contribute to altered mitochondrial metabolism and structure alteration [22]. Gamma-linolenic and arachidonic acids have been reported to cause a 60–70 % inhibition of tumor cell CPT-I activity and 45–50 % inhibition of palmitic acid oxidation to CO_2 in Walker 256 carncinosarcoma cells [23]. Therefore, it seems that both n-3 and n-6 PUFA have a considerable impact on mitochondrial FAO and OXPHOS, which can explain, at least in part, the inhibition of cell proliferation by these FAs.

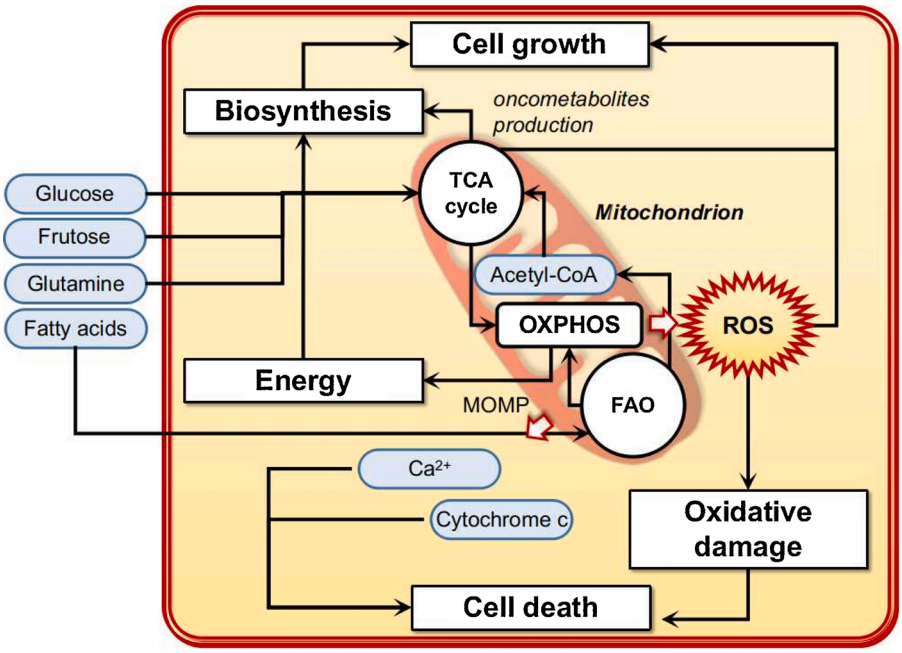

Fig. 1. Mitochondrial central role in cancer biology. The mitochondrion produces energy by its OXPHOS pathway (which is coupled with TCA cycle and FAO pathways) and provides intermediates required for cell components biosynthesis which allows cell growth. Some intermediates o derived molecules of TCA cycle (2D-HG, succinate, and fumarate) referred as oncometabolites can play tumorigenic roles favoring cell growth at elevated concentrations. Mitochondria are also major organelles for generation of ROS, which functions as "redox messengers" in intracellular signaling and promote cancer cell growth. However, excessive ROS production can cause oxidative damage leading to the integrated stress response of mitochondria that ultimately can trigger cancer cell death. On the other hand, mitochondria play an essential role in programmed cell death since it mediates the intrinsic apoptosis program. Moreover, mitochondrial Ca^{2+} release related with sustained opening of mPTP that finally leads to MOMP is able to trigger cell death by necrosis or apoptosis. Abbreviations: OXPHOS: oxidative phosphorylation; TCA: tricarboxylic acid cycle; FAO: fatty acid oxidation; ROS: reactive oxygen species; MOMP: mitochondrial outer membrane permeabilization.

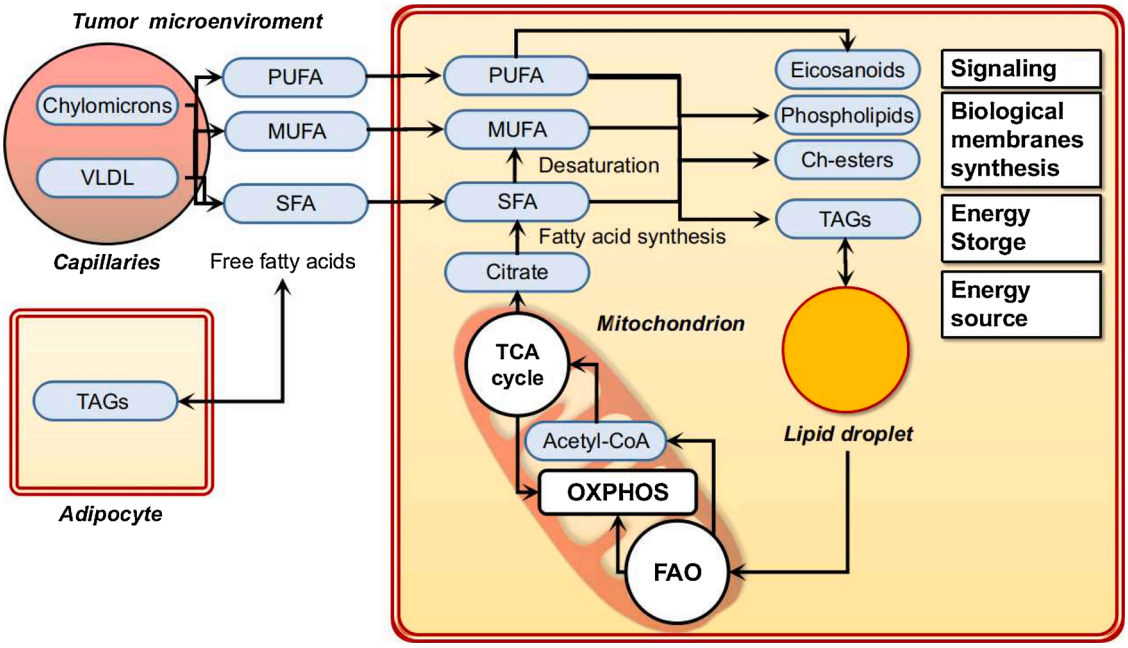

Fig. 2. Lipid metabolism in cancer cells. Lipids travel through bloodstream packaged into chylomicrons or VLDLs to tumor area where they are released into tumor microenvironment and can be taken up by tumor cells. Moreover, lipids can be obtained by *de novo* lipogenesis which starts with export of citrate. Fatty acids are used as substrates for synthesis of TAGs, Ch esters, and plasma membrane phospholipids or can be catabolized by the tumors cells to obtain energy and reducing equivalents. These new-synthesized lipids are essential not only for new cellular membrane during cell division, but also for energy storage and post-translational modification of signaling molecules required for proliferation and oncogenic signaling. Lipid uptake and synthesis have been linked to the formation of lipid droplets, which mainly consist of TAGs and cholesterol esters and represent an additional energy and lipid reservoir for cancer cells. Abbreviations: VLDLs: very low-density lipoproteins; TAG: triacylglycerol; Ch: cholesterol; MUFA: monounsaturated fatty acids; TCA: tricarboxilic acid; OXPHOS: oxidative phosphorylation.

On the other hand, a diet rich in the saturated fatty acid (SFA) palmitic acid has been showed to enhance the proliferation of prostate cancer PC-3 xenografts in comparison with a diet high in unsaturated FAs (UFA). It has been reported that palmitate upregulated the biosynthesis of palmitoyl-CoA and enhanced Src-dependent mitochondrial β-oxidation in prostate PC-3, 22Rv1, DU145, and PNT2 cancer cell lines and xenograft prostate tumors from C57BL/6 J male mice [24]. However, not all SFAs seem to have a similar role. In the murine mammary tumor cell line 4526 treated with FAs with different unsaturation degree, uptake and beta-oxidation rates were much lower for stearic acid than for oleic or linoleic acids. Interestingly, stearic acid inhibited cell growth whereas UFA stimulated it [25]. In the same sense, the saturated lauric acid, that showed to reduce cell proliferation in CT26 mouse colon cancer cells, decreased both, mitochondrial volume and lactate production, particularly under low-glucose conditions [26]. Inhibitory effect against cancer cell growth have also been reported for palmitate in

Table 1
In vitro studies on fatty acids effect in cancer cells.

