Roles of endogenous ether-lipids and associated PUFA in the regulation of ion channels and their relevance for disease

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Running title: Lipids are regulators of ion channels

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Abstract and keywords

Ether lipids (ELs) are lipids characterized by the presence of either an ether linkage (alkyl lipids) or a vinyl ether linkage (i.e. plasmalogens [Pls]) at the sn1 position of the glycerol backbone and they are enriched in PUFAs at the sn2 position. In this review, we highlight that ELs have various biological functions, act as a reservoir for second messengers (such as PUFAs), and have roles in many diseases. Some of the biological effects of ELs may be associated with their ability to regulate ion channels that control excitation-contraction/secretion/mobility coupling and therefore cell physiology. These channels are embedded in lipid membranes, and lipids can regulate their activities directly or indirectly as second messengers or by incorporating into membranes. Interestingly, ELs and EL-derived PUFAs have been reported to play a key role in several pathologies, including neurological disorders, cardiovascular diseases, and cancers. Investigations leading to a better understanding of their mechanisms of action in pathologies have opened a new field in cancer research. In summary, newly identified lipid regulators of ion channels, such as ELs and PUFAs, may represent valuable targets to improve disease diagnosis and advance the development of new therapeutic strategies for managing a range of diseases and conditions.

Keywords: ether lipids, polyunsaturated fatty acid (PUFA), ion channels, cancer, neurological disorder, cardiovascular disease, cell membrane, metastasis, neurodegeneration
Introduction

Since 1990, many papers have reported that ion channels should be considered as new diagnostic and therapeutic tools in cancer and particularly at advanced metastatic stages. Their role was clearly demonstrated in the dysregulation of calcium homeostasis in cancer through their control of processes such as cell differentiation, proliferation and migration (1, 2). One of the particularities of ion channels, as transmembrane proteins, is their close contact with lipids constituting cell membranes and thus the possibility to be regulated by these lipids. Several models of interaction of lipids with ion channels have been discussed by Herrera et al. (3), such as mechanosensitivity (and so membrane state) (4), direct interaction between membrane lipids and proteins (5) or interaction with a protein in close proximity with membrane lipids (6).

One family of lipids, which has been less studied in cancer, is the ether lipids (ELs) family. These lipids have the particularity to possess either an ether linkage (alkyl lipids) or a vinyl ether linkage (plasmalogens [Pls]) at the sn1 position of the glycerol backbone and to be enriched in polyunsaturated fatty acids (PUFAs) at the sn2 position (Figure 1). In fact, ELs are known to be a reservoir of second messengers, such as fatty acids (FAs) and also metabolites derived from FAs (7), indicating that the effects of ELs can be direct or indirect through FA release.

The first studies on ELs in cancer were mostly descriptive and quantified the global EL content in the tissues of patients, leading to the general conclusion that tumor tissues contain more ELs than non-tumor tissues (8, 9). At that time, these lipids had been found to regulate cell proliferation (10). This was only a few decades ago and thanks to advanced research technologies more accurate EL compositions (identification of molecular species of ELs) have been described in tumor tissues (11, 12). These observations went with the discovery of new functions of ELs in cancer biology, such as carcinogenesis, progression, migration and invasion (13, 14). Interestingly, these lipids are present in high quantity in many excitable tissues, such
as in the nervous system and heart, and regulate ion channels and many biological cell functions.

The aim of this review is to point out the importance of ELs and associated FAs from EL metabolization in neurological and cardiac disorders and in cancers, focusing mainly on their role in the regulation of ion channels. The mechanism of action of ELs is also discussed with the perspective to propose these lipids as new diagnostic and therapeutic tools for metastatic cancers.

ETHER LIPIDS AS REGULATORS OF ION CHANNELS IN NEUROLOGICAL DISORDERS

Direct implication of ether lipids

The central nervous system contains a large amount of ELs (compared to other organs), mainly Pls with choline as head group (Pls-Cho), which represent 15 to 30 mole% of total phospholipids, whereas Pls with ethanolamine as head group (Pls-Etn) remain rare (15, 16).

In the central nervous system, the composition of ELs varies with location: grey matter is enriched in Pls with polyunsaturated fatty acids (Pls-PUFAs), whereas Pls of myelin are mainly composed of saturated and monounsaturated FAs (15), allowing for a more compact structure and rigid aspect of the membranes (17). Patients with a lack of EL synthesis suffer from myelinization defects of the central and peripheral nervous systems (18), as observed in adrenoleukodystrophy (19). In addition, demyelination is associated with a decrease of conduction velocity in a model of EL-deficient mice (35). Synaptic vesicles are enriched in ELs (20) that confer an inverted hexagonal phase (HII) structure to membranes, thus enhancing fusion processes (21). Nanodomains also named lipid rafts contain high amounts of Pls-PUFAs.
in favor of soluble N-ethylmaleimide-sensitive-factor attachment protein receptors (SNAREs), which are necessary for endocytosis and exocytosis, protein sequestration and transmembrane protein activity (22). Interestingly, the amounts of ELs in the central nervous system evolve with age and a significant increase is noticed between birth and adulthood (30s). Then, a decrease in ELs is observed with age (22), which could be correlated with a decrease of peroxisomal function (and then EL synthesis) (23), and also with some neurological disorders, such as Alzheimer’s or Parkinson’s disease. Among ELs, the most famous and studied is platelet-activating factor (PAF), which was discovered by the French scientist Benveniste in 1972. It participates in neuronal physiology, more precisely in long-term potentiation, memory formation, inflammation and regulation of glutamatergic neurotransmission (7, 22, 24).

Abnormal repartition and quantity of Pls in the brain have been found in several neurological diseases as reviewed (22, 25). Many studies on Alzheimer’s disease in the brains of post-mortem patients and in cerebrospinal fluid, plasma and red blood cells have described a decrease of EL content, more precisely of Pls (22). Quantities and molecular species of ELs that are reduced vary with studies and organs studied (Table 1). Globally, a decrease of Pls-Etn in Alzheimer’s disease brains (26) was found, underlining a potential role of these lipids despite their small quantity. Interestingly, this reduction is associated with a change of the FA composition of Pls and with a large decrease of docosahexaenoic acid (DHA) content (27).

Thus, Pls content variations have been considered as a potential marker to assess the progression of cognitive decline in patients with Alzheimer’s disease (15, 28).

Moreover, it appears that, in Alzheimer’s disease, enzymes of EL biosynthesis are downregulated. Decrease of EL content is also correlated with an increase of the Pls selective phospholipase A2 (PLA2) activity, leading to degradation of acyl-Pls and production of several metabolites, such as lysoPAF (22). LysoPAF and PAF can cause neurotoxicity and an inflammatory response, leading to deregulation of glyceronephosphate O-acyltransferase
(GNPAT) expression, an enzyme that inserts an acyl group into the dihydroxyacetone phosphate molecule (DHAP) (22). In addition, alkylglycerone phosphate synthase (AGPS) expression, which catalyzes the transformation of acyl-DHAP to alkyl-DHAP, decreases in the presence of beta amyloid peptides and ROS produced in the brains of patients with Alzheimer’s disease, which can explain the observed decrease of EL content (27). Interestingly, in an Alzheimer’s rat model, treatment with eicosapentaenoic acid Pls-Etn (Pls-EPA-Etn) improves regulation of oxidative stress (increase of superoxide dismutase activity) and decreases tau phosphorylation, apoptosis and neuroinflammation (29).

In other pathologies, such as Parkinson’s disease, schizophrenia and bipolar depression, EL homeostasis is also disturbed (22) (Table 1). For example, a decrease of Pls content in lipid rafts has been found post-mortem in the frontal cortex of brains of patients with Parkinson’s disease (14). At the opposite, in a mouse model of Parkinson’s disease, treatment with a precursor of Pls-DHA can prevent and reverse dopamine content loss, and vesicular monoamine transporter 2 binding decreases in the striatum (30). Indeed, more generally, a modification of EL amounts influences neurotransmitter synthesis and their release. In a GNPAT KO mouse model, a decrease in both the quantity and release of dopamine in the striatum has been observed, leading to hyperactive mice, with a loss of social interaction and fear conditioning (31). In contrast to Parkinson’s disease, in a schizophrenia or bipolar depression context, the level of Pls in the frontal cortex of patients was found to be higher than in control patients (32), which illustrates the fine equilibrium of EL quantity necessary for excitation-secretion coupling.

Ion channels are key players in excitation-secretion coupling, and some studies suggest that ELs can regulate ion channels, ionotropic receptors and exchanger activities (see Figure 2 for the potent mechanisms of action of ELs on ion channels). Among ion channels, the SK3 channel has been found in lipids rafts, also called cholesterol-rich nanodomains (2). This
channel, which belongs to small conductance calcium-activated potassium channels, controls the small after-hyperpolarization phase and then the regulation of the frequency of action potential (33). The SK3 channel is sensitive to cholesterol content and membrane state (34). In fact, we reported the effect of 1-O-hexadecyl-2-O-methyl-sn-glycero-3-lactose (Ohmline), a synthetic EL, which inhibits SK3 channel activity by removing the cholesterol OH moieties away from their main binding sites, including the SK3 channel (3). This study suggests that ELs can modulate the lipid environment of ion channels and therefore regulate their activities. Moreover, ELs take part in cholinergic transmission, and a decrease of muscarinic-GTPase coupling has been observed in PIs-deficient cell lines, which decreases physiological amyloid precursor protein synthesis (36). Glutamatergic transmission is also affected by ELs and in synaptosomal preparations from dihydroxyacetone phosphate acyltransferase (DHAPAT - an enzyme of EL biosynthesis) KO mice, calcium-dependent glutamate and acetylcholine releases are weaker than in controls (20). Interestingly, changes caused by a deficit of ELs are also found in the neuromuscular junction with acetylcholine receptor clusters found to be smaller in GNPAT KO mice, in terms of volume and surface area. In this model, miniature end plate potential frequencies and vesicular functions were decreased, whereas the resistance of preparations was increased by 30% (37).

