In: Lipids: Categories, Biological Functions and Metabolism... ISBN: 978-1-61668-464-8
Editor: Paige L. Gilmore, pp. 153-179

Chapter 6

BIOACTIVE LIPIDS

Moghis U. Ahmad, Shoukath M. Ali and Imran Ahmad*
Jina Pharmaceuticals Inc., 28100 N. Ashley Circle,
Suite 103. Libertyville, IL 60048, USA

ABSTRACT

Bioactive Lipids are derived from components of the cellular membrane that mediate the cellular functions. These lipids play a key role in mediating and controlling a wide range of cellular processes including metabolic and gene regulation, protein structure and function, energy production and signaling pathways. Bioactive lipids are also important in the regulation of immune and inflammatory responses, cell proliferation, and converse cell death (apoptosis). They are major determinants in many pathologies, including diabetes, cancer, cardiovascular disease and neurodegenerative disorders. They are also involved in many disease states, often through their absence or through the absence of key metabolic pathways concerning lipids. In this chapter we present an overview of bioactive lipids and direct our discussion towards the nomenclature, structures, chemistry, biochemistry, and recent advances in the main class of bioactive lipids.

1. INTRODUCTION

Lipids are body fats that are either synthesized within cells (endogenous lipids) or derived from dietary fat (exogenous lipids). The lipids are insoluble in water, and have a diverse range of biological functions in cell membranes as phospholipids. Lipids are a major source of stored energy as triacylglycerols in adipose tissue. The triacylglycerols in their cellular context are inert. Indeed, esterification with fatty acids may be a method of de-activating steroidal hormones, until they are actually required. In contrast, polar lipids have hydrophilic sites that can bind via hydrogen bonding to membrane proteins and influence their activities. Lipids have been implicated as both beneficial and at times, detrimental, in a

* Corresponding author: E-mail: Imran@jinapharma.com ; fax: 847-573-0770.

number of human disease states, including cancer and cardiovascular disease. It is now clear that every individual lipid class has been found to have some unique biological role that is distinct from its function as a source of energy or as a simple construction unit of a membrane. For example, glycolipids carry complex carbohydrate moieties which play a key role in regulation of the immune system.

This chapter presents a brief overview of bioactive lipids to students, scientists, and technologists not very familiar with recent advancement in this area of lipid science.

2. ETHER LIPID

2.1. Chemistry

Ether glycerophospholipids represent an important subclass of phospholipids in animal cell membranes [1]. They are abundant in membranes of anaerobic bacteria and protozoa. Plants and fungi do not contain ether lipid.

Ether lipids are lipids in which one or more of the carbon atoms on glycerol are bonded to an alkyl chain via an ether linkage, as opposed to the usual ester linkage (Figure 1).

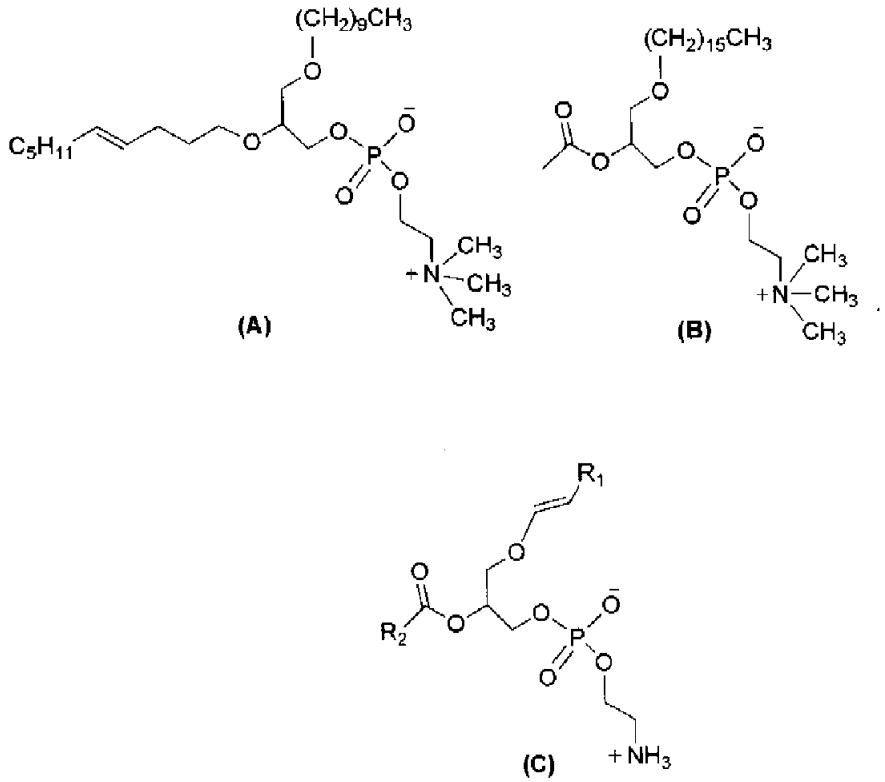

Figure 1. Types of Ether Lipids. A) Ether linkages at first & second positions. B) Platelet-Activating Factor (PAF): Ether at first position and acetyl at second position C) Plasmalogen: Ether at first position, and ester at second position.

Some naturally occurring lipids and synthetic ether lipids are biologically active. In certain cases, the effects of these substances are enhanced. In other cases, they are inhibited by compounds that were isolated from natural sources or prepared by chemical synthesis. In some of the glycerphospholipids, one of the two fatty acyl chains is attached to glycerol in ether, rather than ester linkage. These ether lipids are called plasmalogens. One of its examples is 1-*O*-1' –alkenyl-2-acylglycerophospholipid with an unsaturated vinyl ether group at the first position on the glycerol chain (Figure 1). Three major classes of plasmalogens have been identified that contain ethanolamine, choline, and serine as the head group. Ethanolamine plasmalogen is prevalent in myelin. Choline plasmalogen is abundant in cardiac tissue. One of the choline plasmalogens, 1-alkyl-2-acetyl phosphatidylcholine (Figure 1) has been identified as an extremely potent biological mediator, capable of inducing cellular responses at sub-nanomolar concentration. This molecule is called 'platelet activating factor (PAF)'.

2.2. Platelet Activating Factor (PAF)

The platelet activating factor is defined as an ether lipid which has an acetyl group instead of an acyl chain at the second position (*SN*-2 position). With respect to structure and physicochemical properties, PAF resembles Lysophospholipids.

PAF shows numerous physiological effects [2], and thus it is not surprising that most of its synthetic analogs exhibit many biological effects as well. Ether lipid analogs of PAF (1-*O*-octadecyl-2-*O*-acetyl-glycero-3-phosphocholine) [3] have shown considerable attention since they are potent inhibitors with a broad spectrum of biological properties including antitumor activity [4-6]. The biological and pharmacological effects includes neutrophil activation [7], macrophage activation [8], protein kinase C(PKC) inhibition [9-11], alteration of phospholipids metabolism [10-13], malignant-cell differentiation [14], membrane interaction [15-18], and cytotoxicity and direct tumor-cell destruction [4,5,19]. The most often-studied compound of this type is 1-*O*-octadecyl-2-*O*-methyl-glycero-3-phosphocholine [ET-18-OMe], first reported by Munder et. al. [4-5]. The ability of these analogs to inhibit neoplastic cell growth both *in vitro* and *in vivo* is of particular interest [4-6, 19], and compounds of this class appear to be promising antineoplastic agents.

2.3. Edelfosine [ET- 18-OMe]

A synthetic ether lipid edelfosine [ET-18-OMe] (1-*O*-octadecyl-2-*O*-methyl-glycero-3-phosphocholine) (Figure 2) is an antitumor agent that differs from many other cancer therapeutic agents. ET-18-OMe does not interact directly with DNA and are not myelosuppressive in animal models [20, 21].

ET-18-OMe inhibits two important enzymes involved in intracellular signal transduction, phospholipase C and protein kinase C [22]. Furthermore, ET-18-OMe inhibits transient increases in intracellular Ca^{2+} levels associated with receptor-mediated growth factor and mitogen binding, perhaps by modulating the phosphatidylinositol turnover pathway [23-25]. ET-18-OMe elicited acute transient intracellular [Ca^{2+}] increases, which may be related to

inositol triphosphate-induced [Ca^{2+}] transients [26-27]. ET-18-OMe has also been reported to interfere with cell cycle progression in transformed cells. For example, ET-18-OMe induced DNA fragmentation and morphological changes, indicative of programmed cell death in both BAC.2F5 and HL-60, human leukemia cell lines [28, 29]. These studies suggest that the anticancer effects of ET-18-OMe are mediated by modulation of intracellular signal transduction and/or cell cycle progression.

Although ET-18-OMe has demonstrated antitumor activity in various animal models, only modest clinical activity has been demonstrated, accompanied with significant clinical toxicities, including hemolysis [20, 30]. ET-18-OMe has been administered orally using milk as the vehicle in large scale clinical trials in patients with non-small cell lung cancer. Major toxicities were G.I. related disorder, lack of appetite, nausea, vomiting, diarrhea or constipation. It is suggested that ET-18-OMe exert some activity in human cancer. If levels of ET-18-OMe could be raised in the vicinity of cancer cells and toxicity is significantly reduced and/or doses increased, improved responses would be seen. ET-18-OMe has significant toxicity against leukemic cells compared to normal bone marrow cells and hence, has considerable potential in the area of leukemia and breast cancer.

To reduce toxicity and enhance delivery, the biophysical characterization of a number of ET-18-OMe liposome formulations, growth inhibitory properties, effects on intracellular Ca^{2+} mobilization, and the effects on DNA fragmentation of liposome formulations were compared to those of free ET-18-OMe [31-33]. Ahmad et. al. [34] compared "free" ET-18-OMe and a stable, well-characterized, liposome-based formulation of ET-18-OMe *in vivo* toxicity in normal mice and for therapeutic efficacy in three mouse tumor model systems. The entrapment of ET-18-OMe in liposomes decreased the acute toxicity of ET-18-OMe after i.v. administration. The maximum tolerated dose for a single i.v. dose of free ET-18-OMe was reported 25 mg/kg, whereas the maximum tolerated dose for ET-18-OMe in liposomes was approximately 200 mg/kg. The therapeutic efficacy of free ET-18-OMe and ET-18-OMe in liposome was investigated against i.p. P388 leukemia, Lewis lung cancer metastases, and B16/F10 melanoma (lung tumor nodules) in mice. Although ET-18-OMe had some anticancer activity, it was reported that ET-18-OMe in liposomes was more effective in all three tumor models at lower and nontoxic dose schedules. These results suggests that association of ET-18-OMe in liposomes transforms it into an effective antitumor agent, and this may be a useful drug with reduced side effects. Liposomal ET-18-OMe has potential for use in combination chemotherapy.