Compounds	Experimental Model	Dosage & duration	Effects	Ref.
DHA *vs* OA	AML KG1a, THP-1, HL-60, ML-2 & U937, MOLM-13 cells	10−50 μM for 24−48 h	• ↓ Cancer cell viability in a dose- & dependent-manner • ↓ Mitochondrial respiration in U937, MOLM-13 & HL-60 cells • ↑ Glycolysis in U937, MOLM-13 & HL-60 cells • ↑ Nrf2 signaling in U937, MOLM-13 & HL-60 cells • ↑ Disorganization of the mitochondrial network and mitochondrial swelling in U937, MOLM-13 & HL-60 cells	[20]
EPA *vs* OA	AML KG1a, THP-1, HL-60, ML-2 & U937, MOLM-13 cells	50−150 μM for 24−48 h	• ↓ Cancer cell viability in a dose- & dependent-manner • ↓ Mitochondrial respiration in U937, MOLM-13 & HL-60 cells • ↑ Glycolysis in U937, MOLM-13 & HL-60 cells • ↑ Nrf2 signaling in U937, MOLM-13 & HL-60 cells • ↑ Disorganization of the mitochondrial network and mitochondrial swelling in U937, MOLM-13 & HL-60 cells	[20]
FO *vs* SO	AML KG1a, THP-1, HL-60, ML-2 & U937, MOLM-13 cells	0−100 μg/mL for 24−48 h	• ↓ Cancer cell viability in a dose- & dependent-manner	[20]
FO	Primary leucoblasts from from patients with hyperleucocytic AML	0−50 μM for 48 h	• ↓ Cancer cell viability	[20]
GLA & EPA	Walker 256 rat carcinosarcoma cells	150 μM for 24−48 h	• ↓ Cancer cell proliferation • ↑ Apoptosis • ↑ ROS • ↑ Lipid peroxidation • ↑ Deposition of large amounts of TAGs in the form of lipid droplets • ↓ Mitochondrial respiratory chain complexes I + III and IV activity • ATP maintained at 70–80 % • ↓ MMP • ↑ Cytochrome c release & caspase-3-like activation.	[21]
GLA	Human larynx tumour Hep2 & Walker 256 rat carcinosarcoma cells	150 μM for 6 h	• ↓ Cancer cell proliferation • ↓ CPT I & II activities • ↓ PA oxidation	[23]
AA	Human larynx tumour Hep2 & Walker 256 rat carcinosarcoma cells	150 μM for 6 h	• ↓ Cancer cell proliferation • ↓ CPT I & II activities • ↓ PA oxidation • ↑ PGE2 production • ↑ CPT I mRNA	[23]
AA + COX inhibitor indomethacin	Human larynx tumour Hep2 & Walker 256 rat carcinosarcoma cells	150 μM for 6 h of AA +4 μg/mL of indomethacin	• ↓ PGE2 production • Cancer cell proliferation & CPT I & II activities remained unaffected	[23]
LA & OA	Colorectal cancer HT29 cells	150 μM for 6 h	• No effect on cancer cell proliferation or CPT I & II activities	[23]
LA, OA, GLA & AA	Colorectal cancer HT29 cells	150 μM for 6 h	• No effect on cancer cell proliferation or CPT I & II activities	[23]
PA	Prostate epithelial cancer PC-3, 22Rv1, DU145 cells	15 min	• ↑ Palmitoyl-CoA biosynthesis • ↑ Src-dependent mitochondrial beta-oxidation. • ↑ C16-ceramide & total saturated ceramides • ↑ Src kinase localized in the cell membrane & its downstream signaling	[24]
SA	Murine mammary tumor 4526 cells	40 μM for 5 d	• ↓ Cancer cell growth • ↓ FA uptake & oxidation rates *vs* OA or LA	[25]
OA, LA or SA + LA	Murine mammary tumor 4526 cells	40 μM for 5 d	• ↑ Cancer cell growth	[25]
HBA + LAA	Mouse CT26 colon cancer cells	1 mM of HBA + 1.5 mM of LAA for 24 h	• ↓ Cancer cell proliferation • ↓ Mitochondrial volume • ↓ Lactate production • ↑ Oxidative stress, particularly in low-glucose conditions. • ETC enzymes imbalance	[26]
MA & SA	Breast MDA-MB-231 cancer cells	0.1 mM for 24 h	• ↓ Cancer cell proliferation • ↑ Apoptosis	[27]
PA	Breast MDA-MB-231 cancer cells	0.1 mM for 24 h	• ↓ Cancer cell proliferation • ↓ MMP • ↑ Apoptosis • ↑ Cytochrome c release • ↑ Cardiolipin turnover • ↓ Cardiolipin levels	[27]
PA + OA *vs* PA	Breast MDA-MB-231 cancer cells	0.1 mM for 24 h	• ↓ PA-induced apoptosis • ↑ Cardiolipin levels • ↑ PA esterification to TAGs • ↑ β-oxidation with the AMPK activator	[27]

(*continued on next page*)

Table 1 (*continued*)