The regulation of membrane channels and transporters (collectively named the transportome) by PAF remains better documented (mainly PAF-C16) compared to any other EL (Figure 2E). This EL, by binding to its receptor, enhances store-operated calcium entry (SOCE) (38) and drives many neuronal processes, such as neuronal development and neurodegeneration according to its concentration (39). For example, the lack of PAF in a mouse model of Zellweger syndrome led to a decrease of NMDA glutamate receptor-mediated calcium entry, which regulates cell neuronal migration in cerebral cortex development30. PAF also induces cell depolarization and nitric oxide (NO) production, leading to an activation of L-type voltage-
gated calcium channels, which increases blood-brain barrier permeability (41), a process that could play an important role in inflammation. PAF is found in great quantity in rat brains with anticonvulsive treatment (22), where it inhibits the activity of ionotropic GABA receptors in hippocampal neurons, leading to a decrease in chloride currents. Bazan et al. (42) mainly reviewed the involvement of PAF in seizure-induced damage, especially by modulating the glutamate system.

**Indirect effects through fatty acid release**

Arachidonic acid (AA) and DHA, and more generally PUFAs, have been described to be a major part of lipids in the components of neuronal membranes. For example, DHA has been found in great amounts in phospholipids of the cerebral cortex (43). These lipids have the ability to modulate membrane fluidity and lipid environment of a huge range of embedded proteins into the membranes, including ion channels. Moreover, they constitute a reservoir of second messengers that can modulate several enzymes, such as PLA2, or more globally, neurotransmission, such as AA metabolites, that constitute a huge family of lipid messengers (*e.g.* eicosanoids) (42). PUFAs participate in several other neuronal processes, including inflammation, regulation of cell oxidation and gene expression (44). We can cite as an example that AA is able to activate neurite growth by the activation of N- and L-type calcium channels via the cell adhesion molecules pathway (45).

Interestingly, these lipids are able to modulate, in different ways, many ion channels involved in neurotransmission (see Figure 2 for the potent mechanisms of action of ELs on ion channels). Several potassium channels are regulated by PUFAs. DHA can inhibit the outward potassium current in neocortical neurons via direct interaction with Kv 1.2 and 3.1 channels (46). The same effect in rat olfactory neurons leads to a change of coding odorant information (47). EPA
has also been shown to have an effect on Kv (44). In the rat hypothalamus, stimulation by angiotensin II leads to an activation of PLA2 and a release of AA, which activates a delayed rectifier potassium current (48). AA can also activate the K2P potassium channel TRAAK (49). PUFAs were also found to modulate the calcium signaling in neurons. In sympathetic neurons, AA can inhibit L- and N-type calcium currents (50). Voltage-gated calcium (CaV) currents are generally sensitive to DHA and α linolenic acid (ALA) (44). DHA and EPA can also modulate Ca²⁺ ATPases. In fact, EPA can regulate PKC activity and the phosphorylation state of Ca²⁺ ATPases, leading to their inhibition, whereas DHA can induce a different conformation of these ATPases by changing their lipid environment and then decreasing their activities. However, DHA has been reported to be an activator of Ca²⁺ ATPases in calcium depleted cells (51). DHA, EPA and AA are also able to inhibit a non-voltage-gated calcium channel in neurons, the TRPM8 (52). Finally, DHA and EPA are also inhibitors of sodium currents in neurons by blocking NaV activity through a direct interaction (53) or by inhibiting Na⁺/K⁺ ATPase (51). Regulation of neuronal ion channels by PUFA plays an important role in pathophysiological processes. In fact, phospholipids containing AA are necessary for the functional activation of mechanoelectrical transduction channels, such as TRP channels, involved in sensory mechanotransduction and touch sensation (54). This regulation takes a great interest in aging. In fact, an inverted association has been described between consumption of n-3 PUFAs and cognitive impairment or development of Alzheimer’s disease and associated symptoms, such as dementia or cognitive decline (44). It was found that the release of PUFAs from Pls degradation, which quantity is decreased in Alzheimer’s disease, can reduce the formation of nitric oxide from microglial cells after lipopolysaccharide stimulation. In fact, PUFAs from Pls are able to inhibit NFKB and MAPK pathways activated by lipopolysaccharide. These lipids appear to be essential for neuroprotection under oxidative stress conditions, which are found in neurodegenerative diseases (55). Thus, it appears that, in a rat model of aging and dementia,
chronic treatment with n-3 PUFAs can increase the density of muscarinic receptors and have positive effects on learning and memorization (56).

Interestingly, in a context of ischemia-reperfusion syndrome, increased cytosolic calcium concentration (from the endoplasmic reticulum and mitochondria stores) leads to an increase of PLA2 and phospholipase C activities and a consequent release of AA (57). This release of AA can inhibit GABA-Cl⁻ neurotransmission and then increases neuronal excitability, which can result in neuronal damage after ischemia (58). DHA and ALA have neuroprotective properties in an ischemic context by facilitating the TREK-1 potassium current, which can decrease neuronal excitability (59, 60).

PUFAs also appear to be pain regulators. In fact, it has been demonstrated that pain is mediated by two TRP channels, TRPA1 and TRPV1(61). EPA, DHA and AA can activate TRPA1 in sensory neurons and then regulate pain (62). Moreover, DHA and EPA can inhibit the TRPV1 channel, which is involved in inflammatory pain (63). ASICs channels that are activated by an acid extracellular pH also regulate pain. Interestingly, in inflammatory conditions, AA can activate ASIC1a and ASIC3 currents (64). More recently, it has been demonstrated that AA can drive pain through activation of ASIC3, independently of acidification of the extracellular medium. This leads to a depolarization and an increased activity of nociceptive neurons in a rat model (65).

Even if we don’t know if neurological disorders are the cause or the consequence of the changes of ELs and associated PUFAs, collectively, all these data obtained in the nervous system lead us to propose that these changes would have profound effects on ion channels known to control excitation-secretion coupling of neuron cells, thus leading to exacerbation of these neurological disorders (Figure 3).

ETHER LIPIDS AS REGULATORS OF ION CHANNELS IN CARDIAC DISEASES
Direct effect of ether lipids

ELs, and more precisely Pls, constitute a huge part (50%) of phospholipids of the sarcolemma of cardiomyocytes (66), with mainly AA at the sn2 position of the glycerol. In fact, Pls-Etn accounts for about 58% of total phospholipids-Etn and Pls-Cho and 26% of phospholipids-Cho. Interestingly, despite their small proportion in front of total phospholipids quantity, Pls-Etn represent the greatest amount of Pls in heart. This repartition is mainly found in organs known to contain a large amount in Pls, such as the brain or the skeletal muscle (15). In the human heart, Pls are present in higher extent compared with alkyl lipids (16.3% against 2.4% of total phosphocholine species, respectively and 14.9% against 0.9% of total phosphoethanolamine species, respectively (67), which can suggest a major role for Pls compared to alkyl lipids. A study on swine hearts reveals that Pls-Etn appears to be a reservoir for AA, whereas Pls-Cho are enriched in palmitic (PA), oleic (OA) and linoleic acids (LA) (68). However, these results have to be interpreted cautiously, since the Pls quantity and composition of Pls in the heart is species-dependent (69). Pls are also found in high quantity in the sarcoplasmic reticulum of myocytes, where they are found as 53% of total phospholipids (70, 71).

The quantity of Pls in heart tissues evolves with age with an increase of Pls-Cho, whereas the Pls-Etn pool remains quite stable along time (72). In heart pathologies and more precisely ischemia, the EL pool is disturbed (see Table 2). Interestingly, a study aiming to quantify Pls-Cho in the serum of patients with myocardial infarction found that these lipids are inversely correlated with the risk of myocardial infarction (73). During ischemia, a calcium-independent phospholipase A2 selective for Pls is activated. This induces the hydrolysis of Pls and leads to production of lyso-Pls (up to 10 times more in a rabbit myocardial ischemia model (74–77)).
This is supported in a study by Caldwell on rabbit cardiomyocytes at early stages of infarction (78). The importance of PIs in heart is illustrated by supplementation experiments with chimyl alcohol (ether lipid precursor), which decreases the effects of ischemia-reperfusion by enhancing ventricular function and decreasing lipid peroxidation (79). In addition, it has been reported that cytochrome c released from mitochondria can cleave the ether link of PIs in the ischemia-reperfusion syndrome (80). In the plasma of hypertensive patients and in the aorta of patients with atherosclerosis, PIs are decreased (81, 82). In a model of atherosclerosis in mice, supplementation with batyl alcohol (an ether lipid precursor) led to a decrease of atherosclerosis (83). In contrast, an increase of PIs has been observed in diabetic heart rats with cardiomyopathy, and this increase is partly corrected with insulin treatment (84).