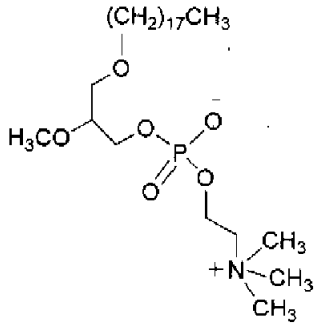

Figure 2. Structure of Edelfosine (ET-18-OCH_3)

2.4. Edelfosine[ET-18-OMe] and Apoptosis

Edelfosine [ET-18-OMe] has been known to be a potent inducer of apoptosis in several tumor cell lines and primary tumor cells from cancer patients [35]. Unlike most conventional chemotherapeutic drugs, ET-18-OMe does not target DNA but rather acts on the tumor cell membranes, thereby inducing apoptosis [36]. The molecular mechanism underlying ET-18-OMe-induced apoptosis is associated with inhibition of *de novo* synthesis of phosphatidylcholine at the endoplasmic reticulum [37]. Inhibition of protein kinase C, phosphatidylinositol 3-kinase, and coenzyme A independent transacylase, as well as the blockade of arachidonate-phospholipid remodeling, also contributed to ET-18-OMe-induced apoptosis [38-41]. In addition, ET-18-OMe-induced apoptosis was accompanied by intracellular activation of the death receptor Fas/CD95 and its recruitment together with downstream signal molecules into lipid rafts, independently of FasL ligand [42].

It has been shown that cyclooxygenase-2(COX-2) over expression provides tumor cells with a survival advantage, by conferring resistance to apoptosis and increasing invasiveness or angiogenesis [43, 44]. The selective COX-2 inhibitors have been shown to exert anti-carcinogenic activity *in vivo* and *in vitro* experiments [45, 46]. Certain anticancer agents with pro-apoptotic activity were found to up-regulate COX-2 expression in human hepatic myofibroblasts cells [47], and neuroglioma cells [48]. Thus, COX-2 derived prostaglandins are likely to be implicated in sensitizing these cells to apoptotic death. It is observed that some COX-2 products induce apoptosis in several types of cancer cells [48, 49]. A recent study explained that COX-2 product prostaglandin E_2 (PGE_2) induces apoptosis in MCF10A-*ras*-cells treated with ET-18-OMe [50]. In addition, ET-18-OMe-induced apoptosis as well as COX-2 up regulation was associated with the suppression of extracellular-signal-regulated kinase ½ (ERK1/2) and AKt.

Another example of ET-18-OMe induced apoptosis is reported through intracellular activation of Fas/CD95 into membrane rafts in human leukemic cells [51]. Results of this study showed that ET-18-OMe induces co-capping of Fas and membrane rafts (specialized plasma membrane regions involved in signaling), before the onset of apoptosis in human leukemia cells. ET-18-OMe reorganizes membrane rafts to trigger apoptosis in human leukemia cells, and that Fas co-aggregation with membrane rafts is required for ET-18-OMe-induced apoptosis. Thus, the findings involve, for the first time membrane rafts in cancer chemotherapy and Fas-mediated apoptosis. The generation of stabilized membrane lipid domains from a highly dispersed distribution may represent a general mode of regulating Fas activation. Membrane rafts could serve as platforms for coupling adaptor proteins required for Fas signaling.

Several studies revealed that the anticancer activity of ET-18-OMe is caused by the induction of apoptosis [51, 52], through interaction with cell membranes [53, 54]. It is shown that ET-18-OMe treatment induced a loss of E-cadherin-mediated cell-cell adhesion in MCF-7/AZ breast cancer cells [55], representing a critical step in tumor cell invasion and metastasis. The loss of cell-cell adhesion was not detected in the MCF-7/6 breast cancer cells and enabled to identify differences responsible for the ET-18-OMe-induced effect. ET-18-OMe did not affect the cadherin-catenin complex but induced the loss of cell-cell adhesion due to the clustering and co-localization of E-cadherin and episialin in the plasma membrane which caused a sterical hindrance of E-cadherin by episialin. Antibodies against episialin restored the E-cadherin function as these antibodies removed episialin from the clustering. In

a recent study [56], it is demonstrated that the ether lipid ET-18-OMe induced the translocation of E-cadherin and episialin to membrane micro-domains, enriched in glycosphingolipids, known to be involved in cell-cell adhesion and cell signaling. In addition, it is reported that E-cadherin and clusters of episialin co-localized and associated with the glycosphingolipid, MSGb5, upon treatment with ET-18-OMe. Together, these results suggest that ET-18-OMe inhibits cell-cell adhesion by inducing the translocation of E-cadherin and episialin into MSGb5-enriched membrane micro-domains, which leads to clustering and co-localization of the pro-adhesive E-cadherin and the anti-adhesive episialin thereby inhibiting cell-cell adhesion. In conclusion, the recent study showed that ET-18-OMe alters cellular adhesion, through the translocation and reorganization of crucial molecules in membrane micro-domains. This study highlighted that the differential composition of membrane micro-domains is important for understanding basic cellular activities and mechanisms.

2.5. Miltefosine

Antineoplastic ether lipids comprise two classes – alkyllysophospholipid derivatives with the prototypical 1-*O*-octadadecyl-2-*O*-methyl-glycero-3-phosphocholine (ET-18-OMe, edelfosine), and alkylphosphocholines with the prototypical hexadecylphosphocholine (HePC, miltefosine). Miltefosine (hexadecylphosphocholine, HePC) (Figure 3) represent another synthetic ether lipid analog with anti-tumor activity.

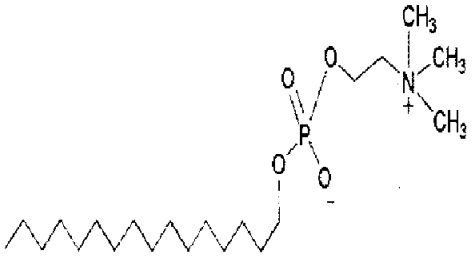

Figure 3. Structure of Miltefosine (HePC)

The mechanism of action of this class of drugs against tumor cell lines, is associated with (i) nonspecific ion channel formation, (ii) cell signaling inhibition through phospholipase C inactivation, and (iii) inhibition of *de novo* phosphatidylcholine (PC) and sphingomyelin synthesis, leading to the accumulation of ceramides and apoptosis [57]. Further, miltefosine is useful topical treatment for cutaneous metastases in breast carcinoma. Cutaneous local recurrences and skin metastases from breast cancer present a difficult clinical problem. They are frequently multifocal and often arise in areas which previously have been subject to surgical manipulation or intensive radiotherapy. Systemic hormonal or chemotherapy is usually considered when surgery or radiotherapy is unsuitable or when skin lesions arise in the presence of distant metastases. However, diminished penetration of these agents as a result of vascular damage from previous surgery or radiotherapy often limits their efficacy. Miltefosine solution (6% miltefosine solution: Miltex, ASTA Medica AG, Frankfurt, FRG) is a topically applicable cytostatic which has shown activity against cutaneous metastases from

breast cancer and cutaneous T-cell lymphomas in early clinical studies. The active ingredient of miltefosine, hexadecylphosphocholine, is similar to naturally occurring phospholipids, allowing its incorporation into cell membranes where its main action is to inhibit membrane-linked protein Kinase C and to interfere with membrane signal transduction [58]. Miltefosine, when used alone or in conjunction with other therapies for distant metastases, is an effective and tolerable local treatment for cutaneous breast cancer.

In addition to its antineoplastic effects, miltefosine is useful for the treatment of human visceral leishmaniasis [59, 60], and is also toxic to other protozoan parasites [61-63]. Visceral leishmaniasis (VL) or Kala-azar is an infectious disease caused by hemiflagellate protozoan parasites (Leshmania donovani) and transmitted to humans by the phlebotomine sandfly. Leishmaniasis, affects more than 6 million people worldwide, with 400,000 new cases each year [64]. There are several problems with standard treatment, including a lack of efficacy against visceral leishmaniasis and human immunodeficiency virus co-infections, the development of resistance, and high costs. Originally developed as an anticancer drug, miltefosine (HePC) is the first drug approved for oral treatment of visceral leishmaniasis [65], including antimony-resistance cases [66] and cutaneous leishmaniasis [67].

2.6. Ilmofosine

Ilmofosine (1-hexadecylthio-2-metoxymethyl-1, 3-propanediol-3-phosphocholine) is a thio-ether phospholipids with cytostatic/cytotoxic properties (Figure 4). The physiological lysophosphatidylcholine molecule was modified at two sites. Firstly, the ester bond at the *sn*-1 position of the glycerol moiety was replaced by a thio-ether linkage that is not cleaved by phospholipases. Secondly, the hydroxyl group at the *sn*-2 position was replaced by methoxymethyl group, thereby preventing acylation at position 2 of the lysophospholipid *via* acyltransferases [68, 69].

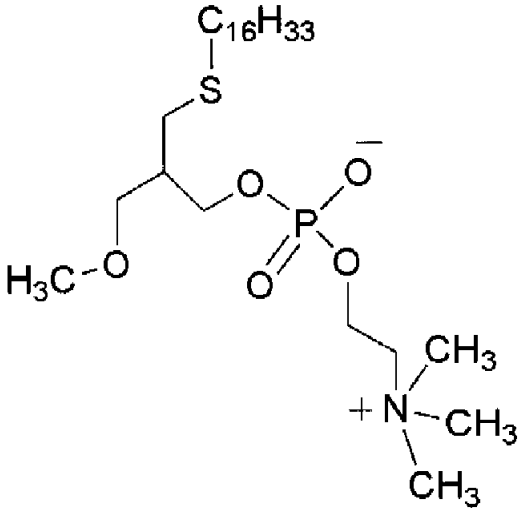

Figure 4. Structure of Ilmofosine

The antineoplastic activity of this compound was investigated *in vivo* in the Lewis-lung carcinoma system. Ilmofosine caused a significant dose-related response on tumor growth and metastases, expressed in terms of tumor diameter, tumor weight, survival time and number of metastases-free animals as compared to sham-treated and positive (cyclophosphamide) controls. The animal data suggests that the therapeutic activity of Ilmofosine *in vivo* relates to its direct cytostatic/cytotoxic effect against tumor cells rather than to immunomodulatory properties as reported for alkyl lysophospholipids (ALP), mainly based on *in vitro* studies [70]. Low toxicity, lack of mutagenicity, along with its dose-dependent anti-tumor and antimetastatic activity make Ilmofosine an interesting candidate for adjuvant cancer chemotherapy.