Compounds	Experimental Model	Dosage & duration	Effects	Ref.
PA + FAO inhibitor etomoxir *vs* PA	Breast MDA-MB-231 cancer cells	0.1 mM for 24 h	• ↑ PA-induced apoptosis	[27]
PA + FAS inhibitor triacsin C *vs* PA	Breast MDA-MB-231 cancer cells	0.1 mM for 24 h	• ↓ PA-induced apoptosis	[27]
PA + ACR *vs* PA	Breast MDA-MB-231 cancer cells	0.1 mM for 24 h	• ↑ cardiolipin levels • ↓ PA-induced apoptosis.	[27]
OA	Breast MDA-MB-231 cancer cells	0.1 mM for 24 h	• ↑ Cancer cell proliferation • ↓ Apoptosis	[27]
DHA, LA, AA	Breast MDA-MB-231 cancer cells	0.1 mM for24 h	• ↑ Cancer cell proliferation	[27]
LA & ALA	MGC & SGC gastric carcinoma cells	0−200 μM for 48 h	• ↓ Cancer cell growth at 200 μM • ↑ Lipid droplets • ↑ Apoptosis • ↑ ROS formation • ↑ lipid peroxides • ↑ SOD activity • ↑ LXA4	[29]
AA	MGC & SGC gastric carcinoma cells	0−200 μM for 48 h	• ↓ Cancer cell growth from 120 μM • ↑ ROS formation • ↑ lipid peroxides • ↑ SOD activity • ↑LXA4	[29]
EPA & DHA	MGC & SGC gastric carcinoma cells	0−200 μM for 48 h	• ↓ Cancer cell growth, but they were less effective *vs* LA ALA & AA. • ↑ ROS formation • ↑ lipid peroxides • ↑ SOD activity • ↑LXA4	[29]
LA	Colorectal cancer semi-differentiated RKO & undifferentiated LOVO cells	0.3−20 mM for 12–36 h	• ↓ Tumour cell growth (RKO cells were more sensitive) • ↑ ROS formation • ↑ MDA accumulation • ↓ SOD activity • ↓ mitochondrial membrane potential • ↑ Apoptosis intrinsic pathway (caspase-3 was less activated in LOVO cells)	[29]
LA	Colorectal cancer semi-differentiated RKO & undifferentiated LOVO cells	0.1-0.2 mM for 12–36 h	• ↑ Tumor cell proliferation	[29]
LA	Colorectal cancer semi-differentiated RKO & undifferentiated LOVO cells	Pre-incubation with 100 μM for 24h	• ↑ Sensitivity to LA	[29]
DHA & EPA	Colon carcinoma SW480 & SW620 cells derived from a primary tumor & a metastasis of the same tumor, respectively	35−70 μM for 24-144h	• ↓ Tumor cell growth with DHA showing the strongest effect specially in SW620 cells • ↑ % cells in G2/M phase, particularly for SW620 cells • ↑ Lipid droplets • ↑ Total cholesteryl esters & DHA-containing cholesteryl esters in SW620 cells after DHA treatment. • ↑ DHA-enriched TAGs in SW480 cells • ↓ SREBP1 by DHA • No effect on lipid peroxidation, GSH or GPX activity.	[29]
AA	Colon carcinoma SW480 & SW620 cells derived from a primary tumor & a metastasis of the same tumor, respectively	35−70 μM for 24-144h	• ↑ Total cholesteryl esters in SW620 cells • ↑ AA-enriched TAGs in SW480 cells	
OA	Colon carcinoma SW480 & SW620 cells derived from a primary tumor & a metastasis of the same tumor, respectively	35−70 μM for 24-144h	• ↑ OA-enriched TAGs	
ALA, EPA, DHA & AA	Human pancreatic cancer MIA PaCa-2, PANC-1 & CFPAC cells	1.25 μM–50 μM for 24 h	• ↓ Cancer cell proliferation, with EPA being the most potent • Lipid peroxidation level did not always correlate with the extent of cell death.	[29]
ALA, EPA, DHA & AA + COX inhibitors indomethacin & piroxicam	Human pancreatic cancer MIA PaCa-2, PANC-1 & CFPAC cells	1.25 μM–50 μM for 24 h	• No effect on cell proliferation	[29]
EPA + OA	Human pancreatic cancer MIA PaCa-2, PANC-1 & CFPAC cells	1.25 μM–50 μM for 24 h	• No effect on EPA-induced effect on proliferation	[29]
EPA + vit E	Human pancreatic cancer MIA PaCa-2, PANC-1 & CFPAC cells	1.25 μM–50 μM for 24 h	• No effect on EPA-induced effect on proliferation	[29]
PA, OA, SA & LAA	Human pancreatic cancer MIA PaCa-2, PANC-1 & CFPAC cells	1.25 μM–50 μM for 24 h	• No effect on cell proliferation	[29]
OA	Low metastatic breast MCF-7 & gastric carcinoma SGC7901 cells	400 μM for 24–72h	• ↓ Cancer cell growth & survival • Pharmacological activation of AMPK rescued the cell viability by maintained ATP levels by increasing fatty acid β-oxidation	[29]
OA	High-metastatic gastric carcinoma HGC-27 & breast cancer MDA-MB-231 cells	400 μM for 24–72h	• ↑ Cancer cell growth • ↑ Migration under serum deprivation • ↑ AMPK activation	[29]

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Table 1 (*continued*)

Compounds	Experimental Model	Dosage & duration	Effects	Ref.
			• ↑ FAO and ATP production • Inactivation of AMPK attenuated these activities	
DHA & EPA	Estrogen-dependent breast cancer MCF-7, ZR-75 & T-47-cells	20 μg/ml for 1–9 d	• ↓ Cell growth except in MCF-7 cells • ↑ Lipid peroxidation in ZR-75	[35]
ALA	Estrogen-dependent breast cancer MCF-7, ZR-75 & T-47-cells	20 μg/ml for 1–9 d	• ↓ Cell growth in T-47-D cells • ↑ Lipid peroxidation in ZR-75 cells	[35]
GLA	Estrogen-dependent breast cancer MCF-7, ZR-75 & T-47-cells	20 μg/ml for 1–9 d	• ↓ Cell growth in ZR-75 cells • ↑ Lipid peroxidation in ZR-75 cells	[35]
OA	Estrogen-dependent breast cancer MCF-7, ZR-75 & T-47-cells	20 μg/ml for 1–9 d	• No effects	[35]
DHA & EPA	Estrogen-independent breast cancer MDA-MB-231 & HBL-100 cells	20 μg/ml for 1–9 d	• ↓ Cell growth • ↑ Lipid peroxidation in HBL-100 cells	[35]
ALA & GLA	Estrogen-independent breast cancer MDA-MB-231 & HBL-100 cells	20 μg/ml; for 1–9 d	• ↓ Cell growth, although they were less effective • ↑ Lipid peroxidation in HBL-100 cells	[35]
OA	Estrogen-independent breast cancer MDA-MB-231 & HBL-100 cells	20 μg/ml for 1–9 d	• ↑ Cancer cell proliferation	[35]
GLA, AA & EPA	Meth-A induced sarcoma cells	10−200 μg/ml for 30 min	• ↓ Cancer cell growth • ↑ Lipid peroxidation • ↑ ROS formation	[39]
GLA, AA, EPA + vit E	Meth-A induced sarcoma cells	100 μg/ml + 200 μg/ml of vit E for 30 min	• FA cytotoxicity was partially blocked	[39]
DHA	Human lung adenocarcinoma A549 cells	40−55 μg/m for 24–72	• ↓ Cancer cells proliferation in a dose- & time-dependent manner • ↑ Apoptosis in a dose- & time-dependent manner • ↑ Autophagosomes formation	[41]
EPA	Human lung adenocarcinoma A549 cells	45−60 μg/ml for 24–72 h	• ↓ Cancer cells proliferation in a dose- & time-dependent manner • ↑ Apoptosis in a dose- & time-dependent manner • ↑ Autophagosomes formation	[41]
DHA & EPA	Human neuroblastoma LA-N-1 cells	0–70 μM for 24–72 h	• ↓ Cancer cells proliferation in a dose- & time-dependent manner. • ↓ CDK2 & cyclin E • G0/G1 cell cycle arrest • ↑ Apoptosis • ↓ MMP • ↑ Bax, activated caspase-3 & caspase-9 • ↓ Bcl-XL	[43]
DHA & EPA	Human pancreatic cancer MIA-PaCa-2 & Capan-2 cells	0-100 μM for 24–72 h	• ↑ ROS accumulation • ↑ Caspase-8-dependent cell death • EPA was accumulated in pancreas at a level markedly higher than other tissues	[43]
EPA, AA, ALA & LA	Cancer colon Caco-2 cells	0–160 μM for 24–72 h	• ↓ Cancer cells proliferation *vs* ALA & LA • ↑ Lipid peroxidation	[46]
AA, GLA & EPA	Rodent glioma C6, MOG, U87 & U373 cells	0.1 μM-500 mM for 0–7d	• ↓ Cancer cells proliferation • ↑ Apoptosis	[47]
AA, GLA & EPA	Primary cell suspensions prepared from human glioma samples	0.1 μM-500 mM for 0–7 d	• ↓ Cancer cells proliferation • ↑ Apoptosis	[47]
AA, GLA & EPA	Multicellularr spheroids derived from rodent glioma C6, MOG, U87 & U373 cells	0.1 μM-500 mM for 0–7d	• ↓ Cancer cells proliferation • ↑ Apoptosis	[47]
AA, GLA & EPA	Multicellularr spheroids derived from primary cell suspensions prepared from human glioma samples	0.1 μM-500 mM for 0–7d	• ↓ Cancer cells proliferation • ↑ Apoptosis	[47]
LAA	Human breast cancer SkBr3 & Ishikawa endometrial cancer cells	1–100 μM for 4-24h	• ↑ ROS levels • ↑ EGFR, ERK & c-Jun activation • ↑ c-fos expression. • ↑ p21Cip1/WAF1 leading to p53-independent manner apoptosis	[48]
LAA	Human colon cancer HCT-15 & human hepatocellular carcinoma HepG2 cells & Raw 264.7 cells	0−80 μg/mL for 48h	• ↑ Apoptosis in a dose-dependent manner by LAA • ↓ EGFR in HCT-15 by LAA • LAA was found to be the most active and showed a higher affinity towards EGFR & TS *in silico*	[49]
LAA *vs* BA	Colorectal cancer Caco-2 cells & intestinal IEC-6 cells	0.1−5 mM for 24−96 h	• ↑ Apoptosis • ↓ GSH availability • ↑ ROS generation • ↑ Cells arrested in S & G2/M phases	[50]
DHA	Hepatocellular carcinoma HepG2 (with and without p53 knockdown), Hep3B (p53 null) & Huh7 (p53 mutant) cells	0−200 μM for 24h	• ↑ Apoptosis • ↑ Oxidative stress • ↓ MMP • ↑ cytochrome c release • ↑ Bcl2 family proteins • ↑ Cytochrome c release • ↑ Caspase signaling	[51]
CLA-enriched *vs* non-enriched egg yolk FA extracts	Breast cancer MCF-7 cells	0.5 mg/ml for 48 h	• ↑ p53 and mothers against decapentaplegic homolog 2 tumor suppressors • ↑ p38 MAPK & JNK activation • ↓ ERK1 & 2 activation	[52]