It has been observed that ELs could regulate excitation-contraction coupling and ion channels in cardiac diseases (see Figure 2 for the potent mechanisms of action of ether lipids on ion channels). LysoPIs, whose synthesis is increased in several heart diseases, can affect cardiac electrophysiology (85, 86) and thus cause arrhythmias. For example, lysoPIs-Cho can induce spontaneous contractions faster than LPC. In fact, lysoPIs-Cho application leads to a depolarization, which can be reversed by a decrease of extracellular sodium concentration (78). Thus, we can hypothesize that lysoPIs-Cho activates a sodium conductance or inhibits potassium channels. Moreover, in rabbit cardiomyocytes, lysoPIs-Cho has been found to activate PKA (87). This data is interesting, since it is well-known that the activity of some ion channels are regulated by this kinase, such as the SK3 channel for example (88), which participates in atrial action potential repolarization (89–91). PIs can also modulate the activity of the sodium-calcium exchanger (NCX), which is crucial for heart activity (92). In fact, in synthetic vesicles containing PIs and negative phospholipids (such as phosphatidyl serine), NCX conformation is modified, leading to an increase of its activity. These lipids interact with
the cationic exchanger inhibitory peptide (XIP) site of NCX, leading to a change of the three-dimensional structure (71). Furthermore, NCX can be activated by Pls with a phosphatidic acid as head group (Pls-PA). Pls-PA can also directly modulate NCX activity via this XIP domain (93). As evoked in the previous part of the review, the effect of PAF remains better documented than other ELs in heart pathophysiology. This EL is known to induce coronary vasoconstriction and has negative cardiac inotropic effect (94). Moreover, it appears to be implied in the ischemia-reperfusion syndrome by causing arrhythmias. In an animal model of infarction, an increase in the amount of PAF has been observed, as in the blood of patients with acute myocardial infarction. This increase is even more important in patients with acute myocardial infarction and arrhythmia (95). Some studies found a decrease of action potential duration in the papillary muscles of guinea pigs treated with PAF. These results were also found in guinea pigs models of myocardial ischemia (95). Interestingly, in this model, the effect of PAF is time dependent with an increase in the action potential duration at the beginning of reperfusion, which follows a period of ischemia of the papillary muscles (95). Another study reported a decrease of cytosolic calcium concentration in cardiomyocytes after treatment with PAF (96). In a model of atrial frog, a change in the equilibrium of potassium and calcium at the myocardial sarcolemma after treatment with PAF has been described, with PAF increasing the activity of the delayed outward potassium current (Kv) and decreasing the slow inward calcium current (CaV) (97). In a model of guinea pig ventricles, this lipid was also found to increase the duration of action potential (without affecting the resting membrane potential) by decreasing both the cardiac delayed rectifier and the cardiac inward rectifier potassium currents, which control the repolarization phase of the action potential (98). However, in the absence of ATP, PAF activates $K_{ATP}$ channels, which decreases action potential duration (98). In contrast, another study shows a decrease of atrial and ventricular action potential duration
after treatment with an antagonist of the PAF receptor (PAF-R). This effect was prevented by a treatment with glibenclamide, a blocker of K\textsubscript{ATP} (99).

Altogether, these results show that PAF is a bivalent actor, which can modulate action potential duration, depending on cell states concerning ischemia (pre-ischemia or ischemia reperfusion syndrome), leading to arrhythmias. PAF arrhythmogenic effects are also attributed to its ability to inhibit the potassium TASK-1 channel activity via the PAF-R and PKC, leading to an automaticity with a maintained depolarization state in mouse ventricular myocytes (100, 101). Interestingly, PAF is also described as a cardioprotective lipid via activation of mitochondrial K\textsubscript{ATP} channels and redox signaling. Pre-treatment with low concentrations of PAF can decrease the infarct size (102) and exerts positive ionotropic effects (97).

**Indirect effect through fatty acids release**

As previously mentioned, ELs are also known to be a reservoir of second messengers, such as FAs. Nutritional intervention concerning PUFAs has been shown to decrease the risk of developing cardiac diseases. Studies analyzing the FA effect on cardiovascular disease first appeared in a study of Eskimos from Greenland. This population has a diet rich in fish and marine mammals (and therefore rich in n-3 PUFAs) and they develop few cases of coronary artery disease (103). Many other epidemiological studies have confirmed this association between the low risk of cardiovascular diseases and a diet rich in n-3 PUFAs (104). Intake of n-3 PUFAs prevents arrhythmias (tachycardia and ventricular fibrillation), decreases heart rate and blood pressure and improves efficiency of the left ventricle. They also have antithrombotic actions by reducing plasma cholesterol levels, thus protecting against atherosclerosis. N-3 PUFAs also decrease mortality due to cardiac arrest or cardiovascular disease (105–108). In contrast, for n-6 PUFAs, few studies have investigated the roles of LA and AA in
cardiovascular disease, and the results are contradictory (109). For example, Kark et al. showed a positive association between AA quantities in the adipose tissue of patients and the incidence of myocardial infarction, whereas there was no association for LA rates (110). Conversely, Cho et al. suggest a protective effect of LA and AA on cardiovascular disease by decreasing serum low-density lipoprotein (LDL) and increasing serum high-density lipoprotein (HDL) (111). Part of these discrepancies may be resolved when studies are focused on the importance of the n-6:n-3 ratio rather than on the individual role of each lipid in cardiovascular disease. Indeed, as in several pathologies, a high n-6:n-3 ratio (equal or superior to 10) is considered unfavorable, while a n-6:n-3 ratio close to 1 is considered to be protective. However, the use of this ratio as a marker (risk factor or predictor) has been discussed given not only the contradictory effects of n-6 PUFAs (including LA and AA) but also because this ratio does not take into account the different interactions between foods (108, 112, 113). Thus, Von Schacky and Harris have proposed the “Omega-3 index” as a new marker for cardiovascular diseases. This index is the percentage (of total serum FA) of EPA+DHA, representing the n-3 PUFAs rate (114). Concerning the saturated fatty acids (SFAs), most studies do not determine the individual effect of SFAs but the effect of their replacement by monounsaturated fatty acids (MUFAs) or PUFAs (112, 113, 115). Thus, despite few contradictory studies, the World Health Organization, the American Dietetic Association, the dietitians of Canada, the American Heart Association and the American College of Cardiology recommend reducing the intake of SFAs for a healthier cardiovascular system. SFAs should be limited to at least 10% of total energy and less than 7% for high-risk groups. Indeed, studies in primates, human prospective observational studies and randomized clinical trials have shown that lower consumption of SFAs and its replacement by unsaturated fats, in particular PUFAs, decreases the incidence of cardiovascular disease and reduces atherosclerosis by lowering LDL levels (112, 113, 115).
Heart energy comes mainly from oxidative phosphorylation (95%) and from glycolysis (5%) (116). However, these processes are altered during ischemia-reperfusion injury and FA accumulation increasing the beta-oxidation is observed (117). Moreover, the presence of PUFAs in phospholipids makes them more sensitive to oxidation and leads to the oxidized phospholipids formation involved in several cardiovascular diseases (105). Currently, there is a pharmacological approach aiming to inhibit FA oxidation (trimetazidine) and to improve cardiac efficiency with a decrease of ischemic heart disease (118).

There are different mechanisms by which FAs, in particular n-3 PUFAs, can prevent arrhythmias. Indeed, FAs can modulate ion channel activities by a direct interaction or by their incorporation into the myocyte membrane (see Figure 2 for the potent mechanisms of action of ether lipids on ion channels). Indeed, it has been demonstrated that n-3 PUFAs decrease the activity of NaV in cardiomyocytes, increasing the threshold of depolarization of the membrane potential and reducing the heart frequency (119, 120). The n-3 PUFAs modulate the activity of L-type calcium channels (from CaV) and NCX, reducing the cytosolic free calcium concentration and the excitability of myocytes, permitting them to prevent arrhythmias (121, 122). Several studies suggest that n-3 PUFAs also modulate the activity of the Kv11.1 channel, whose mutations can cause long QT syndrome, and Kv7 channels, which are potent vasodilators (123).

Same as observed in neurological disorders, cardiac diseases are the cause or the consequence of the changes of ELs and associated PUFAs, and all these data lead us to propose that these changes would have profound effects on ion channels that control cardiac excitation-contraction coupling leading to or exacerbating cardiac disorders (Figure 3).
ETHER LIPIDS AS REGULATORS OF ION CHANNELS IN CARCINOGENESIS AND METASTATIC DEVELOPMENT

History

At the end of the 1960s, an association between endogenous ELs and cancer had been described in many studies, first in order to characterize these lipids in tumor tissues and then to identify their lipid chain composition in the sn1, sn2 and sn3 positions of the glycerol. Snyder and Wood (8, 9, 124) described a higher amount of ELs in both rat and mouse tumor tissues compared to normal tissues. These results have been confirmed in a huge range of human tumors (125), such as in the lungs, liver and brain. For example, glioblastoma contained high quantities of Pls-Cho when compared to normal brain tissue (126, 127). Soodsma, Piantadosi and Snyder (128) observed that the higher content of ELs in tumors of rat liver compared to normal rat liver could be explained by the suppression of the activity of the ether cleavage system of ELs. Later, Howard et al. (10) showed a correlation between EL content and growth rate of rats bearing hepatomas in vivo and also in cell lines in vitro. In membranes of cancer cells, ELs can be metabolized into free FAs, for example, by the plasmalogen-selective PLA2, leading to FA release with biological activity. These pioneer studies led to an increased interest for this family of lipids in cancer, more precisely for Pls, that could be potential markers of carcinogenesis (129).