The mechanism of cytotoxicity of this class of drugs is unknown, but they appear to act primarily in the cell membrane and can affect signal transduction pathways that are involved in cell differentiation and apoptosis [71, 72]. Ilmofosine has demonstrated dose-dependent *in vivo* and *in vitro* antitumor activity in various solid tumor models [70, 73-77]. *In vitro* testing of ilmofosine against human tumor explants in a colony-forming assay indicated concentration-dependent activity against non-small cell lung, breast cells, colorectal, gastric, renal cell, and ovarian carcinomas and melanoma [78]. A dose-dependent response was observed in mice bearing xenograft of Lewis lung carcinoma and methylcholanthrene-induced fibrosarcoma [70, 79]. Gastrointestinal toxicity and a decline in performance status is dose limiting when ilmofosine is administered as a weekly 2h infusion and 450mg/m^2 recommended as the dose for phase II study [80]. Based on clinical phase I/II study, the role of ilmofosine as an anticancer agent is uncertain at this stage [80-83].

2.7. Perifosine

A structural analog of alkylphosphocholine, octadecyl-(1,1-dimethyl-4-piperidynio-4-yl)-phosphate(perifosine), in which the choline head group has been substituted by a piperidine moiety (Figure 5) has received mounting attention as an anticancer agent, especially in combination with other pharmacologic drugs [84-89] as well as with radiotherapy [90-92].

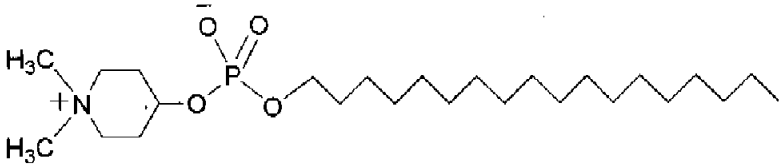

Figure 5. Structure of Perifosine

Single-chain alkylphospholipids, unlike conventional chemotherapeutic drugs, act on cell membrane to induce apoptosis in tumor cells. The differential efficacy of apoptosis induction by the alkyl phospholipids is likely related to their different chemical structure. Edelfosine, the most effective one, contains a glycerol backbone with two ether-linked substituents; a long alkyl chain and a short O-methyl group, that allow its easy partitioning into lipid rafts [93-95]. In model membranes, hexadecylphosphocholine (miltefosine, lacking the glycerol

backbone) was less miscible with sphingomyelin than edolfosine, yet stabilized sphingomyelin-cholesterol-rich ordered domains, similar to edelfosine [95]. Like edelfosine, perifosine accumulates in raft fractions but possibly in weaker association with sphingomyelin [96]. The lower efficacy of perifosine to induce apoptosis cannot be ascribed to metabolic breakdown because the molecule remained essentially intact within the cell [97]. When comparing the most potent alkylphospholipid, edelfosine, with the least effective one, perifosine, both compounds accumulate in rafts, but they differ in the capacity to inhibit phosphatidylcholine synthesis. It is possible that different alkyl phospholipids have different inhibitory effects on the CTP phosphocholine cytidylyltransferase per se. Overall, this study [96] suggests that lipid rafts are critical membrane portals for cellular entry of alkyl phospholipids depending on sphingomylein synthase (SMS1) activity. Therefore, lipids rafts are potential targets for alkylphospholipid anticancer therapy.

3. PLASMALOGEN

A plasmalogen is an ether lipid, with an ether-linked alkene (double bond next to the link), also known as vinyl-ether, at the *sn*-1 position of the glycerol. The second carbon (*sn*-2) has a typical ester- linked fatty acid, and the third carbon usually has a phospholipids head group like serine, choline, or ethanolamine (Figure 6).

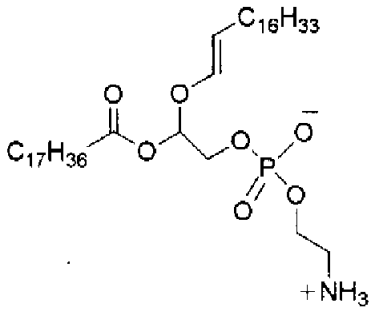

Figure 6. Structure of Plasmalogen

In many tissues plasmalogens are minor constituents, but in heart tissue nearly 50% of phosphatidylethanolamine contains the alkenyl ether at position *sn*-1. Alkenyl ether-containing phospholipids can protect cells against the damaging effects of singlet oxygen, which at high concentrations can kill cells. Nervous tissues, testis, and kidneys also contain significant amount of plasmalogens.

3.1. Biosynthesis of Plasmalogens

The polar head group of the plasmalogens is composed of ethanolamine, serine, or choline. Plasmalogens are relatively rare in some tissues but form a significant fraction of the

other as described above. Some of the steps in plasmalogens biosynthesis are localized in peroxisomes (Figure 7). Some peroxisomal disorders impair plasmalogens biosynthesis.

One of the starting materials for plasmalogen biosynthesis is dihydroxyacetone phosphate from glycolysis, which is used to form the glycerol backbone of the plasmalogen. In the first step, the three-carbon backbone is esterified with a fatty acid. The fatty acid ester is then exchanged leaving an ether-linked long-chain alcohol bound. Reduction of the carbonyl on the dihydroxyacetone backbone leaves a hydroxyl group to be esterified with another fatty acid side chain. The polar head group such as ethanolamine is then added, and the alcohol chain modified in the last step to form the vinyl-alcohol side chain that characterizes plasmalogens. Genetic defects in biosynthetic pathway are known to be the basis for peroxisomal disorders such as Zellweger's syndrome [98].