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Table 1 (*continued*)

Compounds	Experimental Model	Dosage & duration	Effects	Ref.
DHA	Acute lymphoblastic leukemia Molt-4 cells	50−200 μM for 48-72h	• ↓ RAC-alpha serine / threonine-protein kinase, • ↓ Hsp 27, • ↓inhibitor of NFκβ, • ↓TGFbeta-activated kinase 1 • ↓ Survivin proteins • ↓ Cancer cells proliferation • ↑ Apoptotic cell number in a dose-dependent manner. • ↑ p53 accumulation & caspase-3 activation • ↓ Survivin	[53]

Abbreviations: AA: arachidonic acid; ACR: 5-aminoimidazole-4-carboxamide-1- β-D-ribonucleoside; ALA: alpha linolenic acid; AML: acute myeloid leukemia; AMPK: AMP-activated protein kinase; BA: butyric acid; CO: corn oil; CoA: coenzyme A; COX: cyclooxygenase; CLA: conjugated linoleic acid; DHA: docosahexaenoic acid; EGFR: estrogen growth factor receptor; EPA: eicosapentaenoic acid; ERK: extracellular signals regulated kinase; FA: fatty acids; FAO; fatty acid oxidation FO: fish oil; GLA: gamma-linolenic acid; GPX; GSH: reduced glutathione; HBA: 3-hydroxybutyric acid; Hsp:heat-shock proteins, JNK; LA: linoleic acid; LAA: lauric acid; LXA4: lipoxin A4; MA: myristic acid; MAPK: mitogen-activated protein kinase; MDA: malondialdehyde; MMP: mitochondrial membrane potential; NFκβ: nuclear factor κβ; nSREBP1: nuclear sterol regulatory element-binding protein 1; OA: oleic acid; PA: palmitic acid; PGE2: prostaglandin E2; ROS: Reactive oxygen species; SO: soybean oil; SOD: superoxide dismutase; TGF-beta: transforming growth factor *beta*; Vit: vitamin.

MDA-MB-231 breast cancer cells, although it was shown not to be linked to FAO [27]. The correlation between effects on *in vitro* growth and the ability to assimilate these FAs may partially explain the stimulation by UFA and inhibition by SFA *in vivo* 4526 cell line tumorogenesis since uptake and oxidation rates were much lower for SFAs [25].

3.2. Dietary lipids and redox homeostasis in cancer cells

It is well known that PUFA are more susceptible to peroxidation than SFA or monounsaturated fatty acids (MUFA) lipids [28]. PUFA have been reported to increase lipid peroxidation in several cancer cell lines (*e.g.* MGC and SGC gastric carcinoma cells [29]) in parallel to its cytostatic or cytotoxic effects. Since mitochondrial electron transport chain (mETC) is the major site of ROS production, mETC complex activity deficits or interference are linked with both, reduced energy and ROS release. On other hand, some antioxidant defenses can be reduced by PUFA treatments as it has found for superoxide dismutase (SOD) activity in the semi-differentiated RKO and the undifferentiated LOVO colorectal cancer cell line [30]. However, an *in vitro* assay in colon carcinoma cells derived from a primary tumor (SW480) and a metastasis of the same tumor (SW620) has evidenced that lipid peroxidation could be only partly responsible for cytotoxic effects on cancer cells [31] since there are no changes in lipid peroxidation markers, glutathione (GSH) or glutathione peroxidase (GPX) activity correlating with effects on cell growth. Another *in vitro* study suggest that n-6 PUFA effects on cell growth is dose-dependent [30]. There are evidences suggesting that the reactive PUFA-derived free radicals from cyclooxygenase (COX)-catalyzed lipid peroxidation are somehow responsible for the n-6 PUFA anti-cancer activities.

As expected, incubation with MUFA or SFA resulted in no inhibition of cell growth of the human pancreatic cancer cell lines MIA PaCa-2, PANC-1 & CFPAC [32]. In another study, oleic acid (OA) suppressed cell growth and survival in both low metastatic cell lines, breast cancer MCF-7 and gastric carcinoma SGC7901 cells, but this effect was restrained by pharmacological activation of AMP-activated protein kinase (AMPK), which rescued cell viability by increased beta-oxidation of FAs resulting in maintenance of ATP levels. In contrast AMPK activity was up-regulated in high-metastatic gastric carcinoma HGC-27 and breast cancer MDA-MB-231 cell lines treated with OA, which promoted cancer growth and migration [33]. In fact, treatment with the MUFA OA significantly stimulated the proliferation of estrogen-independent breast cancer (MDA-MB-231 and HBL-100) cells, although it had no effect on the proliferation of hormone-dependent (MCF-7, ZR-75 and T-47) cells [34]. Notwithstanding, this FA was able to inhibit the growth of methylcholanthrene-induced sarcoma cells *in vitro*, although this effect was much lower than those exerted by PUFA also tested. Moreover, no increased generation of ROS or levels of lipid peroxidation marker were observed [35].

These results evidence that certain FAs present in tumor microenvironment could be relevant for suppressing tumor growth despite the enhancement of lipogenesis found in many cancer cells. However, the effect of the presence of such FA in the diet need to be confirmed *in vivo*. PUFA effects on lipid peroxidation at cancer cells has been confirmed *in vivo* for n-3 PUFA but not for n-6 PUFA or other UFA. In contrast to corn oil, olive oil, linseed oil, primrose oil or canola oil in the diet at 20 %, a diet rich in fish (Menhaden) oil suppressed MDA-MB231 human breast carcinoma growth in female athymic nude mice and enhanced lipid peroxidation as suggested the elevated concentrations of thiobarbituric acid reactive substances (TBARS) found in carcinomas derived from the fish oil-fed mice) [36]. However, in mice consuming this experimental diet supplemented with vitamin E, the increase in lipid peroxidation markers was suppressed [37]. A combination of alpha-linolenic acid and linoleic acid led to an increase in hepatic levels of TBARS in Syrian Golden hamsters with N-nitrosobis (2-oxopropyl) amine (BOP)-induced pancreatic adenocarcinoma. Importantly, an increase in the incidence and the number of liver metastases in response to the FA combination was also observed [38]. In comparison to soya oil-containing (n-6 PUFA-rich) diet or a diet prepared with soya oil, olive oil rich in OA, fish oil enriched with n–3 PUFAs and medium chain triacylglycerols (UFA-rich), a diet that only contained fish oil (n-3 PUFA-rich) decreased incidence of liver metastasis which also showed higher levels of TBARS in a similar model of pancreatic cancer. However, animals fed experimental diets containing a combination of, soya oil, olive oil rich in OA and fish oil enriched with n–3 PUFA showed lower levels of lipid peroxidation markers (TBARS) in liver metastases as well as in non-metastatic tissue correlating with the absence of effect on the incidence of liver metastases [39]. The dose-dependent inhibition of cell proliferation induced by gamma linolenic acid in rats with carcinosarcoma LLC-WRC256 cells was correlated with an increase in lipid peroxides and ROS levels [22].