Quantification and composition of ether lipids and associated fatty acids in human cancer samples

Ether lipids
Several studies described changes in the content of ELs in the plasma of cancer patients compared to healthy subjects (Table 3). An increase in the content of PIs was observed in several types of tumors, such as lung, breast, gastric and prostate cancer (11, 130, 131). Interestingly, it was proposed that some specific lipids in the plasma could be used as specific biomarkers of prostate cancer, such as alkyl-glycerophosphocholine. Similar studies have been obtained for breast cancer (132). In some cases, a switch inside EL species composition was observed, and in pancreatic cancer, blood alkyl-glycerophosphocholine species decreased (compared to control patient blood) in benefit for PIs-Etn (133).

Surprisingly, in other types of cancers, such as oral squamous cell carcinoma and acute leukemia, the plasma content of some EL species appeared to decrease in advanced stages (134, 135). Table 3 reports and summarizes the quantity and the composition of ELs found in human tumors. In 2018, Messias et al. (12) reviewed studies on human gastrointestinal tumors and modification of PIs metabolism. Interestingly, the quantity of PIs varied with organ and disease progression. In an accurate way, Lopez et al. (136) reported alterations in the levels of PIs depending on colon cancer progression. In human breast cancer, ELs, more precisely PIs-Etn, are increased in tumors compared to normal tissues (137, 138).

Few studies have quantified PAF in tumors. One of them reported increased PAF in human breast tumors compared to normal tissues, but this increase was lost at advanced stages of the disease (139). Others available studies described PAF-R expression, which could be considered as a reflection of PAF-induced activity. In gastric adenocarcinoma, the PAF-R is mainly expressed in tumors with good prognosis (well-differentiated, small size and without metastases) (140). Such observations have also been observed in hepatocellular carcinoma (141). It is important to consider that PAF is a second messenger involved in the immune
system, and a loss of this lipid and its receptor in high-grade and invasive tumors could be the result of disturbed immunity in the context of cancer.

**Associated fatty acids**

FAs from the degradation of Pls, especially in blood samples, represent an interesting biomarker of breast, prostate and lung cancers, and their presence correlates with cancer aggressiveness (11).

In breast carcinogenesis, studies using a dietary questionnaire show an association between LA and reduction of breast cancer risk, as already observed in serum dosage. However, no association between LA content in breast adipose tissue and breast cancer risk has been observed (142). For ALA, studies reported by the French Agency of Food Safety are contradictory, and if a high level of ALA in adipose tissue is associated with a decreased risk of breast cancer (142, 143), most studies based on serum do not show any association. For longer-chain n-3 PUFAs (EPA and DHA), the dietary questionnaire data did not show any association between breast cancer risk and fish consumption. There are more studies based on several biological samples, such as serum or adipose tissue. Although contradictory, the majority of them show a negative association between DHA and EPA levels and breast cancer risk (142). Moreover, inflammatory breast cancers (144) and multifocality in breast cancer (145) are associated with low levels of EPA and/or DHA. In addition, a high n-3:n-6 ratio in breast adipose tissue is inversely associated with the risk of breast cancer (146). Interestingly, Bougnoux et al. reported that rather than a single FA, a composite indicator combining elevated monounsaturated and low n-6:n-3 FA ratio is associated with decreased breast cancer risk and propose the lipidome as a composite biomarker of the modifiable part of the risk of breast cancer (147, 148).
In prostate and colon carcinogenesis, most studies are based on data collected from dietary questionnaires. There are still few studies analyzing FA levels in biological samples (serum or adipose tissue). Although studies reported by the French Agency of Food Safety are contradictory, overall, there is no significant correlation between the consumption or dosage of different classes of FA and both prostate and colon cancer risk (142). However, in prostate cancer, it has been shown recently that LA and EPA quantified in peri-prostatic adipose tissue are inversely associated with cancer aggressiveness. Moreover, the same study observed that FA composition of the peri-prostatic adipose tissue and prostate cancer aggressiveness could depend on the ethno-geographical origin of patients (149).

In summary, currently, epidemiological studies and their contradictory results do not allow to answer conclusively whether FAs represent a risk (or a protective) factor for breast, prostate or colon cancer (142). These contradictory results can be explained by the use of different methods of analysis (food questionnaire or biological samples) and by the heterogeneity of the population, without stratification with some factors, such as age or ethno-geographical origin. Moreover, the FA composition of both adipose tissue and serum samples reflects dietary profiles over different time periods. Indeed, the serum FA composition reflects the last weeks (or months) diet, while the adipose tissue FA composition determines the long-term diet, due to its slow turnover. Therefore, adipose tissue better reflects dietary intake than the blood composition, especially for essential FAs (150). Thus, an association between alimentation and cancer development and progression could constitute a new tool for cancer prevention and/or adjuvant treatment. However, this remains quite unexplored.

**Regulation of biological cancer cells properties by ether lipids and associated fatty acids**

*In vitro studies*
ELs, PIs-Etn in particular, are present in a larger amount in some breast cancer cell lines than in non-cancer cell lines (137, 138), as well as in melanoma cells (13). The role of ELs in the biology of cancer cells has been mainly studied by modulating the enzymes of EL biosynthesis. AGPS represents one of the most studied enzymes in EL biology, and more precisely, in the cancer field. Recently, Benjamin et al., (13) showed that AGPS is overexpressed in breast tumors compared to normal tissues as well as in aggressive cancer cell lines compared to less aggressive ones in prostate, breast and melanoma models. Moreover, this enzyme participates in cell migration, invasion and proliferation, and some ELs can rescue cell migration in AGPS KO cells. This enzyme was found to be implied in epithelial to mesenchymal transition (EMT) of glioma and hepatocarcinoma cell lines, and its suppression leads to a decrease of key transcription factors implied in EMT, such as Snail or Twist (151). Moreover, this enzyme, through alkyl LPA and PGE2 pathways, increases cancer cell resistance to chemotherapy (14). Some chemical inhibitors of AGPS have been developed (152, 153), and they decrease cell migration and expression of EMT transcription factors. Moreover, GNPAT expression, which catalyzes the transformation of DHAP into acyl-DHAP, has been described as amplified in hepatocarcinoma and its suppression, in vivo, decreases tumor growth (154). Among ELs, PAF has been reported to increase cancer cell proliferation, migration and metastasis through its receptor in several cancers, such as prostate, breast, ovarian or skin cancers (155–162).

Contrary to ELs, FAs have been widely studied in several cancer cell lines and animal models. Thus, several FAs and their mechanisms of action have been described and elucidated in breast, prostate and colon cancers. In breast carcinogenesis, it has been shown that saturated FAs inhibit cell proliferation by inducing apoptosis (163, 164). Concerning OA, the results are more contradictory, but this FA seems to stimulate cell proliferation by activating the PI3K pathway (164, 165) in a dose-dependent manner (166). LA also stimulates cell proliferation, an effect
that depends on estrogens (167). For n-3 PUFAs, all data show anti-proliferative (37,42,45–48), pro-apoptotic (45–49), anti-migratory and anti-invasive effects (168, 169) of DHA, EPA, and ALA. The anti-proliferative effect of DHA is associated with a decrease of cyclin B1 phosphorylation (G1-S transition) (170) and Akt inhibition. Moreover, it was demonstrated that DHA and EPA increase in vitro cytotoxicity of anti-cancer agents, such as doxorubicin (171–173), docetaxel (174, 175), mitoxantrone (176) and paclitaxel (175, 177). The results depend mainly on the cell lines used and on the FA concentrations tested.

In prostate carcinogenesis, there are few in vitro studies. A recent one described a downregulation of the EMT pathway, mediated by calcium signaling (178), by EPA and LA, two PUFAs found in peri-prostatic adipose tissue, inversely correlated with the disease progression (149). Treatment with these two lipids resulted in a decrease of cancer cell migration, invasion and store-operated calcium entry, with a decrease of Zeb-1 expression, a key EMT transcription factor implied in prostate cancer progression (179). Some studies have reported the anti-proliferative, anti-migratory and pro-apoptotic effects of EPA and DHA (180–185) by inhibition of the Akt signaling pathway (186–188). It has also been shown that DHA improves the effectiveness of some treatments (celecoxib and docetaxel) (189, 190). In contrast, AA appears to promote the migration and invasion of PC3 prostate cancer cells (191, 192).

In colonic carcinogenesis, EPA and DHA have been shown to inhibit cell proliferation, in particular by arresting the G1 phase cell cycle. These lipids also induce cell apoptosis by inhibiting COX2/PGE2, PI3K/Akt and p38 pathways. ALA was found to have the same effects as its metabolites (EPA and DHA). For n-6 PUFAs, the results are more discordant. Indeed, some studies do not show any in vitro effect of n-6 PUFAs, while others studies show a protective effect of AA and LA by inducing cell apoptosis (for review Brandão and Ribeiro, 2018) (193).
In vivo studies

Studies on the role of ELs in tumor growth and metastasis in animal models are based on the knock-down of EL biosynthesis enzymes. In a rodent model of breast cancer, AGPS suppression in cancer cells led to a drastic decrease in tumor growth (13). The same conclusions were found after GNPAT suppression (154). Interestingly, the suppression of IIF-secreted PLA2, which degrades ELs, in fibroblasts injected into mice reduces the number of large skin tumors and decreases the quantity of LysoPls-Etn, which suggests an important role of Pls metabolites in skin carcinogenesis (194).