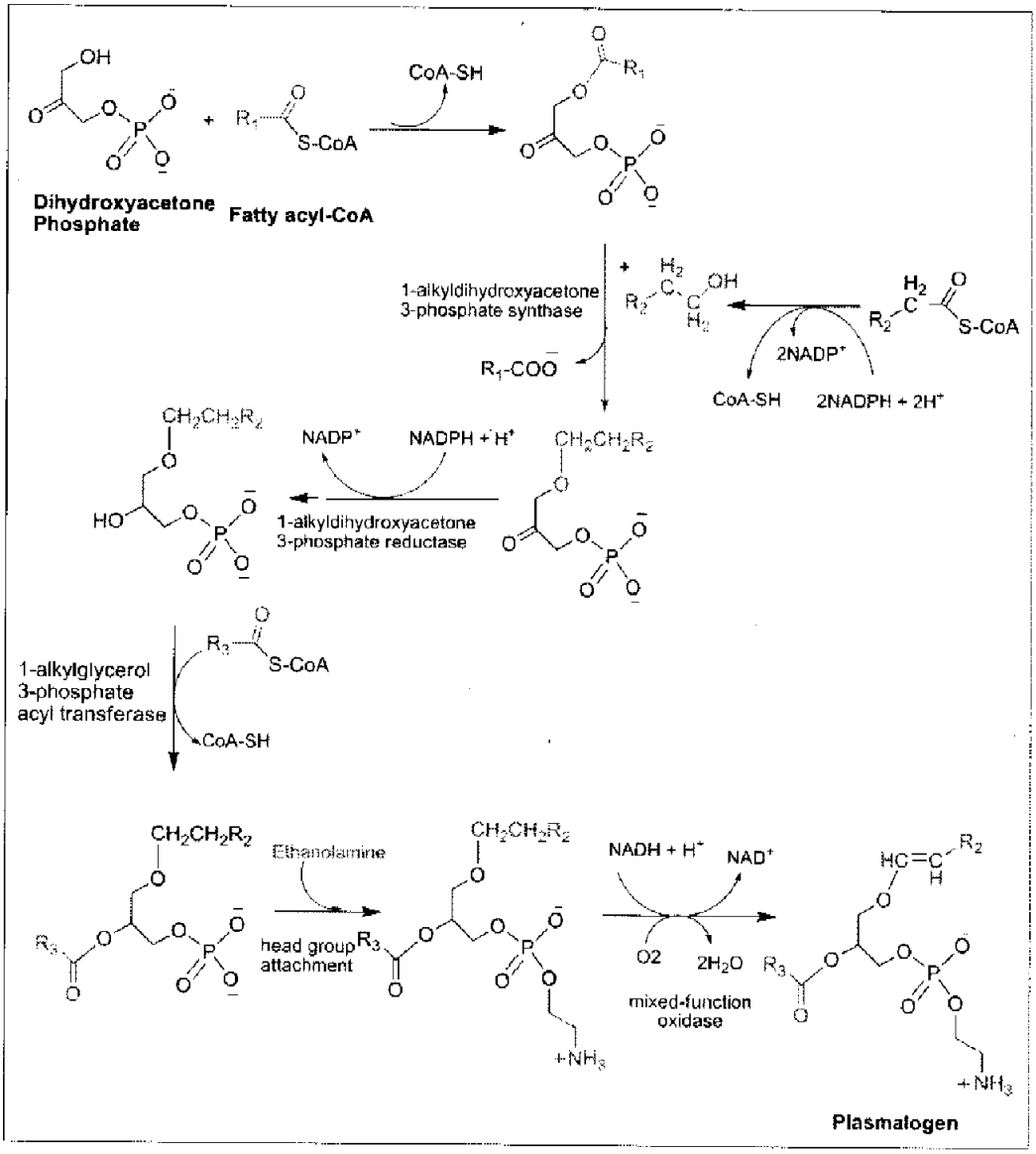

Figure 7. Biosynthesis of Plasmalogens

3.2. Plasmalogens and Zellweger's Syndrome

There is compelling evidence that ethanolamine plasmalogens are critical for human health. This evidence is based on the identification of multiple peroxisomal disorders in which plasmalogen biosynthesis and content are severely compromised. Cerebro-hepato-renal or Zellweger syndrome is an autosomal recessive disorder caused by mutations in the PEX gene family, which encodes peroxisomal matrix proteins. This disorder is characterized by impaired peroxisome biogenesis and function, with consequent plasmalogen deficiency [99]. Patients with Zellweger syndrome accumulate very long chain fatty acids [100], bile acid intermediates, and other acidic constituents [101]. They are born with craniofacial abnormalities, and they display hypotonia, seizures, hearing impairment, growth retardation, and severe neurological abnormalities [99]. Analyses of Zellweger and other peroxisomal disorders suggest that plasmalogens deficiencies in the brain tissue may play a role in neurological abnormalities [102]. There are also single-gene defects, such as Rhizomelic chondrodysplasia punctata (RCDP), an autosomal recessive condition characterized by a loss of peroxisomal function, though the loss does not occur in every case, as it does in Zellweger syndrome. RCDP is genetically heterogeneous and three degrees of severity (type-1, type-2, and type-3) have been classified. The type-1 and type-2 RCDP patients experience exclusive plasmalogen biosynthesis deficiencies. The pathogenesis of other peroxisomal disorders such as infantile Refsum disease [103,104], X-linked adrenoleukodystrophy [105,106], and neurological disorder, such as Alzheimer's disease [107,108], have all been demonstrated to have plasmalogen deficiencies. Brites et.al. [109] compiled an excellent review on plasmalogen-associated disorders.

3.3. Plasmalogens and Alzheimer's Disease

It has been recognized that aging, Alzheimer's disease, and dementia are intricately linked. However, a direct causal relationship has yet to be established between these conditions. The prevalence of dementia and Alzheimer's disease increases with advancing age, but all elderly people do not exhibit dementia or develop Alzheimer's disease. Dementia can arise from numerous neurological conditions, but signs of dementia do not automatically develop with advancing age.

Goodenowe et.al. [110] have shown that people with Alzheimer's disease and related conditions exhibit decreased blood levels of an important brain chemical called ethanolamine plasmalogen, even at the very early stages of the disease. The decrease is found more pronounced when the symptoms are more severe. Alzheimer's disease and related conditions, grouped under the name "dementia of the Alzheimer's type (DAT)," mostly affect elderly people. These conditions are not easily diagnosed because they can arise from many different causes, some of which are not well known. Although the relationship between blood levels of ethanolamine plasmalogens and the severity of DAT is not completely understood the new discovery may improve the diagnosis of DAT and help patients make decisions about how to cope with the disease. It is suggested that the observed decrease of ethanolamine plasmalogens may result in decreased release and subsequent decreased activity of acetylcholine, a critical brain chemical involved in memory formation and whose activity is

known to be reduced in DAT patients. So correcting the ethanolamine plasmalogen deficit in DAT may slow or correct the acetylcholine deficit in DAT patient.

It is suggested by the above researchers that clinical trials involving the restoration of ethanolamine plasmalogens should be undertaken to determine the efficacy of plasmalogens in the treatment and/or prevention of DAT.

3.4. Synthetic Plasmalogens

Plasmalogens are a class of naturally occurring phospholipids that are characterized by the presence of alkenyl ether at the *sn*-1 position. They are found predominantly within electrically active tissues such as brain, myelin, and heart. Interest in the biochemical and biophysical properties of these unusual natural products has grown because of their role in many important biological processes such as signal transduction [111,112], membrane fusion [113,114], and lipid peroxidation [115]. The reactivity of these compounds towards both acidic conditions [116-120] and photoxidation [121-122] suggests that plasmalogen derivatives are promising candidates for the development of environmentally responsive gene (119) and drug delivery system [116-118, 120-121].

Naturally occurring plasmalogen mixtures are generally isolated from phosphocholine extracts that are derived from a number of animal sources. Because these extracts contain mixtures of alkyl chain lengths at the *sn-1* and *sn-2* positions, they are difficult to obtain as discrete molecular species without extensive HPLC purification, limiting their utility in biophysical studies and drug delivery applications. Since these lipids have not been isolated using conventional separation approaches, attention has shifted to synthetic methods as a means to obtain these compounds in pure form. This situation can be partially solved by the preparation of semi synthetic plasmenylcholine [122]. Rui and Thompson [123,124] reported the first synthetic pathway to produce pure plasmenylcholines with (*Z*)-vinyl ether stereo-specificity. Qin et. al. [125] subsequently reported a multistep synthesis of plasmenylcholine. Unfortunately, both of these pathways are tedious and produce low overall yields of plasmalogens. Thompson et. al. [126] developed new, synthetic methods for the preparation of palmitoyl plasmenylcholine (PPlsC); 1, 2-di-*O*-(1-*Z*-hexadecenyl)-*sn*-glycero-3-phosphocholine (DPPlsC) and other plasmenyl-type lipids. A method for the preparation of plasmenyl-type liposome was also described. These authors report a simple and adaptable approach for the stereo controlled synthesis of plasmenyl derivatives with variations at the *sn*-1, *sn*-2, and *sn*-3 positions of the glycerols backbone [127].

3.5. Plasmalogens: As Antioxidants and Targets for Oxidants

Peroxidation of lipids has been proposed to promote the development of several common diseases, including atherosclerosis [128] and neurodegenerative disorders, such as Alzheimer's disease [129]. This has fostered research into the endogenous antioxidant mechanisms capable of preventing or delaying lipid oxidation. Substantial evidence accumulated in the last decade that plasmalogens, a class of ethanolamine and choline phospholipids could represent a major lipid-soluble antioxidant component [130-135]. The

potential biological functions of plasmalogens have been reviewed [136,137]. However, recent evidence also suggests that the canonical type of ethanolamine phospholipids, the unsaturated diacyl phosphatidylethanolamine could act as an important pro-oxidant factor [138]. Thus, phosphatidylethanolamine, an abundant phospholipids fraction carrying most of the polyunsaturated fatty acids in many organisms, could be a branching point for lipid oxidation, either inhibiting or propagating oxidation depending on the type of subgroup initially targeted by the oxidants.

Maeba et al. [139] reported that ethanolamine plasmalogen, 1-alkenyl-2-acyl-*sn*-glycerol-3-phosphoethanolamine, could act as a physiological antioxidant for cholesterol in biomembranes, because ethanolamine plasmalogen is abundant in biomembranes containing large amounts of cholesterol, such as nervous-system myelin and red-blood cells membranes. These biomembranes appear to possess structures capable of resisting oxidative stress, especially cholesterol oxidation, because these tissues have long life spans, despite high levels of oxygen consumption and frequent exposure to oxygen. Although the physiological role of plasmalogens is not fully understood, but recent studies on plasmalogen-deficient mutant cells led to the proposal that these ether lipids serve to protect cells from oxidative stress as endogenous antioxidants by scavenging radicals at the vinyl-ether linkage [130,135].

4. GLYCOLIPID

A glycolipid is a lipid molecule that contains one or more carbohydrate groups. Glycosphingolipids (GSLs) are glycosides of ceramide, a fatty acid amide of the amino alcohol sphingosine. Galactosyl ceramide is enriched in brain tissue and is a major component of the myelin sheath around nerves. Glucosyl ceramide is present in the cell membranes of many cell types and is abundant in the serum.

4.1. Glycosphingolipids

Glycosphingolipids (GSLs) are characteristic membrane components of eukaryotic cells where they are found in the carbohydrate-rich glycocalix, which consists of glycoproteins and glycosaminoglycans in addition to GSLs [140]. Each GSL carries a hydrophobic ceramide moiety and a hydrophilic extracellular oligosaccharide chain which protrudes from the membrane surface. Because of their great structural variations they are classified in four groups (Figure 8):

- Cerebrosides (containing one sugar residue)
- Sulfatides (containing one sugar residue with a sulfate group)
- Neutral Glycosingolipids (containing one to thirty uncharged sugar residue)
- Gangliosides (containing one or more neuraminic acid residues)

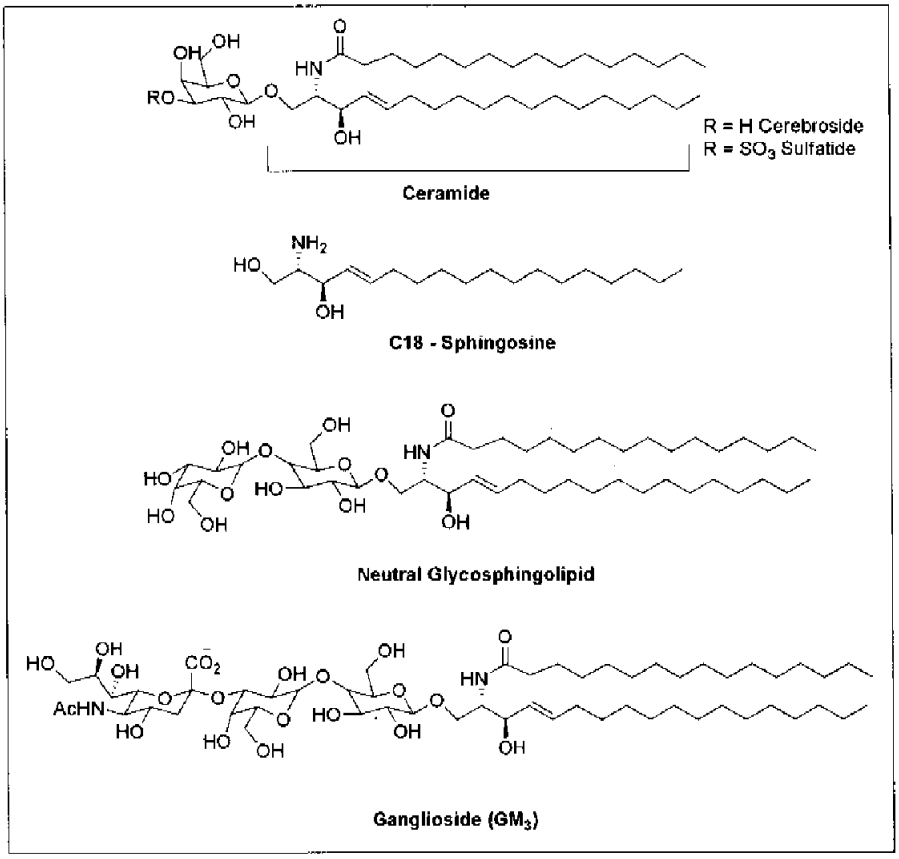

Figure 8. Structures of Glycosphingolipids (GSLs)

The ceramide part is made up of a sphingosine moiety having a long chain amino alcohol with 18-20 carbon atoms, and a long chain fatty acid. The sphingosine most frequently found in a glycosphingolipid is C_{18} - Sphingosine, although large amounts of C_{20}-sphingosine have been reported in brain ganglioside with C_{18} - sphingosine. Glycosphingolipids may be structurally related to one another through the stepwise addition or removal of single monosaccharide. Such glycolipids can therefore be arranged in series. The main families of GSLs start with lactose as the first building block. Further extension by N-acetylglucosamine, galactose or N-acetylgalactosamine leads to the formation of oligosaccharides of the *lacto-*, *globo-* or the *ganglio-* series, respectively.