3.3. Dietary lipids and mitochondrion-dependent cell death

Cancer cells usually have mutations that allow them to evade programmed cell death mechanisms. In most of cases, anticancer activities reported for the different FAs have been linked to the induction of apoptosis. The anticancer effect of the treatment with DHA has been widely related with the induction of apoptosis in multiple cancer cell lines (*e.g.* [40]). Likewise, incubation with EPA also has shown to induce apoptosis in A549 lung cancer [41], human neuroblastoma LA-N-1 [42] and human pancreatic cáncer MIA-PaCa-2 cells [43]. *In vivo*, the pro-apoptotic activity of n-3 PUFA has been also reported in MIA-PaCa-2 human pancreatic cancer xenografts from athymic nude mice fed a diet supplemented with 5 % fish oil for 5 weeks [43]. This has also been

Table 2
In vivo preclinical and clinical studies on fatty acids effect in cancer cells.

Compounds	Experimental Model	Dosage & duration	Effects	Ref
FO + CO	Male Wistar rats with DMH-induced colon cancer	at 1:1 & 2.5:1 ratio in diet for 12 wks	• ↑ Apoptosis in a dose-dependent manner	[4]
GLA	Male Wistar rats with Walker 256 tumor xenograft	5.5 % in diet for 12 d	• ↓ Tumor growth • ↑ Apoptosis • ↑ TAG, n-6 PUFA & lipid droplet content of the tumor • ↓ n-3 PUFA & MUFA content • ↓ mitochondrial metabolic activity TEM sings • ↑ Cytoplasmic acyl CoA in tumor • ↓ Hexokinase mitochondrially bound form & maximal activity of OM CPT I • ↓ malonyl CoA sensitivity and a decrease in affinity for palmitoyl CoA substrate.	[22]
Intraperitoneal OA, LA, ALA, GLA, AA, EPA or DHA	Mice bearing Meth-A induced sarcoma cells	5 mg in diet for 3, 4 & 5 d after tumor inoculation	• ↑ Survival of animals	[35]
FO *vs* CO	Athymic nude mice bearing human breast carcinoma MDA-MB-231 xenografts	20 % w/w of diet for 5–8 wks	• ↓ Carcinoma growth • ↑ Lipid peroxidation • ↑ (125) IUrd loss rate & cell loss factor (phi) • No effect on DNA synthesis of carcinomas	[39]
RO, LO, CAO, OO *vs* CO	Athymic nude mice bearing human breast carcinoma MDA-MB-231 xenografts	20 % w/w of diet for 5–8 wks	• No effect on growth of breast carcinomas	[39]
FO conc. + CO *vs* CO	Athymic nude mice bearing human breast carcinoma MDA-MB-231 xenografts	3 % of FO conc. + 2 % of CO vs 5 % of CO in diet for 2 wks	• ↓ Tumor growth • ↑ Lipid peroxidation in tumors • ↓ GPX activity • ↓ Tumor-induced cachexia • ↑ sensitivity to DOX	[39]
FO conc. + Vit E *vs* CO	Athymic nude mice bearing human breast carcinoma MDA-MB-231 xenografts	2000 IU/kg diet of Vit E for 2 wks	• ↓ Lipid peroxidation in tumors	[39]
ALA & LA	Syrian hamsters with BOP - induced pancreatic ductal adenocarcinoma	1.8 % of ALA + 0.3 % of LA vs 11 % of LA + 2 % of ALA in diet for 24 wks	• ↑ Liver metastases incidence • ↑ Hepatic SOD activity • ↑ Lipid peroxidation • ↓ Hepatic GPX activity	[39]
FO *vs* soya oil	Syrian hamsters with BOP - induced pancreatic ductal adenocarcinoma	2.9 % of dietary fat for 16 wks	• ↓ Liver metastasis number • ↓ Hepatic lipid peroxidation with intrametastatic > extra metastatic TBARS • ↓ Intrametastatic hepatic SOD activity & intrametastatic < non-metastatic activity • No effect on GPX	[39]
OO + FO *vs* soya oil	Syrian hamsters with BOP - induced pancreatic ductal adenocarcinoma	2.9 % of dietary fat for 16 wks	• ↓ Hepatic lipid peroxidation • ↓ Intrametastatic hepatic SOD activity & intrametastatic < non-metastatic activity • No effect on GPX	[39]
FO	Athymic nude mice with MIA-PaCa-2 human pancreatic cancer xenografts	5 % of diet for 5 wks	• ↑ Apoptosis • ↑ Oxidative stress	[43]
GLA	Rat with glioma C6 xenograft	1−2 mM for 3–7 d administered intra-tumoral by infusion using osmotic mini-pumps	• Glioma regression • ↑ Apoptosis • Adjacent normal neural tissue and vasculature were preserved • Little evidence of acute inflammatory infiltration	[47]
Highly purified EPA in free FA form	Patients with colorectal adenomas	Daily 2 g in diet for 3 m	• ↓ Crypt cell proliferation • ↑ Apoptosis in normal colonic mucosa	[44]
Lean *vs* oil FO-rich diet	Multi-center RCT in patients with colorectal polyps, inactive ulcerative colitis, or no macroscopic signs of disease	300 g/wk in diet for 6 m	• No effect on apoptosis & mitosis within the colonic crypt	[45]

Abbreviations: AA: arachidonic acid; ALA: alpha linolenic acid; BOP: N-nitrosobis (2-oxopropyl) amine; CAO: canola oil; CO: corn oil; CoA: coenzyme A; Conc: concentrate; CPT I: carnitine palmitoyltransferase I; d: days; DHA: docosahexaenoic acid; DMH: N,N-Dimethylhydrazine; EPA: eicosapentaenoic acid; FA: fatty acids; FO: fish oil; GLA: gamma linolenic acid; GPX: glutathione peroxidase; HFD: high-fat diet; LA: linoleic acid; LO:linseed oil; m: months; MUFA: monounsaturated fatty acids; OA: oleic acid; OM: outer membrane; OO: olive oil; PUFA: polyunsaturated fatty acids; RCT: randomized controlled trial; RO: rapeseed oil; SOD: superoxide dismutase; TAG: triacylglycerol; TBARS: thiobarbituric acid reactive substances; TEM: transmission electronic microscopy; Wks: weeks.

observed in male Wistar rats with colon cancer induced by N, N-Dimethylhydrazine dihydrochloride (DMH) fed on a diet rich in fish and corn oil at different ratios (1:1 and 2.5:1) for 12 weeks. Interestingly, the observed effects were stronger for diets with a higher concentration of n-3 PUFA, so the responsible for apoptosis induction was expected to be n-3 PUFA that, in addition, did it in a dose dependent manner [4]. Thirty patients with colorectal adenomas were randomly placed in a control group or in a treatment group receiving a highly purified EPA in the form of free fatty acids (2 g/day). After three months of treatment, crypt cell proliferation was reduced and apoptosis was increased in normal colonic mucosa of the EPA-treated group as compared to the control group [44]. In contrast, a multi-center randomized controlled trial investigating the effect of a 6-month intervention with a fish or lean oil-rich diet on apoptosis and mitosis within the colonic crypt found no marked changes in these parameters [45]. N-6 PUFA have been reported to induce apoptosis [46]. Exogenous n-6 PUFA gamma-linolenic acid treatment was also reported to induce apoptosis in human and rat glioma cell lines *in vitro*. Likewise, *in vivo* in a C6 glioma

rat model, the infusion of gamma-linolenic acid increased the frequency of cell apoptosis, cell death, and regression in tumours [47]. Apoptosis was also induced by gamma-linolenic acid in an implanted WRC256 rat model [22]. On the other hand, the SFA lauric acid also showed pro-apoptotic effects in human SkBr3 breast Ishikawa endometrial cancer [48], HCT-15 colon cancer [49] and Caco-2 cells [50].