Studies on the role of FAs in animal models are mainly through FA-enriched oil diets, despite the difficulty to determine the most relevant control diet (isocaloric or isolipidic). In fact, this control diet could also affect the FA composition of animals, which could include some bias. In breast carcinogenesis, LA stimulates tumor growth and increases the frequency of murine or human mammary tumor metastases in mice. N-3 PUFAs, such as ALA, have been poorly studied but appear to inhibit mammary carcinogenesis. Long-chain n-3 PUFAs (EPA and DHA) are mainly provided by supplementation with fish oils. Compared with n-6 PUFAs, EPA and DHA not only inhibit tumor growth but also lung metastases (for review, Bougnoux and Menanteau, 2005) (195). They can also increase the effectiveness of several anti-cancer drugs (doxorubicin, epirubicin, and docetaxel) and have anti-angiogenic properties (196, 197). The quantities of n-3 and n-6 PUFAs need to be close to get the anti-tumor effects of n-3 PUFAs.

In prostate carcinogenesis, studies focus on the comparison between n-6 PUFAs and n-3 PUFAs. As described in mammary tumors, n-6 PUFAs were found to stimulate tumor growth in tumors transplanted from human prostate cells (198–201) or in spontaneous tumors from murine cells (202–205). In contrast, long-chain n-3 PUFAs inhibit tumor growth. The most
convincing example is the Kelavkar study, which showed a regime switch from n-6 to n-3 PUFAs induced a decrease in tumor growth previously induced by LA. On the contrary, the tumors grew more rapidly when the mice switched from an n-3 PUFAs enriched diet to an n-6 PUFAs enriched diet (201). The n-6:n-3 ratio of PUFAs is also important, since it leads to a reduction in tumor volume and an increase in cell apoptosis (206).

In colonic carcinogenesis, similar results were found to what has been observed in prostate and breast cancer studies. Indeed, compared to n-6 PUFAs, n-3 PUFAs inhibit tumor growth of both chemotherapy-induced and transplanted scenarios and also inhibit aberrant crypt formation (the most frequent risk marker used in colon cancer) and the formation of liver metastases. The protective effect of n-3 PUFAs is not observed when tumours are implanted at other sites, which shows the importance of the microenvironment of colon tumors. ALA also appears to have a protective effect, whereas OA has no effect (for review, Bougnoux and Menanteau, 2005) (195). In summary, in vivo studies show that n-6 PUFAs promote while n-3 PUFAs reduce breast, colon and prostate cancer development (195).

**Ether lipids and associated PUFAs as regulators of ion channels implied in cancer cell migration and metastatic development**

Ion channels regulating calcium signaling participate not only in several mechanisms implied in tumor development and progression but also in cancer cell migration and metastatic development. Thus, some CaVs, such as CaV1.3, are abnormally expressed in several cancers, such as prostate, ovarian, colon (207) and breast cancers (1) and participate in prostate and colon cell proliferation, migration and invasion (208). The same observations have been made for some TRP and SOC channels (Orai and TRP families) (209). Several studies described that associations between both potassium and calcium channels can also fuel these processes with
potassium channels acting as amplifiers of calcium entry. Gueguinou et al. described associations between calcium activated potassium channels and calcium channels, which control proliferation and migration of breast and prostate cancer cells (210). More precisely, we demonstrated that an association of the SK3 channel with the calcium channel Orai1 within cholesterol-rich nanodomains (also called lipid rafts) promotes constitutive calcium entry and breast cancer cell migration and metastasis in a metastatic rodent model (2). This association in cholesterol-rich nanodomains appears to be necessary, since channel delocalization outside these nanodomains decrease SK3-dependent constitutive calcium entry, cancer cell migration and metastatic development.

Interestingly, a synthetic EL we called Ohmline was found to decrease SK3 current, breast SK3-dependent constitutive calcium entry, cell migration and bone metastasis development (2). We demonstrated that this synthetic EL, by interacting with the carbonyl and phosphate groups of stearoylphosphatidylcholine, sphingomyelin and cholesterol can induce a membrane disorder (3). More precisely, it seems that Ohmline can change membrane lipid arrangement by competing with cholesterol, inhibiting its interactions with its binding sites. These observations could explain the observed delocalization of SK3 and Orai1 channels outside cholesterol-enriched nanodomains leading to the decrease of SK3 activity (2). These results can lean on the fact that SK3 activity is sensitive not only to cholesterol content in pig and rat arteries but also in breast and colorectal cancer cells, where its activity is decreased by MβCD (34, 211) and strongly associated with caveolin-rich domains (2, 211). We hypothesize that the presence of many cholesterol recognition/interaction amino acid consensus sequence (CRAC) domains, allowing tight interactions with cholesterol, on SK3 protein sequences could explain its sensitivity to cholesterol.

These observations are especially interesting, since endogenous ELs and cholesterol homeostasis appear to be tightly linked. In fact, Jiménez-Rojo and Riezman (212) reviewed
that a decrease of EL content decreased esterified cholesterol content, whereas an increase of PIs decreases the stability of squalene monooxygenase, a key enzyme of steroid biosynthesis. Moreover, the effects of ELs on cell membranes are closely linked to the concentration of sterols, which allow a better incorporation of high concentrations of ELs, leading to an increase of lipid interactions and membrane packing (213). We hypothesize that the presence of several ELs in cancer cell membranes can increase membrane packing, stabilizing SK3 and Orai1 channels within nanodomains enriched in cholesterol (see Figure 2 for the potent mechanisms of action of ether lipids on ion channels). In fact, we observed that in EL enriched breast cancer cells, SK3-dependent constitutive calcium entry and cell migration were enhanced (unpublished data). Thus, ELs could increase SK3 activity by stabilizing interactions between cholesterol and the SK3 channel. Moreover, we showed that PAF increases SK3 current by 30% (214), as well as several others channels we previously described. We can also consider that if SK3 has a XIP domain (as we discussed with the NCX exchanger), direct interactions between some ELs and SK3 should be possible, leading to a modulation of SK3 activity.

SK3 has also been described as associated with TRPC1 and Orai1 in colon cancer. This association led to an increase of SOCE, which mediates colon cancer cell migration. Interestingly, treatment with Ohmline decreased SK3 current and associated cell migration, showing that Ohmline’s effect is not limited to breast cancer cells (215).

In prostate cancer, SOCE mediated by SK3 after treatment with TGFβ is also sensitive to Ohmline, leading to a decrease of calcium entry and cancer cell migration. Interestingly, this pathway is also sensitive to EPA and LA: in fact, these lipids repress SK3 expression and calcium entry and cancer cell migration as a consequence. The main hypothesis is that EPA and LA can regulate SK3 and associated calcium channels at the plasma membrane, probably by dissociation of these complexes outside nanodomains enriched in cholesterol, where they are supposed to complex themselves (178). The effect of PUFAs is also found in breast cancer
cells, where AA and LA can reduce TRPC3 SOCE and associated cell proliferation and migration (216).

Same as observed in excitable cells pathologies, cancer could be the cause or the consequence of the changes of ELs and associated PUFAs. We propose that tumors changes of ELs would have profound effects on ion channels that control excitation-mobility coupling leading to exacerbation of cancer (Figure 4).

To conclude this review shows that EL and associated PUFAs are lipids that regulate ion channels in neurological, cardiac and cancer physiology. Interestingly, in pathologies such as Alzheimer’s and Parkinson’s diseases or myocardial infarction, EL homeostasis is dysregulated, which impairs the ion transportome. Thus, ELs and associated PUFAs start to be proposed and used as diagnostic tools and markers to follow disease progression, such as in Alzheimer’s disease. ELs are even suggested as therapeutic tools, especially via nutritional intervention in order to increase the EL pool in neurological disorders.

In cancer, endogenous EL rediscovery in these last years has lead to the development of new therapeutic tools and new diagnostic tools through lipidomic analysis of patient biopsies and blood samples. We can speculate that ELs and associated PUFAs may be used as predictive markers of activity or expression of ion channels and thus of cancer progression. We can propose that ELs and associated PUFAs could be used as supplemental interventions with potential EL inhibitors of some ion channels, such as the SK3 channel in breast cancer.
Data availability statement

All data are contained within the manuscript.
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Footnotes to text

| Abbreviation | Description |
|--------------|-------------|
| AA           | Arachidonic Acid |
| AGPS         | AlkylGlycerone Phosphate Synthase |
| ALA          | α-Linolenic Acid |
| CaV          | Voltage-gated Calcium channel |
| CRAC         | Cholesterol Recognition/interaction Amino acid Consensus sequence |
| DHA          | Docosahexaenoic Acid |
| DHAP         | DiHydroxyAcetone Phosphate |
| EL           | Ether Lipid |
| EMT          | Epithelial-to-Mesenchymal Transition |
| EPA          | EicosaPentaenoic Acid |
| FA           | Fatty Acid |
| GABA         | Gamma-AminoButyric Acid |
| GNPAT        | GlyceroNePhosphate O-AcylTransferase |
| HDL          | High-Density Lipoprotein |
| KATP         | ATP-sensitive Potassium channel |
| KCa          | Calcium-activated Potassium channel |
| Kv           | Voltage-gated Potassium channel |
| LA           | Linoleic Acid |
| LDL          | Low-Density Lipoprotein |
| LPA          | LysoPhosphatidic Acid |
| LPC          | LysoPhosphatidyl Choline |
| MβCD         | Methyl-β-CycloDextrin |
| MUFA         | Monounsaturated Fatty Acid |
| NaV          | Voltage-gated sodium channel |
NCX  Sodium/Calcium eXchanger
NMDA  N-Methyl-D-Aspartate
OA  Oleic Acid
Ohmline  1-O-hexadecyl-2-O-methyl-αn-glycero-3-lactose
PA  Phosphatidic Acid
PAF  Platelet-Activating Factor
PAF-R  Platelet-Activating Factor Receptor
PGE2  ProstaGlandin E2
PLA2  PhosphoLipase A2
Pls  Plasmalogen
Pls-Cho  Plasmalogen with phosphoCholine
Pls-Etn  Plasmalogen with phosphoEtanolamine
PUFA  Polyunsaturated Fatty Acid
Pls-PUFAs  Plasmalogen with PUFA
SFA  Saturated Fatty Acid
SOCE  Store-Operated Calcium Entry
XIP  eXchanger Inhibitory Peptide
## Tables