Glycosphingolipids serve a variety of functions [141] through interactions with many bio-factors by inhibiting or interfering with the physiological effects of these factors or cells [142]. At the cell surface, GSLs can interact with toxins, viruses and bacteria [143]. These pathogens benefit from the close spatial neighborhood of specific carbohydrate recognition site on the cell surface and the plasma membrane. Cell adhesion phenomena of this type result from a binding of the carbohydrate moiety of the membrane-bound GSLs to proteins on the surface of neighboring cells. Interactions of GSLs with receptors and enzymes which are located in the same membrane have been described to be of some physiological significance. Lipophilic intermediates of GSL metabolism such as sphingosine, ceramide, and their phosphorylated derivatives have been recently identified as novel signal substances [144].

Glycosphingolipids are also essential for the function of human skin where they contribute to the formation of the water permeability barrier [145]. Many GSLs are blood group antigens and their studies not only offer chemical structures of blood group antigens, but also delineate their immunological significance [146]. A number of GSLs play a role as tumor associated antigens and in immunotherapy of individual cancer forms [146]. Most neurons, especially of the central nervous system, contain a variety of gangliosides which are present in relatively high overall concentration. Immunochemical and biochemical studies demonstrate those changes in GSLs of neuronal membranes are related to degenerative changes, for instance, in characteristics of Alzheimer's disease [147]. GSLs also display neuro-protective and neurodegenerative effects in diseases like Parkinson's disease or ischemic stroke [147].

4.2. Glycosphingolipid Lysosomal Storage Diseases

Glycosphingolipid (GSL) lysosomal storage diseases are a family of human metabolic diseases that may cause death in early infancy, as a result of progressive neurodegeneration. They are caused by mutations in the genes encoding the glycohydrolases or the activator proteins that catabolise GSLs within lysosomes. In these diseases, the GSL substrate of the defective enzyme accumulates in the lysosome, where it is stored and leads to cellular dysfunction and disease. Gaucher disease is the most common of these disorders. Type1 Gaucher disease is a typical disease compared with other related disorders because the central nervous system is not affected. Gaucher disease is caused by mutations in the gene coding for the enzyme glucocerebrosidase and the resultant storage of galactosylceramide [148]. The cell type that is most affected by the defect is the macrophage because these cells accumulate galactosylceramide from the cells that they ingest as part of their normal phagocytic activity. In addition to the increased concentration of galactosylceramide in cells, the concentration of galactosylceramide is also found elevated in the serum.

The therapeutic options for treating these diseases are limited. During the past decade, several advances have been made to cure GSLs lysosomal storage disease [149-151], such as i) the first clinical application of enzyme-replacement therapy for the treatment of type 1 Gaucher disease, (ii) the clinical application of bone-marrow transplantation (BMT) for the treatment of several of these disorders, (iii) gene-therapy trials, and (iv) the imino-sugar drugs, such as N-butyldeoxynojirimycin (NB-DNJ) (Figure 9) as the inhibitor of GSL biosynthesis. The NB-DNJ has emerged as potential therapeutics. These complementary strategies could be used in combination, and would be expected to provide therapeutic options for the treatment of these severe human diseases.

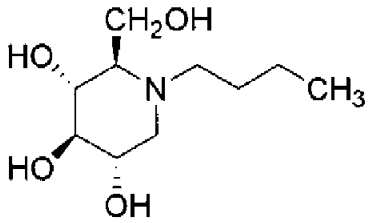

Figure 9. Structure of Inhibitor, *N*B-DNJ (*N*-butyldeoxynojirimycin)

5. SYNTHETIC CERAMIDE-ANALOGS

Ceramide (N-Acyl-D- *erythro*- sphingosine) (Figure 10) is a structural component of mammalian glycolipids and of a phospholipids, sphingomyelin [141]. Ceramide derivatives attracted attention as potential therapeutic agents for the treatment of cancer, allergy, and other diseases originating from cell regulation disorders. Ceramide itself is a signaling substance that can be released from sphingomyelin in response to extracellular and intracellular stimuli. In general, it mediates antimitogenic cellular effects like differention, apoptosis, or cellular senescence [152]. Details of the pathway including the identity of the ceramide binding proteins are not clear. One reason for this is the metabolic coupling of ceramide with other bioactive lipids like ceramide-1-phosphate, sphingosine, and sphingosine-1-phosphate.

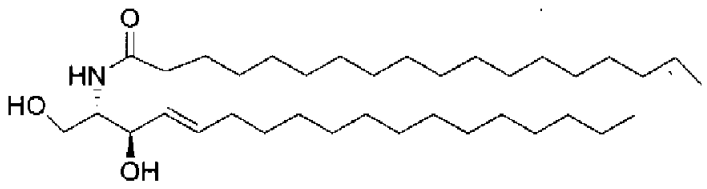

Figure 10. Structure of Ceramide

It is well established that either endogenous or exogenous ceramide can initiate apoptotic cell death in physiological and pharmacological settings [153-156]. As a possible new approach to experimental anticancer chemotherapy, unnatural analogs of ceramide were employed. These analogs can escape recognition as substrates of sphingolipid-utilizing enzymes present in most mammalian cells and thus evade metabolic conversion to mitogenic sphingolipids, such as ceramide 1-phosphate, glycosylceramide, and sphingosine 1-phosphate. Some newer unnatural ceramide analogs may also elevate the level of endogenous ceramide levels by inhibiting enzymes involved in ceramide turnover. To investigate this approach, Bittman et.al. [157] synthetically modified the structure of ceramide at different sites in the molecule. The ceramide analogs may represent new experimental therapeutic agents in breast cancer treatment by triggering tumor cell apoptosis. The most effective analogs would be metabolically stable, raise the level of intracellular ceramide, appropriately activate stress-induced signaling pathways, and increase the vulnerability of cancer cells to oxidative stress, perhaps by depleting cellular glutathione (GSH) levels and elevating levels of reactive oxygen species.

6. CONCLUSION

In this chapter we introduced the multifaceted roles of bioactive lipids in health and disease. A thorough review of all the bioactive lipids, natural or synthetic, known today is beyond the scope of the present discussion. However, in this chapter, representative example have been presented that illustrate how the chemical synthesis of lipid analogs is a powerful tool for addressing issues involving the properties of selected bioactive lipids. Modern lipid

synthesis and lipid chemistry have developed molecules which can be studied as cytotoxic drugs either alone, or in combination with other cytotoxic agents, biological response modifiers, or other treatment modalities. We hope that this book chapter will contribute to the advancement of lipid research, and inspire students and scientists to consider this fascinating area for further development.

REFERENCES

[1] Snyder, F., ed. (1972). Ether Lipids: *Chemistry and Biology*, Academic Press, New York, 177-425.

[2] Ostermann, G., Kertscher, H. P. & Hofmann. B. (1990). Der Plättchenaktivierende Faktor - ein biologisch hochwirksames Phospholipid. *Pharmazie*, *45*, 465-487.

[3] Lee, T. C. & Snyder, F. (1985). In: J. F. Kuo, (Ed). Phospholipids and Cellular Regulation, CRC Press, *Boca Raton*, Fla. *Vol II*, 2-39.

[4] Berdel, W. E., Andreessen, R. & Munder, P. G. (1985). In: J.F.Kuo (Ed). Phospholipids and Cellular Regulation, CRC Press, *Boca Raton*, Fla. *Vol II*, 41-73.

[5] Berdel, W. E. & Munder, P. G. (1987). Antineoplastic actions of Ether Lipids Related to Platelet- Activating Factor. In: F. Snyder, (Ed). *Platelet-Activating Factor and Related Lipid Mediators*, Plenum Press, New York. 449-497.

[6] Modest, E. J., Daniel, L. W., Wykle, R. L., Berens, M. E., Piantadosi, C., Surles, J. R. & Morris-Natschkle, S. (1987). In: K. Harrap., & T. Conners (Eds). New Avenues in Development Cancer Chemotherapy, *Bristol-Myers Cancer Symposia*, Academic Press, New York, *Vol. 8*, 387-400.

[7] O'Flaherty, J. T., Wykle, R. L., Miller, C.H., Lewis, J. C., Waite, M., Bass, D. A., McCall, C. E. & DeChatelet, L. R. (1981). 1-O-Alkyl-*sn*-glyceryl-3-phosphorylcholines: A Novel Class of Neutrophil Stimulants, *Am . J . Pathol*, *103*, 70-78.

[8] Munder, P. G., Modolell, M., Bausert, W., Oetlgen, H. F. & Westphal, O. (1981). In: E. M., Hersh, M. A. Chirigos. & M. J. Mastrangelo, (Eds). *Augmenting Agents in Cancer Therapy*, Raven Press, New York. 441-458.

[9] Helfmann, D. N., Baines, K. C., Kinkade, J. M., Vogler, W. R., Shoji, M. & Kuo, J. F. (1983). Phospholipid-sensitive Ca^{2+}-dependent Protein Phosphorylation System in Various Types of Leukemic Cells from Human Patients and in Human Leukemic Cell Lines HL60 and K562, and Its Inhibition by Alkyl-lysophospholipid, *Cancer Res.*, *43*, 2955-2961.