In most of cases, cell death is expected to be triggered by mitochondrial-dependent pathways. Several studies have confirmed a loss of mitochondrial membrane potential (MMP) in parallel with effects on mitochondrial function for n-3 PUFAs and certain n-6 PUFAs. In Wistar rats bearing subcutaneous implants of the Walker 256 tumor, a diet high in DHA and EPA has shown to largely cause a loss of MMP [21]. Similarly, decreased MMP has been detected in EPA-exposed cells, which correlated with a decreased number of cells in the treated cultures [21]. EPA and DHA also caused an increase in DNA fragmentation, phosphatidylserine externalization and mitochondrial membrane depolarization in LA-N-1 cells [42]. In HepG2 (with and without p53 knockdown), Hep3B (p53 null) and Huh7 (p53 mutant) cells, DHA caused loss of MMP and the release of cytochrome c from mitochondria [51]. In turn, gamma-linolenic acid triggered cytochrome c release in rat carcinosarcoma cells [21]. Likewise, n-6 PUFA have been reported to trigger cytochrome c release and increase caspase 3 activity [52]. In consistency with these results, apoptosis induction was also correlated with an increase in pro-apoptotic proteins (BAD, BID, BAX and PUMA) participating in apoptotic intrinsic pathway. DHA treatment effects on apoptosis have been also related to p53 accumulation in Molt-4 acute lymphoblastic leukemia cells which would lead to surviving down-regulation, and caspase-3 activation [53]. Shifting the balance of the so-called Bcl-2 family protein rheostat towards pro-apoptotic members provides a powerful means to initiate mitochondrial outer membrane permeabilization (MOMP)-dependent apoptosis. DHA and EPA-induced apoptosis was associated with up-regulation of Bax and down-regulation of Bcl-XL in LA-N-1 cells [42]. The reported abilities of the different PUFA to induce oxidative stress in cancer cells could explain these pro-apoptotic effects since MOMP could also result from FA-induced oxidative stress. The results provided by assays combining FAs with pretreatment or cotreatment with antioxidants indicated that cell viability was maintained, which supports this idea.

3.4. Dietary lipids and autophagy in cancer cells

In the last few years, also the role of dietary lipids in modulating the autophagic process has gained increasing attention from the scientific community in an effort to understand if they could represent a therapeutic tool against cancer [14]. In this context, the most studied dietary lipids are DHA and EPA, that have been shown to exert anticancer activity by modulating the autophagic process in different types of tumours. For example, in human PC3 and DU145 prostate cancer cells

Table 3
Effects of dietary lipids on the modulation of autophagy and mitophagy in different *in vitro* and *in vivo* cancer models.

Compounds	Experimental Model	Dosage and duration	Effects	Reference
DHA	Human PC3 and DU145 prostate cancer cells with mutant p53	10, 20, 30, 40, 50 μM for 24 h	- Induction of autophagy (increase of lipidated form LC3B) - Induction of apoptosis (PARP cleavage) - Increase of mitochondrial ROS - Downregulation of Akt/mTOR pathway - Decrease of cell viability	[54]
DHA	Human hepatoma HepG2 (with and without p53 knockdown), Hep3B (p53 null) and Huh7 (p53 mutant) cells	60, 120, 200 μM for 24 h	- Induction of autophagy by oxidative stress - Loss of mitochondrial membrane potential and release of cytochrome c from mitochondria	[51]
DHA	Human SW620 and Caco-2 colon cancer cells	70 μM for 3, 6, 12, 24, 48 h	- Induction of autophagy by inducing oxidative stress	[55]
	Human MIA-PaCa-2 pancreatic cancer cells	100 μM for 24 h		
EPA	Xenografts athymic nude mice	Diet supplemented with 5 % fish oil for 5 weeks	- Induction of autophagy (increase of Beclin1) - Induction of apoptosis (increase of caspases and PARP) - Increase of intracellular ROS	[43]
DHA	Human SiHa cervix carcinoma cells	50 μM for 0, 6, 12 or 24 h	- Induction of autophagy (increase of microtubule associated protein 1 light chain 3 and number of autophagic vacuoles) - Induction of apoptosis - Reduction of p53 and mTOR - Activation of AMPK	[56]
DHA	Human A549 lung cancer cells	50 μg/mL for 24 h		
EPA		60 μg/mL for 24 h	- Induction of autophagy (increase of autophagosomes) - -Induction of apoptosis (activation of caspase-3/7)	[41]
DHA EPA	Human A549 lung cancer cells	25, 50 or 100 μM for 24 h	- Induction of autophagy (increase of intracellular autophagic vacuolization) - Induction of apoptosis (activation of caspase-3/7) - Induction of oxidative stress (oxidative damage to DNA and proteins)	[57]
DHA	Human D54MG, U87MG and U251MG glioma cell lines Mouse GL261 glioma cell line *Fat-1* tg xenograft mouse	20, 30,40, 50 μM for 24 h	- Induction of autophagy (increased LC3-II levels, GFP-LC3 puncta and autophagic flux activation) - Induction of apoptosis (PARP cleavage, increased sub-G1 cells and increased number of TUNEL-positive cells)	[56]
Fish oil	Male Wistar rats injected with N,N-Dimethylhydrazine dihydrochloride	Fish and corn oil diet (1:1 and 2.5:1) for 12 weeks	- Induction of mitophagy and cristae loss - Induction of apoptosis - Impairment of mitochondrial functions - Decrease of cardiolipin and cholesterol levels	[4]

Abbreviations: AMPK: AMP-activated protein kinase; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; mTOR: mammalian target of rapamycin; PPAR: peroxisome-proliferator-activated-receptor.

with mutant p53, DHA treatment (0–50 μM for 24 h) induced autophagy, through the increase of lipidated LC3B [54]. Similar results were found in HepG2 (with and without p53 knockdown), Hep3B (p53 null) and Huh7 (p53 mutant) cells, where DHA treatment (0–200 μM for 24 h) promoted autophagy [51]. Additionally, DHA (70 μM for 3−48 h) increased autophagy in SW620 and Caco-2 colon cancer cells, even if at diverse time points and to diverse extent [55], while in human pancreatic MIA-PaCa-2 cancer cells EPA treatment (100 μM for 24 h) induced autophagy; these results were confirmed also *in vivo*, in xenografts athymic nude mice fed with a diet supplemented with 5 % fish oil, with high levels of DHA and EPA for 5 weeks [43]. Moreover, in human SiHa cervix carcinoma cells the treatment with DHA (0–75 μM for 0−24 h) induced autophagy expression and mammalian target of rapamycin (mTOR) activity and stimulated the AMPK expression [56], whereas in lung cancer A549 cells, EPA or DHA treatments were able to activate autophagy [41], mainly by inducing oxidative stress [57]. Table 3 summarizes main finding from cell-based studies on autophagy, dietary lipids and cancer. Interestingly, DHA exerts anticancer activity also in glioblastoma, both *in vitro*, in different types of cells, and *in vivo*, in xenograft mice, by promoting autophagy activating AMPK pathway and decreasing mTOR activity, suggesting its potential role against this type of brain cancer [56]. To the best of our knowledge, only one study has evaluated the anti-tumour effects of dietary lipids through the modulation of mitophagy. In this study, Wistar rats were injected with DMH to induce colon cancer and the consumption of fish and corn oil (1:1 and 2.5:1) for 12 weeks promoted mitophagy [4]. Even if promising, the potential of dietary lipids in targeting autophagy/mitophagy remains to be explored. Indeed, more *in vitro* and *in vivo* studies are needed to evaluate some fundamental aspects of dietary lipids, including their effects on different cancers, the molecular mechanisms involved in the modulation of autophagy and the intricate interplay with apoptosis.