### Table 1: Ether-lipids in neuronal disorders

| Pathology       | Tissue          | Lipid   | Quantity in Controls | Quantity in Patients | Unit            | % variation of quantity in patients | Reference |
|-----------------|-----------------|---------|----------------------|----------------------|-----------------|-------------------------------------|-----------|
| Alzheimer’s     | Frontal lobe -  |         | 168,2 +/- 6,4        | 113 +/- 8,3          | nmol per mg of proteins | -32,82 |
| Disease         | grey matter     | PIs-Etn |                      |                      |                 |                                     | (217)     |
|                 | Parietal lobe - |         | 188,9 +/- 8,4        | 137,0 +/- 5,8        |                 | -27,47                             |           |
|                 | grey matter     |         |                      |                      |                 |                                     |           |
|                 | Temporal lobe - |         | 175,3 +/- 5,8        | 129,4 +/- 6,5        |                 | -26,18                             |           |
|                 | grey matter     |         |                      |                      |                 |                                     |           |
| Alzheimer’s     | Cerebellum -    |         | 195,9 +/- 3,1        | 205,0 +/- 20         | mmol per mg of proteins | 4,65    |
| Disease         | grey matter     | PIs-Etn |                      |                      |                 |                                     |           |
|                 | Frontal lobe -  |         | 458,9 +/- 24,2       | 300,4 +/- 53,2       |                 | -34,54                             |           |
|                 | white matter    |         |                      |                      |                 |                                     |           |
|                 | Parietal lobe - |         | 476,2 +/- 24,1       | 346,7 +/- 29,5       |                 | -27,19                             |           |
|                 | white matter    |         |                      |                      |                 |                                     |           |
|                 | Temporal lobe - |         | 469,8 +/- 15,9       | 284,1 +/- 29,3       |                 | -39,53                             |           |
|                 | white matter    |         |                      |                      |                 |                                     |           |
| Alzheimer’s     | Cerebellum -    |         | 501,4 +/- 13,4       | 335,6 +/- 17,8       |                 | -33,07                             |           |
| Disease         | white matter    |         |                      |                      |                 |                                     |           |

Alzheimer’s Disease

| Tissue          | Lipid   |     |          |          |          |          |          |
|-----------------|---------|----|----------|----------|----------|----------|----------|
| Frontal lobe    | PIs-Etn |    | Decrease |          |          |          |          |
| Hippocampus     | PIs-Etn |    | Decrease |          |          |          |          |
| White Matter    |         |    | Decrease |          |          |          |          |
| Frontal lobe    | Alkyl-acyl-Etn | | No change |          |          |          |          |
| Hippocampus     | Alkyl-acyl-Etn | | No change |          |          |          |          |
| White Matter    |         |    | No change |          |          |          |          |
|                         | Frontal lobe | Hippocampus | White Matter | Frontal lobe | Hippocampus | White Matter | Frontal lobe | Hippocampus | White Matter |
|-------------------------|--------------|-------------|--------------|--------------|-------------|--------------|--------------|-------------|--------------|
|                         | Pls-Cho      | 0.21 +/- 0.06 | 0.18 +/- 0.05 | 0.21 +/- 0.06 | 0.18 +/- 0.05 | 0.21 +/- 0.06 | 0.18 +/- 0.05 | 0.21 +/- 0.06 | 0.18 +/- 0.05 |
| Pls-Etn 18:1 n-9        | Alkyl-acyl-Etn | 0.3 +/- 0.11 | 0.29 +/- 0.05 | 0.35 +/- 0.10 | 0.29 +/- 0.05 | 0.35 +/- 0.10 | 0.29 +/- 0.05 | 0.35 +/- 0.10 | 0.29 +/- 0.05 |
|                         | Pls-Etn 20:1  | 0.4 +/- 0.07  | 0.35 +/- 0.08 | 0.46 +/- 0.07  | 0.35 +/- 0.08 | 0.46 +/- 0.07  | 0.35 +/- 0.08 | 0.46 +/- 0.07  | 0.35 +/- 0.08 |
|                         | Pls-Etn 20:4  | 0.45 +/- 0.09 | 0.53 +/- 0.14 | 0.46 +/- 0.07  | 0.53 +/- 0.14 | 0.46 +/- 0.07  | 0.53 +/- 0.14 | 0.46 +/- 0.07  | 0.53 +/- 0.14 |
|                         | Pls-Etn 22:4  | 1.31 +/- 0.21 | 1.21 +/- 0.25 | 1.31 +/- 0.21 | 1.21 +/- 0.25 | 1.31 +/- 0.21 | 1.21 +/- 0.25 | 1.31 +/- 0.21 | 1.21 +/- 0.25 |

**Alzheimer's Disease**

|                         | Gyrus Frontalis | Pls-Etn | Decrease | (219) |
|-------------------------|----------------|---------|----------|-------|
| Frontal lobe - grey matter | Pls-Etn 40:6 | Decrease | (32) |
| Frontal lobe - white matter | Pls-Etn 40:6 | No change | |
| Frontal lobe - grey matter | Pls-Etn 36:2 | No change | |

|                         | Pre-frontal cortex | Pls-Etn | 10521 +/- 3438 | 8478 +/- 4398 | nmol per g of brain wet weight | -16.85 | (220) |
|-------------------------|-------------------|---------|---------------|---------------|-------------------------------|-------|-------|
|                         | Pls-Cho           | 4061 +/- 3438 | 1111 +/- 637  | -72.64 | (220) |

|                         | Frontal cortex | Pls-Etn | Decrease | (221) |

|                         | Combined brain regions | Pls-Etn | 20,4 +/- 0,6 | 22,9 +/- 0,3 | mol% | 12,25 | (222) |
|-------------------------|-----------------------|---------|---------------|---------------|------|-------|-------|
|                         | Cerebellum            | Pls-Etn | 21,5 +/- 0,9  | 21,1 +/- 0,6  | -1.86 | (222) |
| Region                          | Plasma Alcohols (16:0/18:1; 16:1/18:2; 18:0/18:1; 18:0/18:2; 16:0/20:4; 16:0/22:6; 18:0/20:4; 18:0/22:6; 22:6) | Decrease with severity of Alzheimer’s Disease | (223) |
|--------------------------------|-------------------------------------------------------------------------------------------------|-----------------------------------------------|-------|
|                                | Alkyl-acyl-Etn (16:0/22:6)                                                                       | Decrease with severity of Alzheimer’s Disease |       |
| **Alzheimer’s Disease**        |                                                                                                 |                                               |       |
| **Occipital lobe**             | 22.1 +/- 1.4 23.8 +/- 0.7 7.69                                                                 |                                               |       |
| **Superior / Middle Frontal lobe** | 23.1 +/- 1.7 24.3 +/- 0.7 5.19                                                              |                                               |       |
| **Inferior parietal lobe**     | 18.9 +/- 1.4 22.1 +/- 0.7 16.93                                                               |                                               |       |
| **Temporal lobe**              | 19.3 +/- 0.9 23 +/- 0.7 19.17                                                                |                                               |       |
| **Superior Temporal lobe**     |                                                                                                 |                                               |       |
| **Parkinson’s Disease**        |                                                                                                 |                                               |       |
| **Lipid raft of total cortex** | 3.47 +/- 0.11 1.54 +/- 0.20 -55.62                                                            |                                               | (224) |
| **Frontal Cortex**             | 1.49 +/- 0.38 0.79 +/- 0.16 -46.98                                                            |                                               |       |
| **Parkinson’s Disease**        | 0.76 +/- 0.13 0.84 +/- 0.9 10.53                                                               |                                               |       |
| **Pls-Cho 32:0; Pls-Cho 34:0; Pls-Etn 38:3** | No change                                                                                       |                                               | (225) |