[10] Parker, J., Daniel, L. W. & Waite, M. (1987). Evidence of Protein Kinase C Involvement in Phorbol Diester-stimulated Arachidonic Acid Release and Prostaglandin Synthesis, *J. Biol. Chem.*, *262*, 5385-5393.

[11] Daniel, L. W., Etkin, L. A., Morrison, B. T., Parker, J., Morris-Natschke, S., Surles, J. R. & Piantadosi, C. (1987). Ether lipids Inhibit the Effects of Phorbol Diester Tumor Promoters, *Lipids*, *22*, 851-855.

[12] Modolell, M., Andreesen, R., Pahlke, W., Brugger, U. & Munder, P. G. (1979). Disturbance of Phospholipid Metabolism during the Selective Destruction of Tumor Cells Induced by Alkyl-lysophospholipids, *Cancer Res.*, *39*, 4681-4686.

[13] Herrmann, D. B. J. (1985). Changes in Cellular Lipid Synthesis of Normal and Neoplastic Cells during Cytolysis Induced by Alkyl Lysophospholipid Analogues. *J. Natl. Cancer Inst*, *75*, 423-430.

[14] Honma, Y., Kasukabe, T., Hozumi, M., Tsushima, S. & Nomura, H. (1981). Induction of Differentiation of Cultured Human and Mouse Myeloid Leukemia Cells by Alkyl-lysophospholipids, *Cancer Res.*, *41*, 3211-3216.

[15] Storme, G., Berdel, W. E., Van Blitterswijk, W., Bruyneel, E. A., DeBruyne, G. K. & Mareel, M. M. (1985). Anti-invasive Effect of Racemic 1-*O*-Octadecyl-2-*O*-methyl-glycero-3-phosphocholine on MO_4 Mouse Fibrosarcoma Cells *In Vitro*, *Cancer Res.*, *45*, 351-357.

[16] Van Blitterswijk, W. J., Hilkmann, H. & Storme, G. A. (1987). Accumulation of an Alkyl Lysophospholipid in Tumor Cell Membranes Affects Membrane Fluidity and Tumor Cell Invasion, *Lipids*, *22*, 820-823.

[17] Noseda, A., White, J. G. & Modest, E. J. (1987). Effects of Ether Lipid Analogues and Platelet Activating Factor on the Physical Properties of Model Membranes *Proc. Am. Assoc. Cancer. Res.*, *28*, 13.

[18] Noseda, A., Godwin, P. L. & Modest, E. J. (1988). Effects of Antineoplastic Ether Lipids on Model and Biological Membranes. *Biochim. Biophys. Acta*, *945*, 92-100.

[19] Marx, M. H., Piantadosi, C., Noseda, A., Daniel, L. W. & Modest, E. J. (1988). Synthesis and Evaluation of Neoplastic Cell Growth Inhibition of 1-N-Alkylamide Analogues of Glycero-3-phosphocholine, *J. Med. Chem.*, *31*, 858-863.

[20] Houlihan, W. J., Lohmeyer, M., Workman, P. & Cheon, S. A. (1995). Phospholipid Antitumor Agents, *Med. Res. Rev.*, *15*, 157-223.

[21] Brachwitz, H. & Vollgraf, C. (1995). Analogs of Alkyl Lysophospolipids: Chemistry, Effects on the Molecular Level and their Consequences for Normal and Malignant Cells, *Pharmac. Ther.*, *66*, 39-82.

[22] Powis, G. (1994). Recent Advances in the Development of Anticancer Drugs that Act Against Signalling Pathways, *Tumori*, *80*, 69-87.

[23] Villereal, M. L. & Byron, K. L. (1992). Calcium Signals in Growth Factor Signal Transduction, *Rev. Physiol. Biochem. Pharmacol*, *119*, 67-121.

[24] Seewald, M. J., Olsen, R. A., Sehgal, I., Melder, D. C., Modest, E. J. & Powis, G (1990). Inhibition Growth Factor-Dependent Inositol Phosphate [Ca^{++}] Signaling by Antitumor Ether Lipid Analogues, *Cancer Res.*, *50*, 4458-4462.

[25] Berridge, M. J. (1993). Inositol Triphosphate and Calcium Signaling, *Nature*, *361*, 315-325.

[26] Lohmeyer, M. & Workman, P. (1993). The Role of Intracellular Free Calcium Mobilization in the Mechanism of Action of Antitumor Ether Lipids SRI 62-834 and ET-18-OMe, *Biochim. Pharmacol.*, *45*, 77-86.

[27] Bergmann, J., Junghahm, I., Brachwitz, H. & Langen, P. (1994). Multiple Effects of Antitumor Alkyl-Lysophospholipid Analogs on the Cytosolic Free Ca^{2+} Concentration in a Normal and Breast Cancer Cell Line, *Anticancer Res.*, *14*, 1549-1556.

[28] Boggs, K. P., Rock, C. O. & Jackowski, S. (1995). Lysophosphatidylcholine Attenuates the Cytotoxic Effects of the Antineoplastic Phospholipid 1-*O*-Octadecyl-2-*O*-methyl-*rac*-glycero-3-Phosphocholine, *J. Biol. Chem.*, *270*, 11612-11618.

[29] Diomede, L., Colotta, F., Piovani, B., Re, F., Modest, E. J. & Salmona, M. (1993). Induction of Apoptosis in Human Leukemic Cells by Ether Lipid 1-Octadecyl-2-

methyl-*rac*-glycero-3- phosphocholine. A Possible Basis for its Selective Action, *Int. J. Cancer*, *53*, 124-130.

[30] Drings, P., Gunther, I. Gatzemeier, U., Ulbrich, F., Khanavkar, B., Schreml, W., Lorenz, J., Brugger, W., Schick, H. D., Pawel, J. V. & Nordstrom, R. (1992). Final Evaluation of a Phase II Study on the Effects of Edelfosine (an Ether Lipid) in Advanced Non Small-Cell Bronchogenic Carcinoma, *Onkolgie*, *15*, 375-382.

[31] Perkins, W. R., Dause, R. B., Li, X., Franklin, J. C., Carbal-Lily, D. J., Dank, E. H., Mayhew, E. & Janoff, A. S. (1997). Combination of Antitumor Ether Lipid with Lipids of Complementary Molecular Shape Reduces Its Transfer to RBCs, *Biochim. Biophys. Acta*, *88*, 61-68.

[32] Mayhew, E., Ahmad, I., Bhattia, S., Dause, R., Filep, J., Janoff, A. S., Kaisheva, E., Perkins, W. R., Zha, Y. & Franklin, J. C. (1997). Stability of Association of 1-*O*-Octadecyl-2-*O*-methyl-*sn*-glycero-3- phosphacholine with Liposomes is Composition Dependent, *Biochim. Biophys. Acta*, *1329*, 139-148.

[33] Peters, A. C., Ahmad, I., Janoff, A. S., Pushkreva, M. Y. & Mayhew, E. (1997). Growth Inhibitory Effects of Liposome-Associated 1-*O*- Octadecyl-2-*O*-methyl-*sn*-glycero-3-phosphocholine, *Lipids*, *32*, 1045-1054.

[34] Ahmad, I., Filep, J. J., Fraklin, J. C., Janoff, A. S., Masters, G. R., Pattassery, J., Petters, A., Schupsky, J. J., Zha, Y. & Mayhew, E. (1997). Enhanced Therapeutic Effects of Liposome-associated 1-*O*-Octadecyl-2-*O*-Methyl-*sn*-glycero-3-phosphocholine, *Cancer Res.*, *57*, 1915-1921.

[35] Mollinedo, F., Fernandez-Luna, J. L., Gajate, C., Martin-Martin, B., Benito, A., Martinez-Dalmau, R. & Modolell, M. (1997). Selective Induction of Apoptosis in Cancer Cells by the Ether Lipid ET-18- OCH_3 (Edelfosine): Molecular Structure Requirements, Cellular Uptake and Protection by Bcl-2 and Bcl-X (L), *Cancer Res.*, *57*, 1320- 1328.

[36] Jendrossek, V. & Handrick, R. (2003). Membrane Targeted Anticancer Drugs: Potent Inducers of Apoptosis and Putative Radiosensitisers, *Cur. Med. Chem. Anticancer Agents*, *3*, 343-353.

[37] Vander Luit, A. H., Vink, S. R., Klarenbeck, J. B., Perrissond, D., Solary, E., Verheij, M. & Van Blitterswijk, W. J. (2007). A New Class of Anticancer Alkyl phospholipids Uses Lipid Rafts as Membrane Gateways to Induce Apoptosis in Lymphoma Cells, *Mol. Cancer Ther*, *6*, 2337-2345.

[38] Guo, H. B., Shen, Z. H., Huang, C. X., Ma, J., Haung, Y. & Chen, H. L. (2000). Modulation of the Basal Activity of Phosphatidylinositol-3-Kinase/Protein Kinase B Signaling Pathway in Human Hepato Carcinoma Cells, *Glycoconj. J*, *17*, 315-322.

[39] Winkler, J. D., Eris,T., Sung, C. M., Chabot-Fletcher, M., Mayer, R. J., Surette, M. E. & Chitton, F. H. (1996). Inhibitors of Coenzyme A- Independent Transacylase Induce Apoptosis in Human HI-60 Cells, *J. Pharmacol. Exp. Ther.*, *279*, 956-966.

[40] Surette, M. E., Winkler, J. D., Fonteh, A. N. & Chitton, F. H. (1996). Relationship between Arachidonate-Phospholipid Remodeling and Apoptosi, *Biochemistry*, *35*, 9187-9197.

[41] Civoli, F. & Daniel, L. W. (1998). Quaternary Ammonium Analogs of Ether Lipids Inhibit the Activation of Protein Kinase C and the Growth of Human Leukemia Cell Lines, *Cancer Chemother. Pharmacol*, *42*, 319-326.

[42] Gajate, C. & Mollinedo, F. (2007). Edelfosine and Perifosine Induce Selective Apoptosis in Multiple Myeloma by Recruitment of Death Receptors and Downstream Signaling Molecules into Lipid rafts, *Blood*, *109*, 711-719.

[43] Ishiko, O., Sumi, T., Yoshida, H., Matsumoto, Y., Honda, K., Deguchi, M., Yamada, R. & Ogita, S. (2001). Association between Over Expression of Cyclooxygenase-2 and Suppression of Apoptosis in Advanced Cancer Of the Uterine Cervix after Cyclic Balloon-occluded Arterial Infusion, *Oncol. Rep.*, *8*, 1259-1263.