4. Metabolomics for the study of the relationship between dietary lipids and cancer

Lipids play an important role in signal transduction, gene expression and the modulation molecular pathways which are relevant to physiological and pathological processes [16]. These functions are supported by a wide molecular and structural diversity since the cellular lipidome comprises around 2000 species [58]. It is recognized that cancer cells undergo profound changes in their metabolism, known as metabolic switch [59]. As stated before, many cancer cells favor a glycolytic metabolism, even in the presence of oxygen (the so-called Warburg effect) [17]. But they retain OXPHOS and, if glycolysis is inhibited, OXPHOS function is restored to compensate a reduced ATP production rate [60]. These new concepts oppose the Warburg effect as initially proposed, since it considered that cancer cells favor aerobic glycolysis due to irreversible mitochondrial impairment [61]. Advances in the field have demonstrated that not all tumor cells rely on glycolysis for survival and growth [62] and that this dependence is influenced by several factors including the differentiation state and the rate of proliferation of the tissue.

Generally, actively proliferating tissues rely primarily on glycolysis [63]. On the contrary, differentiating tissues preferentially use OXPHOS [64]. Environmental cues also drive changes from glycolytic to OXPHOS-directed energy metabolism, such as hypoxia tilts the balance toward glycolysis [65]. A recent study [66] reveal metabolic heterogeneity within the invasive pack during collective cancer invasion, showing the leader invasive cells a marked dependency on OXPHOS for energy production as compared to follower cells. Leader and follower cells in the context of collective cancer cell invasion have been defined on the basis of spatiotemporal cellular and genomic analysis (SaGA) which enables to isolate and select specific cells within a population based on their behavior in physiologically relevant environments for downstream molecular analysis. Using SaGA, Konen et al. [67] demonstrated phenotypic heterogeneity within collective invasion packs in the context of metastasis and isolated leader cancer cells, which initiated the invasion process at the tip of invading chains, and trailing follower cells. Leader cells were shown to attract and provide a scape mechanism for follower cells through VEGF (vascular endothelial growth factor)-driven signaling. In turn, follower cells support leader cells providing survival and proliferative advantages. Therefore, when considering energy metabolism as a target for the design of therapeutic interventions, it is necessary to analyze the metabolic profile of the cancer cell in a context-dependent manner with respect the stage of the disease and the specific characteristics of the tumor, as cancer cells continuously reprogram their metabolism to adapt to environmental pressures and survival restrictions. Likewise, metabolic preferences are driven by specific phenotypes (for instance, proliferative *vs*. invasive [66]), highlighting the potential benefit of targeting both glycolysis and mitochondrial metabolism simultaneously. This plasticity is also translatable to the preferences of tumor cells regarding the biomolecule they select as source of energy. In this regard, lipid metabolism and lipid-derived signaling has been shown to greatly impact cancer cell biology and tumor progression [68]. Early studies using radiolabeled substrates [69] and nuclear magnetic resonance (NMR) [70] revealed that cancer cells display an active lipid metabolism. These experimental evidences were followed by large-scale epidemiologic studies analyzing the causal relationship between dietary lipid intake and cancer [71] (Table 4).

The development of the -omics technologies over the last two decades has provided a large amount of data recurrently identifying key molecular effectors in lipid metabolism pathways as determinants of cancer cell fate. Likewise, functional studies targeting specific enzymes and modulators of lipidic metabolism have pointed it out as a major cellular process affected by cancer progression [72]. Recent analysis of the lipidic profile of biofluids and tumor tissue from cancer patients aim to identify potential markers of disease progression and therapeutic targets. Plasma lipidomics using different mass spectrometry (MS)-based techniques have been evaluated and shown prognostic significance for prostate (e.g [73].), ovarian [74] and lung cancer [75], prostate tumor risk and aggressiveness [76] and therapeutic response in hepatocellular carcinoma [77], ovarian [74] and lung cancer [78]. Likewise, analysis of the lipidomic profile of tumor tissue and tumor cell lines has provided invaluable insights in cancer biology and progression, opening new horizons for the development of targeted therapies. For instance, using a MS-based approach, Rysman et al. [79] found that aggressive prostate tumors with high metastatic potential were characterized by *de novo*

Table 4
Epidemiological data on the impact of dietary fat on breast, prostate and colon cancer.

Cancer type	Fat type	Clinical outcome	Reference
Breast cancer	SFA	Direct association	[109]
	PA and SA	Direct association	[110]
	PA	No association	[111]
	Olive oil	Inverse association	[112]
	w6 PUFA	No association	[113]
	w3/w6 PUFA ratio	Inverse association	[114,115,116]
	long chain w3 PUFA	Inverse association	[117]
	TFA	Direct association	[118,119]
Colon cancer	SFA, MUFA, PUFA	No association	[120]
	Long chain w3 PUFA	No association	[121]
	TFA	Direct association	[30,119,122]
Prostate cancer	SFA	Direct association	[123]
	PA	Direct association	[114]
	PA	No association	[124]
	MA	Direct association	[125]
	w3 PUFA	No association	[126]
	TFA	Direct association	[123]
	TFA	Inverse association	[119]

Abbreviations: MA, myristic acid; MUFAs, monounsaturated fatty acids; PA, palmitic acid; PUFAs, polyunsaturated fatty acids; SA, stearic acid; SFA, saturated fatty acid; TFA, trans fatty acids.

lipogenesis accompanied by an increase in the content of saturated lipids. In addition, the authors found that the higher content in saturated lipids alters the membrane dynamics of the tumor cells and promote chemoresistance. Along the same line, a high content in SFA and MUFA has been identified as a common feature of primary prostate tumor cells [80] and several breast [81] and melanoma [82] tumor cell lines. Interestingly, Roy et al. [83], found that diacylglycerols (DAG) were overexpressed in metastatic osteosarcoma cell lines as compared to their non-metastatic cell lines and that blocking DAG synthesis diminished viability and migration capabilities of the metastatic osteosarcoma cells, therefore providing a rationale for the development of metabolic therapeutic interventions in osteosarcoma. Further development of the MS-based platforms and MS imaging techniques has led to the analysis of the lipidomic profile in clinical tumor samples *vs.* normal tissue, showing a distinctive lipidomic profile of tumor tissue as compared to non-tumor tissue samples [16]. Fatty acid binding proteins (FABPs) modulate the sensing and binding of different fatty acid species to the cell. It has been shown that FABP5 exerts an antitumoral effect through the inhibition of peroxisome proliferator activated receptor β/δ (PPARβ/δ) mediated by the activation of retinoic acid receptor (RAR). In particular, saturated fatty acids bound to FABP5 are able to suppress cancer cell growth through downstream inhibition of PPARβ/δ [84]. On the other hand, FABP5 has been shown to promote tumor cell survival and proliferation through the modulation of estrogen-related receptor α (ERR α) in prostate cancer [85]. Cordero et al. found that overexpression of FAPB7 promotes the formation of brain metastases derived from Her^{2+} breast cancer. Mechanistically, the authors found that FABP7 promoted a glycolytic phenotype [86]. FABP4, has been shown to mediate exogenous lipid uptake from adipocytes in metastatic ovarian cancer [87]. In addition, exogenous FABP4 induce breast cancer cell proliferation [88]. However, tumor cells have not only been found to uptake a larger amount that exogenous lipids as compared to non-transformed cells, but they are also capable of activate *de novo* lipogenesis to increase intracellular concentration of lipids.