Note: Data presented in the table above indicates molecular changes in Alzheimer's and Parkinson's diseases, focusing on specific lipid modifications in different brain regions.
| Disease                        | Sample Type       | Type          | FA methyl ester | Dimethylacetal | % weight / weight of FA methyl ester and Dimethylacetal | % total Pls-Cho FA content | Change |
|-------------------------------|-------------------|---------------|-----------------|----------------|--------------------------------------------------------|-----------------------------|--------|
| Parkinson’s Disease          | Plasma            | Dimethylacetal| 16:0            | 0.47 +/- 0.09  | 0.42 +/- 0.08                                          |                             | -10.64 |
| Bipolar disorder             | Pre-frontal cortex white matter | Pls-Cho Dimethylacetal 18:0 | 0.86 +/- 0.09  | 0.91 +/- 0.09  |                                                        | 5.81                         | (227)  |
| Bipolar disorder and schizophrenia | Dorsolateral pre-frontal cortex grey matter | Total Pls Etn and Cho Dimethylacetal 16:0 and 18:0 | No change | No change |                                                        | No change                   | (228)  |
| Schizophrenia                | Patients fibroblasts | Pls-Cho 40:7  | Pls-Cho 34:1    | Pls-Cho 40:7  | Pls-Cho 34:1                                           | Decrease                    | (229)  |
| Schizophrenia                | Pre-frontal cortex | Pls-Etn 7654 +/- 5773 | 34.03 | Pls-Cho 7897 +/- 5077 | 19.07 +/- 5.85 | 14.4 +/- 5.1 | 39,85 +/- 12.7 | 30 +/- 10.7 | 3,17 | (230) |
| Schizophrenia                | Plasma            | Pls-Etn 16:0  | 13.37 +/- 4.57  | 9.7 +/- 3.3 | 3,37 +/- 4.57  | -27.45 | (231) |
| Schizophrenia                | Plasma            | Pls-Etn 18:0  | 19.07 +/- 5.85  | 14.4 +/- 5.1 | 3,37 +/- 4.57  | -24.49 | (231) |
| Schizophrenia                | Plasma            | Sum Pls-Etn (16:0; 18:0; 18:1 n-7/9) 39.85 +/- 12.7 | -24.72 | Pls-Cho 16:0 24.5 +/- 5.39 | 19.9 +/- 4.4 | 3,37 +/- 4.57  | -18.78 | (231) |
| Schizophrenia                | Plasma            | Pls-Cho 18:0  | 5.79 +/- 1.66  | 4.5 +/- 1.3  | 3,37 +/- 4.57  | -22.28 | (231) |
| Schizophrenia                | Plasma            | Pls-Cho 18:1 n-9 3.33 +/- 0.78 | -24.92 | Pls-Cho 18:0 5.79 +/- 1.66 | 4.5 +/- 1.3  | 3,37 +/- 4.57  | -24.92 | (231) |
| Schizophrenia | Platelets | Plasma |
|---------------|-----------|--------|
| Ptd-Chol 34:1, 34:2, 36:1, 36:2, 34:3, 38:6, 40:6 | Decrease | Decrease |
| Ptd-Etn 34:2, 34:3, 36:2, 38:6, 40:6 | Decrease | Decrease |
| Ptd-Chol 16:0, 18:0, 18:1 | Decrease | Decrease |
| Ptd-Chol 16:0, 18:0, 18:1 | 27.6 ± 6.4 | 23.2 |

**Platelets**

| Plasma |
|--------|
| 34:2, 34:3, 36:1, 36:2, 34:3, 38:6, 40:6 | Decrease |
| 34:2, 34:3, 36:1, 36:2, 34:3, 38:6, 40:6 | Decrease |
| 16:0, 18:0, 18:1 | Decrease |
| 16:0, 18:0, 18:1 | 27.6 ± 6.4 | 23.2 |
### Table 2: Ether-lipids in cardiac disorders

| Pathology               | Tissue | Lipid       | Quantity in CTL | Quantity in Patients | Unit | % variation of quantity in patients | Reference |
|-------------------------|--------|-------------|-----------------|----------------------|------|-------------------------------------|-----------|
| Myocardial infarction   | Serum  | Alkyl-lyso-Cho 18:0 |                |                      |      | Decrease                             | (233)     |
|                         |        | Pls-Etn 16:0/20; 16:0/20:4; 16:0/20; 18:0/18:2; 18:0/20:4; 18:1/20:4; 18:1/22:6 |                |                      |      |                                     |           |
| Myocardial infarction   | Plasma | Pls-Cho 18:0/18:2 | 7,7             | 5,8                  | μM   | -24,68                              | (234)     |
|                         |        | Pls-Cho 18:0/16:0 | 10,1            | 6,4                  |      | -36,63                              |           |
|                         |        | Pls-Cho 16:0/18:1 | 5,6             | 3,2                  |      | -42,86                              |           |
|                         |        | Pls-Cho 16:0/18:2 | 7,5             | 5,1                  |      | -32,00                              |           |
| Myocardial infarction   | Serum  | Alkyl-Cho 36:1; 36:2; 36:4; 38:4; 38:5; 40:7 |                |                      |      |                                     | (73)      |
Table 3: Ether-lipids in cancers

| Pathology       | Tissue       | Lipid                        | Quantity in CTL | Quantity in Patients | Unit | % variation of quantity in patients | Reference |
|-----------------|--------------|------------------------------|-----------------|----------------------|------|-------------------------------------|-----------|
| Breast Cancer   | Breast Tissue| Pls-Etn 38:4                 |                 |                      |      |                                    |           |
|                 |              | Pls-Cho 38:4                 |                 |                      |      |                                    |           |
|                 |              | Pls-Etn 38:5                 |                 |                      |      |                                    |           |
|                 |              | Pls-Cho 38:5                 |                 |                      |      |                                    |           |
|                 |              | Pls-Etn 36:4                 |                 |                      |      |                                    |           |
| Breast Cancer   | Breast Tissue| Pls-Etn + Alkyl-acyl-Etn     | 10,8            | 13,8                 |      | 27,78                               | (138)     |
|                 |              | saturated                    |                 |                      |      |                                    |           |
|                 |              | Pls-Etn + Alkyl-acyl-Etn     | 30,7            | 34,2                 |      | 11,40                               |           |
|                 |              | low unsaturated (1-3 double bonds) |            |                      |      |                                    |           |
|                 |              | Pls-Etn + Alkyl-acyl-Etn     | 58,5            | 52                   |      | Relative abundance -11,11           | (137)     |
|                 |              | High unsaturated (4-6 double bonds) |            |                      |      |                                    |           |
|                 |              | Pls-Cho + Alkyl-acyl-Cho     | 28,3            | 35                   |      | 23,67                               |           |
|                 |              | saturated                    |                 |                      |      |                                    |           |
|                 |              | Pls-Cho + Alkyl-acyl-Cho     | 39,8            | 42,6                 |      | 7,04                                |           |
|                 |              | low unsaturated              |                 |                      |      |                                    |           |
### 1-3 double bonds

| Compounds | Value | Value | Change |
|-----------|-------|-------|--------|
| PIs-Cho + Alkyl-acyl-Cho | 31.9 | 22.5 | -29.47 |
| PIs-Etn + Alkyl-acyl-Etn | | | Decrease |
| PIs-Cho + Alkyl-acyl-Cho | | | No change |
| PIs-Etn 36:4; 38:5; 38:4 | | | Decrease |
| Alkyl-acyl-Etn 38:6; 38:5 | | | Decrease |
| PIs-Cho 36:4; 34:2; 38:5; 38:4; 38:0 | | | Decrease |
| Alkyl-acyl-Cho 34:3; 38:6; 38:5; 38:4 | | | Decrease |