[44] Cianchi, F., Cortesini, C., Bechi, P., Fantappie, O., Messerini, L., Vannacci, A., Sardi, I., Baroni, G., Boddi, V., Mazzanti, R. & Masini, E. (2001). Up-regulation of Cyclooxygenase-2 gene Expression Correlates with Tumor Angiogenesis in Human Colorectal Cancer, *Gastroenterology*, *121*, 1339-1347.

[45] Grosch, S., Maier, T. J., Schiffmann, S. & Geisslinger, G. (2006). Cyclooxygenase-2(Cox-2)-independent Anticarcinogenic Effects of Selective Cox-2 Inhibitors, *J. Natl. Cancer Inst.*, *98*, 736-747.

[46] Chun, K. S., Kim, S. H., Song,Y. S. & Surh,Y. J. (2004). Celecoxib Inhibits Phorbol Ester-induced Expression of Cox-2 and Activation of AP-1 and p38 MAP Kinase in Mouse Skin, *Carcinogenesis*, *25*, 713- 722.

[47] Davaille, J., Gallois, C., Habib, A., Li, L., Mallat, A., Tao, J., Levade, T. & Lotersztajn, S. (2000). Antiproliferative Properties of Sphingosine 1-phosphate in Human Hepatic Myofibroblasts. A Cyclooxygenase-2 Mediated Pathway, *J. Biol. Chem.*, *275*, 34628-34633.

[48] Hinz, B., Ramer, R., Eichele, K.,Weinzier I, U. & Burne, K. (2004). Upregulation of Cyclooxygenase-2 Expression is involved in R (+)-Methanandamide-induced Apoptotic Death of Human Neuroglioma Cells, *Mol. Pharmacol.*, *66*, 1643-1651.

[49] Giucci, A., Gianferreti, P., Piva, R., Guyot, T., Snape, T. J., Roberts, S. M. & Santoro, M. G. (2006). Induction of Apoptosis in Estrogen Receptor-Negative Breast Cancer Cells by Natural and Synthetic Cyclopentenones: Role of the IkB Kinase/nuclear Factor-Kappa B Pathway, *Mol. Pharmacol.*, *70*, 1812-1821.

[50] Na, H. K. & Surh, Y. J. (2008). The Antitumor Ether Lipid Edelfosine (ET-18-OCH_3) induces Apoptosis in H-*ras* Transformed Human Breast Epithelial Cells: By Blocking ERK1/2 and p38 Mitogen-activated Protein Kinases as Potential Targets, *Asia Pac. J. Clin. Nutr.*, *17*, 204-207.

[51] Gajate, C. & Mollinedo, F. (2001). The Antitumor Ether Lipid ET-18- OCH_3 induces Apoptosis through Translocation and Capping of Fas/CD95 into Membrane Rafts in Human Leukemic Cells, *Blood*, *98*, 3860-3863.

[52] Na, H. K., Inoue, H. & Surh, Y. J. (2005). ET-18- OCH_3 Induced Apoptosis is causally linked to Cox-2 Upregulation in H-*ras* Transformed Human Breast Epithelial Cells, *FEBS Lett.*, *579*, 6279- 6287.

[53] Mollinedo, F., Gajate, C., Martin-Santamario, S. & Gago, F. (2004). ET-18- OCH_3 (Edelfosine): A Selective Antitumor Lipid Targeting Apoptosis through Intracellular Activation of Fas/CD95 Death Receptor, *Curr. Med. Chem.*, *11*, 3163-3184.

[54] Dimanche-Boitrel, M. T., Meurette, O., Rebillard, A. & Lacour, S. (2005). Role of Early Plasma Membrane Events in Chemotherapy Induced Cell Death, *Drug Resist. Update*, *8*, 5-14.

[55] Steelant, W. F., Goeman, J. L., Philippe, J., Oomen, L. C., Hilkens, J., Krzewinski-Rechi, M. A., Huet, G., Van der Eycken, J., Delannoy, P., Bruyneel, E. A. & Mareel,

M. M. (2001). Allyl-lysophospholipid 1-*O*-Octadecyl-2-*O*-methyl-3-glycerophospholine Induces Invasion through Episialin-mediated Neutralization of E-Cadherin in Human Mammary MCF-7 Cells *in vitro*, *Int. J. Cancer*, *92*, 527-536.

[56] Slambrouck, S. V., Hilkens, J. & Steelant, W. F. (2008). Ether lipid 1- *O*- Octadecyl-2-*O*-methyl-3-glycerophosphoclone Inhibits Cell-cell Adhesion through and Clustering of E-cadherin and Episialin in Membrane Microdomains, *Oncology Reports*, *22*, 123-128.

[57] Wieder, T., Reutter, W., Orfanos, C. E. & Geilen, C. C. (1999). Mechanism of Action of Phospholipid Analogs as Anticancer Compounds, *Prog. Lipid Res.*, *38*, 249-259.

[58] Clive, S., Gardiner, G. & Leonard, R. C. F. (1999). Miltefosine as a Topical Treatment for Cutaneous Metastases in Breast Carcinoma, *Cancer Chemother. Pharmacol.*, *44*, *(suppl.)*, S29-S30.

[59] Jha, T. K., Sundar, S., Thakur, C. P., Bachmann, P., Kabwang, J., Fischer, C., Voss, A. & Berman, J. (1999). Miltefosine, an Oral Agent, For the Treatment of Indian Visceral Leishmaniasis, *N. Engl. J. Med.*, *341*, 1795-1800.

[60] Sundar, S., Jha, T. K., Thakur, C. P., Engel, J., Sindermann, H., Fischer, C., Junge, K., Bryceson, A. & Berman, J. (2002). Oral Miltefosine for Indian Visceral Leishmaniasis, *N. Engl. J. Med*, *347*, 1739-1746.

[61] Saraiva, V. B., Gibaldi, D., Previato, J. O., Mendonca-Previato, L., Bozz, M. T., Freire-de-Lima, C. G. & Heise, N. (2002). Proinflammatory and Cytotoxic Effects of Hexadecylphosphocholine (Miltefosine) Against Drug-resistant Strains of Trypanosoma Cruzi, *Antimicrob. Agents Chemother.*, *46*, 3472-3477.

[62] Walochnik, J., Duchene, M., Seifert, K., Obwaller, A., Hottkowitz, T., Wiedermann, G., Eibl, H. & Aspock, H. (2002). Cytotoxic Activities of Alkylphosphocholines Against Clinical Isolates of Acanthamoeba spp., *Antimicrob. Agents Chemother.*, *46*, 695-701.

[63] Seifert, K., Duchene, M., Wernsdorfer, W. H., Kollaristsch, H., Scheiner, O., Wiedermann, G., Hottkowitz, T. & Eibl, H. (2001). Effects of Miltefosine and other Alkylphosphocholines on Human Intestinal Parasite Entamoeba Histolytica, *Antimicrob. Agents Chemother.*, *45*, 1505-1510.

[64] Herwaldt, B. L. (1999). Leishmaniasis, *Lancet, 354*, 1191-1199.

[65] Sundar, S., Makharia, A., More, D. K., Agarwal, G., Voss, A., Fischer, C., Bachmann, P. & Murray, H. W. (2000). Short-course of Oral Miltefosine for Treatment of Visceral Leishmaniasis, *Clin. Infect. Dis.*, *31*, 1110-1113.

[66] Jha, T. K., Sundar, S., Thakur, C. P., Bachmann, P., Karbwang, J., Fischer, C., Voss, A. & Bermann, J. (1999). Miltefosine, an Oral Agent, For the Treatment of Indian Visceral Leishmaniasis, *N. Engl. J. Med.*, *341*, 1795-1800.

[67] Sato, J., Toledo, J., Gutierrez, P., Nicholls, R. S., Padilla, J., Engel, J., Fischer, C., Voss, A. & Berman, J. (2001). Treatment of American Cutaneous Leishmaniasis with Miltefosine, an Oral Agent, *Clin. Infect. Dis.*, *33*, 57-61.

[68] Bosies, E., Herrmann, D. B. J., Bicker, U., Gall, R. & Phalke, W. (1987). Synthesis of Thioether Phosphocholine Analogues, *Lipids*, *22*, 947-951.

[69] Hill, E. E. & Lands, W. E. M. (1970). In: S. J. Wakil, Jr., (Ed). *Lipids Metabolism*, Academic Press, New York, 185-277.

[70] Hermann, D. B. J., Optiz, H. G. & Munder, P. G. (1991). Antitumor Activity of Ilmofosine (BM41.440) in the 3Lewis-Lung Carcinoma Model, *Lipids*, *26*, 1431-1436.

[71] Lohmeyer, M. & Workman, P. (1995). Growth arrest *versus* Direct Cytotoxicity and the Improvement Molecular Structure for the *In vitro* Anti-tumor Activity of Ether Lipids, *Br. J. Cancer*, *72*, 277- 286.

[72] Ruiter, G. A., Verheij, M., Zerp, S. F. & Van Blitterwijk, W. J. (2001). Alkyl-lysophospholipid as Anticancer Agents and Enhancers of Radiation-induced Apoptosis, *Int. J. Rad. Oncol. Biol. Phys*, *49*, 415- 419.

[73] Andreessen, R., Modollel, M., Weltzien, H. U., Eibl, H., Common, H., Lohr, W. & Munder, P. G. (1978). Selective Destruction of Human Leukemic Cells by Alkyl-lysophospholipids, *Cancer Res.*, *38*, 3894- 3899.

[74] Berdel, W. E., Fromm, M., Fink, U., Phalke, W., Bicker, U., Reichert, A. & Rastetter, J. (1983). Cytotoxicity of Thioether-lysophospholipids in Leukemias and Tumors of Human Origin, *Cancer Res.*, *43*, 5538- 5543.

[75] Newmann, H. A., Hermannn, D. B. & Boerner, D. (1987). Inhibition of Human Tumor Colony formation by the new Alkyl-lysophospholipid Ilmofosine, *J. Natl. Cancer Inst.*, *78*, 1087-1093.