Physiological *de novo* lipogenesis is restricted to cells in the liver, adipose tissue, and lactating mammary gland, as most of the tissues satisfy their fat need through the uptake from the bloodstream (dietary source) [89]. However, cancer cell lipidome reflects the activation of the *de novo* synthetic pathway from pyruvate and glutamine, which enter the mitochondria to feed the TCA cycle and generate citrate that will be further processed to generated bioactive lipids [90]. *De novo* lipogenesis not only satisfies the increasing demand of growing tumor cells, both in terms of energy and membrane building blocks, but also provide ATP and NADPH in conditions of metabolic stress [91]. Consequently, expression of endogenous lipogenic enzymes, such as ATP-citrate lyase (ACLY), acetyl CoA carboxylase (ACC) and fatty acid synthase (FASN) is activated, which are potential targets for the development of anti-cancer therapies [91]. The core lipogenesis enzyme, FASN, has been blocked both genetically and chemically with promising results in castration resistant prostate cancer [92]. Palmitic acid is the direct endogenous fatty acid synthetized following FASN activity. Since human cells lack the enzymes to produce essential PUFA, *de novo* lipogenesis induces a marked switch towards a high MUFA and SFA content in the cellular membranes [93]. The relative content on MUFA/PUFA in the cell has profound effects on the fluidity and biophysical properties of the membranes and consequently, on cell signaling, function and fate [94]. Phospholipids (PLs) containing SFA have straight acyl chains that pack in a dense fashion decreasing plasma membrane fluidity as compared with plasma membrane with higher content in MUFA and PUFA [95]. Therefore, tumor cells with a marked lipogenic phenotype often present increased membrane fluidity, which has been shown to affect the uptake of chemotherapeutic drugs and promote metastatic progression, being correlated with poorer patient prognosis [96]. In addition, a high content of MUFA in the plasma membrane is protective against lipid peroxidation and ferroptosis under metabolic stress [97].

Stearoyl-CoA desaturase-1 (SCD1)-induced changes in plasma membrane lipid domains that favor the activation of tyrosine kinase-receptor signaling pathways which are critical for oncogenesis and tumor progression [98]. SCD1 is overexpressed across a wide variety of tumors and it has been evaluated as a therapeutic target, although the clinical effectiveness of tested SCD1-blocking drugs against cancer is moderate [94]. A recent study has demonstrated the delta-6 desaturase fatty acid desaturase 2 (FASD2) can bypass the reliance of cancer cells on SCD1 for MUFA production through the generation of the FA sapienate, which replaces palmitoleate as an alternative source of MUFA for cellular membrane biosynthesis [99]. This work highlights the frequently observed metabolic plasticity in tumor cells, which needs to be carefully considered when designing new therapeutical interventions based on tumor cell lipidomics. SCD1-dependent lipid desaturation is important for the biosynthesis of PLs but also affects membrane lipid composition of key organelles in tumor cell biology. Depletion of SCD1 and reduction in the bioavailability of unsaturated acyl chains reduces the synthesis of phosphoglycerides and cardiolipins, leading to mitochondrial dysfunction and ROS generation, increased sensitivity of tumor cells to inhibitors of the mETC and the release of cytochrome c followed by caspase activation [100]. In addition, *de novo* synthesis of palmitate activates epidermal growth factor (EGF)-induced phosphorylation and palmitoylation, which promotes mitochondria fusion and survival of cancer cells. Inhibition of FASN was enough to block EGF induced mitochondrial fusion and increased the sensitivity of prostate cancer cells to EGFR tyrosine kinase inhibitor [101]. Importantly, studies in $scd^{-/-}$ transgenic mice subjected to a low-fat diet show that changes in the intracellular composition of the lipid pool and consequent modification of organelle membranes, including the ER and Golgi, induce endoplasmic reticulum (ER) stress and the induction of the unfolded protein response (UPR) pathway in response to the intracellular increase of misfolded proteins due to dysfunctional ER [102]. While ER stress initially promotes cell survival, sustained activation of this pathways leads to apoptosis. Importantly, autophagy is activated as a survival mechanism that allows coping with sustained ER stress [103]. Given the evident molecular connections between autophagy, lipidic metabolism and mitochondrial function discussed earlier and the regulatory crosstalk between lipid metabolism and ER stress, further characterization of these signaling interrelations and downstream effect on tumor cell fate is warranted.

Cellular FA and cholesterol acquisition and metabolism are transcriptionally regulated by liver X receptors (LXR), peroxisome proliferator-activated receptors (PPARs) and sterol regulatory element binding proteins (SREBP). The central role of these transcription factors in tumor cell biology is shown by their crosstalk with multiple growth factor receptors (GFRs), which regulate lipid metabolism through hey transduction signaling pathways in oncogenesis and cancer progression, such as the PI3K/AKT/mTORC1 and MAPK signaling axes [104]. On the other hand, SREBP-mediated regulation of lipogenic enzymes, such as FASN, is modulated by metabolism and energy sensing molecules (AMPK) and well-known tumor suppressors (phosphatase and tensin homolog, PTEN) [105] and oncogenes (MYC and BRAF) [106]. These interactions and the mutual regulatory connections between lipid metabolism and prominent cancer-related signaling pathways highlight the importance or lipid metabolism rewiring in tumor progression.

Finally, tumor cells show increased FAO were FAs are broken down to acetyl-CoAs which feed the TCA cycle to produce ATP, redox equivalents that maintain redox homeostasis and citrate used in anabolic processes, like lipogenesis [107]. Besides being an important bioenergetic pathway in many cancers, FAO is known to promote proliferation, metastasis, stemness and treatment resistance [15]. An interesting connection between the reductive power generated through FAO and the protection against ER stress and induction of the UPR pathway further interconnect tumor progression and lipid metabolism. Both *de novo* lipogenesis [108] and FAO [107] contribute to mitigate ER stress and mitochondrial dysfunction through avoidance of lipid peroxidation and ROS quenching, respectively.

Growing scientific evidence demonstrates the importance of lipid metabolism and signaling in cancer cell biology, underscoring the enormous potential of lipid metabolizing enzymes, transporters and receptors as therapeutic targets. With increasing development of the MS-based technologies in the time of single cell-focused biology, we are at the verge of witnessing an unprecedented development of the lipidomics field, that will allow the dissection of the molecular mechanisms contributing to cancer progression in a heterogeneous microenvironment. In combination with current -omic approaches, there will be an exceptional opportunity to unfold the intricate crosstalk between lipid metabolism and tumor cell signaling. On the other hand, technological advances in MS imaging will allow spatial analysis of tumor-tumor cell and tumor cell-microenvironment interactions that will contribute to clarify the role of lipids in this complex regulatory network. These new data will aid in the development of new therapeutic regimens of which drug combination holds the most promising potential, in light of previous experiences.

5. Conclusions and future perspectives

Mitochondria are closely related to cancer progression and lipid metabolism. Therefore, it is clear that these organelles may be an important link between dietary lipids and cancer. This is evident from the various points of view analyzed, both bioenergetics and redox biology, cell death and autophagy. Aspects such as *de novo* lipogenesis are very interesting to investigate since there are still many aspects to be clarified. On the other hand, and with a view to the future, it is necessary to use "omic" technologies to delve into the different aspects that relate the relationship between mitochondria, dietary lipids and cancer. An aspect to be developed and that guarantees the performance of new studies is the investigation of the redox metabolome (redoxome). The study of the redoxome will provide us with knowledge to be applied in the design of dietary lipid interventions with the potential to modulate mitochondrial activity and impact cancer progression. In the same way, much of the evidence that has been reflected in this review comes from *in vitro* studies and some models with rodents, with human studies still very scarce. Undoubtedly, this is another challenge for the future, in order to be able to validate some of the findings and allow the practical application of a true translational medicine. Finally, personalized analysis of the lipidomic status of each patient will allow dietary interventions based on lipid profiles reflecting the underlying lipid metabolism alterations affecting the course of the oncological disease of each patient. If implemented in the clinical setting, this personalized approach holds a great potential for nutritional interventions that could greatly contribute to a favorable clinical course and increase disease-free survival rates of the cancer patients.

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