### Breast, lung and prostate cancer

| Tissue | Compounds | Value | Value | µg per mg of protein | Reference |
|--------|-----------|-------|-------|----------------------|-----------|
| Breast Tissue | Alkyl-acyl-Etn | 0.7 +/- 0.1 | 3.9 +/- 0.4 | 457.14 | (11) |
| Lung tissue | Alkyl-acyl-Etn | 4.6 +/- 0.3 | 8.9 +/- 0.5 | 93.48 | |
| Prostate tissue | Alkyl-acyl-Etn | 0.8 +/- 0.2 | 1.5 +/- 0.4 | 87.50 | |
| Breast Tissue | PIs-Etn | 1.1 +/- 0.2 | 5.8 +/- 0.4 | 427.27 | |
| Lung tissue | PIs-Etn | 11.5 +/- 2.4 | 24.1 +/- 2.9 | 109.57 | |
| Prostate tissue | PIs-Etn | 3.3 +/- 0.4 | 12.5 +/- 3.0 | 278.79 | |
| Breast Tissue | Alkyl-acyl-Cho | 0.5 +/- 0.1 | 2.1 +/- 0.3 | 320.00 | |
| Lung tissue | Alkyl-acyl-Cho | 1.0 +/- 0.2 | 2.9 +/- 0.3 | 190.00 | |
| Brain tumors (grey matter) | Prostate tissue | Breast Tissue | Lung tissue | Prostate tissue | Glioblastomas | Astrocytomas | Acoustic neurinoma | Oligodendroglioma | Meningioma | Glioblastomas | Astrocytomas | Acoustic neurinoma | Oligodendroglioma | Meningioma | Glioblastomas | Astrocytomas | Acoustic neurinoma | Oligodendroglioma | Meningioma | Glioblastomas | Acoustic neurinoma | Oligodendroglioma | Meningioma | Glioblastomas | Acoustic neurinoma | Oligodendroglioma | Meningioma | Glioblastomas | Acoustic neurinoma | Oligodendroglioma | Meningioma |
|----------------------------|-----------------|---------------|-------------|-----------------|---------------|--------------|-------------------|-----------------|------------|---------------|--------------|-------------------|-----------------|------------|---------------|--------------|-------------------|-----------------|------------|---------------|--------------|-------------------|-----------------|------------|---------------|--------------|-------------------|-----------------|------------|---------------|--------------|-------------------|-----------------|------------|---------------|--------------|-------------------|-----------------|-----------|
|                            |                 |               |             |                 | 0.6 ± 0.1     | 1.6 ± 0.2     | 2.3 ± 0.3        | 3.6 ± 0.3       | 166.67    | 0.8 ± 0.2     | 3.5 ± 0.7     | 4.4 ± 0.4        | 91.30          | 337.50     | 2.3 ± 0.3        | 4.4 ± 0.4     | 91.30          | 337.50     | 2.3 ± 0.3        | 4.4 ± 0.4     | 91.30          | 337.50     |
| Glioblastomas              | 0.4 +/- 0.1     | 0.5 +/- 0.1    | 0.3         | 0.4 +/- 0.1     | 0.3           | 0.4 +/- 0.1    | 0.3               | 0.4 +/- 0.1     | 0.3       | 0.4 +/- 0.1    | 0.3           | 0.4 +/- 0.1     | 0.3           | 0.4 +/- 0.1    | 0.3               | 0.4 +/- 0.1    | 0.3       | 0.4 +/- 0.1    | 0.3           | 0.4 +/- 0.1     | 0.3           | 0.4 +/- 0.1    | 0.3       |
| Astrocytomas               | 4.9 +/- 0.9     | 8.3 +/- 1.9    | 11.8        | 4.9 +/- 0.9     | 8.3 +/- 1.9   | 4.9 +/- 0.9    | 8.3 +/- 1.9       | 4.9 +/- 0.9     | 8.3 +/- 1.9 | 4.9 +/- 0.9    | 8.3 +/- 1.9   | 4.9 +/- 0.9     | 8.3 +/- 1.9   | 4.9 +/- 0.9    | 8.3 +/- 1.9       | 4.9 +/- 0.9    | 8.3 +/- 1.9 | 4.9 +/- 0.9    | 8.3 +/- 1.9   | 4.9 +/- 0.9     | 8.3 +/- 1.9   | 4.9 +/- 0.9    | 8.3 +/- 1.9   |
| Acoustic neurinoma         | 0.5 +/- 0.1     | 2 +/- 0.6      | 3.4         | 0.5 +/- 0.1     | 2 +/- 0.6     | 0.5 +/- 0.1    | 2 +/- 0.6         | 0.5 +/- 0.1     | 2 +/- 0.6 | 0.5 +/- 0.1    | 2 +/- 0.6     | 0.5 +/- 0.1     | 2 +/- 0.6     | 0.5 +/- 0.1    | 2 +/- 0.6         | 0.5 +/- 0.1    | 2 +/- 0.6 | 0.5 +/- 0.1    | 2 +/- 0.6     | 0.5 +/- 0.1     | 2 +/- 0.6     | 0.5 +/- 0.1    | 2 +/- 0.6   |
| Oligodendroglioma          | 0.1 +/- 0.1     | 1.7 +/- 0.5    | 3.4         | 0.1 +/- 0.1     | 1.7 +/- 0.5   | 0.1 +/- 0.1    | 1.7 +/- 0.5        | 0.1 +/- 0.1     | 1.7 +/- 0.5 | 0.1 +/- 0.1    | 1.7 +/- 0.5   | 0.1 +/- 0.1     | 1.7 +/- 0.5   | 0.1 +/- 0.1    | 1.7 +/- 0.5        | 0.1 +/- 0.1    | 1.7 +/- 0.5 | 0.1 +/- 0.1    | 1.7 +/- 0.5   | 0.1 +/- 0.1     | 1.7 +/- 0.5   | 0.1 +/- 0.1    | 1.7 +/- 0.5   |
| Meningioma                 | 0.1 +/- 0.1     | 3.1           | 3.4         | 0.1 +/- 0.1     | 3.1           | 0.1 +/- 0.1    | 3.1               | 0.1 +/- 0.1     | 3.1       | 0.1 +/- 0.1    | 3.1           | 0.1 +/- 0.1     | 3.1           | 0.1 +/- 0.1    | 3.1               | 0.1 +/- 0.1    | 3.1       | 0.1 +/- 0.1    | 3.1           | 0.1 +/- 0.1     | 3.1           | 0.1 +/- 0.1    | 3.1       |
| Cancer Type                  | Tissue Type | Compound 1 | Compound 2 | Compound 3 | Compound 4 | Fold Change | Peak Area/Peak Area Interne Standard |
|-----------------------------|-------------|------------|------------|------------|------------|-------------|-------------------------------------|
| Meningioma                  | Plasma      | Pls-Etn 34:2 | Pls-Etn 36:2 | Pls-Etn 36:4 | Pls-Etn 38:5 | 0.24        | (134)                               |
| Gastric Carcinoma           | Plasma      | Pls-Cho 38:5; Alkyl-acyl-Cho 38:6 | Pls-Cho 40:5; Alkyl-acyl-Cho 40:6 | Lyso Pls-Cho 16:1; 18:1; 18:2 | Increase | (236)                               |
| Squamous cell carcinoma     | Plasma      | Pls-Cho 38:5; Alkyl-acyl-Cho 38:6 | Pls-Cho 40:5; Alkyl-acyl-Cho 40:6 | Lyso Pls-Cho 16:1; 18:1; 18:2 | Increase | Decrease | (237)                               |
| Rectal adenocarcinoma       | Plasma      | Pls-Etn 36:4; 40:6 | Pls-Etn 38:4; 40:6 | Pls-Etn 36:4; 40:6 | Decrease | (237)                               |
| Hepatocellular carcinoma    | Plasma      | Pls-Etn 16:0/20:4 | Pls-Etn 18:0/20:4 | Pls-Etn 18:0/20:4 | Pls-Etn 18:0/20:3 | -16.67 | (238)                               |
| Hepatocellular carcinoma    | Plasma      | Pls-Etn 16:0/20:4 | Pls-Etn 18:0/20:4 | Pls-Etn 18:0/20:4 | Pls-Etn 18:0/20:3 | -29.21 | (238)                               |
| Hepatocellular carcinoma    | Plasma      | Pls-Etn 16:0/20:4 | Pls-Etn 18:0/20:4 | Pls-Etn 18:0/20:4 | Pls-Etn 18:0/20:3 | -33.33 | (238)                               |
| Hepatocellular carcinoma    | Plasma      | Pls-Etn 16:0/20:4 | Pls-Etn 18:0/20:4 | Pls-Etn 18:0/20:4 | Pls-Etn 18:0/20:3 | -25.00 | (238)                               |

Quantities in the tables are represented as mean, or as mean +/- standard error of the mean, or as median [interquartile range].
Figures and Figure Legends

Figure 1. Structure of ether-lipids families and acyl-glycerolipids.
Ether-lipids are composed of two sub-families: the 1-O-alkyl-glycerolipids characterized by an ether-linkage (A) and 1-O-alkenyl-glycerophospholipids (or plasmalogens) characterized by a vinyl-ether linkage (B), contrarily to acyl-glycerolipids which possess an ester linkage at the sn1 position of the glycerol. Ether-lipids, as acyl-glycerolipids, exist as phospholipids (with mainly a phosphocholine or ethanolamine at R3 position), but also triglycerides (with a fatty acids or fatty alcohol at R3 position). At R2 position, ether-lipids can be composed of a fatty acid (acyl-ether-lipid), a fatty alcohol (ether-lipid with two ether-linkages) or only a OH moiety (lysoether-lipid).
Figure 2. Potential mechanisms of action of ether-lipids for ion channels / transporters regulation.

Ether-lipids exert different functions within cells and regulate numerous proteins such as ion channels or transporters. (A) Ether-lipids are known to be implied in many fusion processes of cells as endo and exocytosis or vesicles trafficking into cells. This property can lead to a modulation of ion channels/transporters translocation to plasma membrane or membranes of intracellular organelles. (B) Ether-lipids, and more precisely those containing PUFA participate to the structuration of nanodomains also named lipid rafts which consist in platforms for cell signalling regulating ion channel/transporters activities. (C) By their incorporation into plasma membrane, ether-lipids can promote interaction between ion channels and their accessory proteins or (D) interact directly with ion channels/transporters and regulate their gating properties for example. (E) Several ether-lipids as PAF or LPAe can be synthesized by cells and secreted in cell microenvironment. These lipids have the particularity to bind some receptors, which are coupled, to some kinases as PKA or PLC, which can regulate directly ion channels/transporters activity, or indirectly through their genetic expression via second messengers. (F) Moreover, receptor binding can lead to the activation of PLA2, which cleaves fatty acids at the sn2 position of the glycerol, leading to a production of PUFA and lyso ether-lipids. These lipids metabolites can directly interact with ion channels/transporters or modulate their genetic expression. PUFA: Polyunsaturated Fatty Acid, PAF: Platelet-Activating Factor, LPAe: LysoPhosphatidic Acid ether, PLA2: PhosphoLipase A2.
Figure 3. Involvement of ether-lipids in the modification of excitation-response couplings observed in excitable cell pathologies.

Cardiac diseases and neurological disorders can be the cause or the consequence of a dysregulation of ether-lipid metabolism and thus of ether-lipids content. We hypothesize that this dysregulation can lead to a modification of ion channels expression and/or activity leading to a modification of excitation-response couplings. Several consequences can be observed as an increase of potassium conductance and/or a decrease of sodium conductance, which leads to a membrane hyperpolarization, leading to a decrease of secretion/contraction. At the opposite, a decrease of potassium conductance and/or an increase of sodium conductance can lead to a membrane depolarization responsible for an increase of secretion/contraction. In these two cases, ion homeostasis is disturbed which results in a pathology development or an increase of the pathology phenotype.
Figure 4. Involvement of ether-lipids in the modification of excitation-response couplings in non-excitable tumor cells.

Cancer can be the cause or the consequence of a dysregulation of ether-lipid metabolism and thus of ether-lipids content. In several cancers, a dysregulation of ether-lipid metabolism and of ether-lipids content has been observed. An increase of ether-lipids content in breast cancer cells leads to an increase of SK3 expression, a potassium channel which hyperpolarizes plasma membrane, promotes calcium entry leading to an increase of cancer cell migration (unpublished data). We previously found that SK3 channel increases calcium entry and calcium mediated breast cancer cell migration and bone metastasis development (2).