[76] Girgert, R., Schweizer, P., Bock, I., Norr, R. & Bruchelt, G. (1995). Cytotoxicity of Ether Phospholipid BM41.440 on Neuroblastoma Cells, *J. Cancer Res. Clin. Oncol.*, *121*, 262-266.

[77] Skala, J. P., Rogers, P. C., Chan, K. W., Khangura, S. S. & Rodriguez, W. C. (1992). *In vitro* Effects of Ilmofosine on Acute Lymphoblastic Leukemia Cells and on Normal Hemopoietic Cells, *Prog. Clin. Biol. Res.*, *377*, 63-69.

[78] Hanauske, A. R., Degen, D., Marshall, M. H., Hilsenbeck, S. G., McPhillips, J. J. & Von Hoff, D. D. (1992). Preclinical Activity of Ilmofosine Against Human Tumor Colony Forming Units *in vitro*, *Anticancer Drugs*, *3*, 43-46.

[79] Hermann, D. B., Pahlke, W., Opitz, H. G. & Bicker, U. (1990). *In vivo* Antitumor Activity of Ilmofosine, *Cancer Trat. Rev.*, *17*, 247-252.

[80] Giantonio, B. J., Derry, C., McAleer, C., McPhillips, J. J. & O'Dwyer, P. J. (2004). Phase I and Pharmacokinetics Study of the Cytotoxic Ether Lipid Ilmofosine administered by weekly Two-hour Infusion in Patients with Advanced Solid Tumors, *Clin. Cancer Res.*, *10*, 1282-1288.

[81] Von Mchren, M., Giantonio, B. J., McAleer, C., Schilder, R., McPhillips, J. & O'Dwyer, P. J. (1995). Phase I Trial of Ilmofosine As a 24 hour Infusion Weekly, *Investig. New Drugs*, *13*, 205-210.

[82] Woolley, P. V., Schultz, C. J., Rodriguez, G. I., Gams, R. A., Rowe, Jr. K. W., Dadey, M. L., VonHoff, D. D. & McPhillips, J. J. (1996). A Phase II trial of Ilmofosine on non-small cell Bronchogenic Carcinoma, *Investig. New Drugs*, *14*, 219-222.

[83] Winkelman, M., Ebeling, K., Strohmeyer, G., Hottenrott, G., Mechl, Z., Berges, W., Schotton, T., Westerhausen, M., Schlimok, G. & Sterz, R. (1992). Treatment Results of the Thioether Lipid Ilmofosine in Patients with Malignant Tumors, *J. Cancer Res. Clin. Oncol.*, *118*, 405-407.

[84] Dasmahapatra, G. P., Didolkar, P., Alley, M. C., Ghosh, S., Sausville, E. A. & Roy, K. K. (2004). *In vitro* combination treatment with Perifosine and UCN-01 Demonstrates Synergism Against Prostate (PC-3) and Lung (A549) Epithelial Adenocarcinoma Cell Lines,*Clin. Cancer Res.*, *10*, 5242-5252.

[85] Li, X., Luwor, R., Lu, Y., Liang, K. & Fan, Z. (2006). Enhancement of Antitumor Activity of the Anti-EGF Receptor Monoclonal Antibody Cetuximab/C225 by Perifosine in PTEN-deficient Cancer Cells *Oncogene*, *25*, 525-535.

[86] Rahmani; M., Reese, E. & Dai, Y. (2005). Coadministration of Histone Deacetylose inhibitors and Perifosine Synergistically induces Apoptosis in Human Leukemia Cells through AKt and ERK1/2 Inactivation and the Generation of Ceramide and Reactive Oxygen Species, *Cancer Res.*, *65*, 2422-2432.

[87] Nyakern, M., Cappellini, A., Mantovani, I. & Martelli, A. M. (2006). Synergistic Induction of Apoptosis in Human Leukemia T Cells by The AKt inhibitor Perifosine and Etoposide through Activation of Intrinsic and Fas-mediated Extrinsic Cell Death Pathways, *Mol. Cancer Ther.*, *5*, 1559-1570.

[88] Momota, H., Nerio, E. & Holland, E. C. (2005). Perifosine Inhibits Multiple Signaling Pathways Inglial Progenitors and Cooperates with Temozolomide to Arrest Cell Proliferation in Gliomas *in vivo, Cancer Res.*, *65*, 7429-7435.

[89] Hideshima, T., Catley, L. & Yasui, H. (2006). Perifosine, an Oral Bioactive novel Alkylphospholipid Inhibits AKt and Induces *In vitro* and *In vivo* Cytotoxicity in Human Multiple Myeloma Cells, *Blood*, *107*, 4053-4062.

[90] Vink, S. R., Lagerwerf, S. & Mesman, E. (2006). Radiosensitization of Squamous Cell Carcinoma by the Alkylphospholipid Perifosine in Cell Culture and Xenografts, *Clin. Cancer Res*, *12*, 1615-1622.

[91] Vink, S. R., Schellens, J. H. & Beijinen, J. H. (2006). Phase I and Pharmacokinetics Study of Combined Treatment with Perifosine and Radiation in Patients with Advanced Solid Tumors, *Radiother. Oncol.*, *80*, 207-2010.

[92] Vink, S. R., Van Blitterswijk, W. J., Schellens, J. H. & Verheij, M. (2007). Rationale and Clinical Application of Alkylphospholipid Analogues in Combination with Radiotherapy, *Cancer Treat Rev.*, *33*, 191-202.

[93] Van der Luit, A. H., Budde, M., Ruurs, P., Verheij, M. & van Blittterswijk, W. J. (2002). Alkyl-lysophospholipids Accumulates in Lipid Rafts and Induces Apoptosis via Raft-Dependent Endocytosis and Inhibition of Phosphotidylcholine Synthesis, *J. Biol. Chem.*, *277*, 39541-39547.

[94] Mattjus, P., Bittman, R. & Slotte, J. P. (1996). Molecular Interactions and Lateral Domain Formation in Monolayers containing Cholesterol and Phosphatidylcholines with Acyl- or Alkyl-linked C16 Chains, *Langmuir*, *12*, 1284-1290.

[95] Heczkova, B. & Slott, J. P. (2006). Effect of Anti-tumor Ether Lipids on Ordered Domains in Model Membranes, *FEBS Lett.*, *580*, 2471-2476.

[96] Van der Luit, A. H., Vink, S. R., Klarenbeek, J. B., Perrissoud, D., Solary, E., Verheij, M. & van Blitterswijk, W. J. (2007). A New Class of Anti-cancer Alkylphospholipids Uses Lipid Rafts as Membrane Gateways to Induce Apoptosis in Lymphoma Cells, *Mol. Cancer Ther.*, *6*, 2337-2345.

[97] Vink, S. R., Schellens, J. H., van Blitterswijk, W. J. & Verh, M. (2005). Tumor and Normal Tissue Pharmacokinetics of Perifosine, An Anti-cancer Alkylphospholipid, *Invest. New Drugs*, *23*, 279-286.

[98] Poulos, A., Bankier, A., Beekman, K., Johnson, D., Robertson, E. F., Sharp, P., Sheffield, L., Singh, H., Usher, S. & Wise, G. (1991). Glyceryl Ethers in Peroxisomal Disease., *Clin. Genet.*, *39*, 13- 25.

[99] Brosius, U. & Gartner, J. (2002). Cellular and Molecular Aspects of Zellweger Syndrome and other Peroxisome Biogenesis Disorders, *Cell Mol. Life Sci.*, *59*, 1058-1069.

[100] Moser, A. B., Kreiter, N., Bezman, L., Lu, S., Raymond, G. V., Naidu, S. & Mooser, H. W. (1999). Plasma Very Long Chain Fatty Acids in 3000 Peroxisome Disease Patients and 29,000 Controls, *Ann. Neurol.*, *45*, 100-110.

[101] Hanson, R. F., Szczepanik-VanLeeuwen, P., Williams, G. C., Grabwski, G. & Sharp, H. L. (1979). Defects of Bile Acid Synthesis in Zellwegr's Syndrome, *Science*, *203*, 1107-1108.

[102] Weller, S., Gould, S. G. & Valle, D. (2003). Peroxisome Biogenesis Disorders, *Annu. Rev. Genomics Hum. Genet.*, *4*, 165-211.

[103] Mihalik, S. J., Morrell, J. C., Kim, D., Sackstedar, K. A., Watkins, P. A. & Gould, S. J. (1997). Identification of PAHX, a Refsum Disease Gene, *Nat. Genet.*, *17*, 185-189.

[104] Jansen, G. A., Ofman, R., Ferdinandusse, S., Ijlst, L., Muijsers, A. O. & Skjldal, O. H. (1999). Refsum Disease is Caused by Mutations in The Phytanoyl-CoA Hydroxylase Gene, *Nat. Genet.*, *17*, 190-193.

[105] Moser, H. W. (1997). Adrenoleukodystrophy: Phenotype, Genetics, Pathogenesis, and Therapy, *Brain*, *120*, 1485-1508.

[106] Dubois-Dalcq, M., Feignebaum, V. & Aubourg, P. (1999). The Neurobiology of X-linked Adrenoleukodystrophy, a Demyelinating Peroxisomal Disorder, *Trends Neurosci.*, *22*, 4-12.

[107] Ginsberg, L., Rafique, S., Xuereb, J. H., Rapoport, S. I. & Gershfeld, N. L. (1995). Disease and Anatomic Specificity of Ethanolamine Plasmalogen Deficiency in Alzheimer's Disease Brain, *Brain Res.*, *698*, 223-226.

[108] Han, X. (2005). Lipid Alterations in the Earliest Clinically Recognizable Stage of Alzheimer's Disease, *Curr. Alzheimer Res.*, *2*, 65-77.

[109] Brites, P., Waterham, H. R. & Wanders, R. J. (2004). Functions and Biosynthesis of Plasmalogens in Health and Disease, *Biochim. Biophys. Acta*, *1636*, 219-231.

[110] Goodenowe, D. B., Cook, L. L., Liu, J., Lu, Y., Jayasinghe, D. A., Ahiahonu, P. W. K., Heath, D., Yamazaki, Y., Flax, J., Krenitsky, K. F., Sparks, D. L., Lerner, A., Friedland, R. P., Kudo, T., Kamino, K., Morihara, T., Takeda, M. & Wood, P. L. (2007). Peripheral Ethanolamine Plasmalogen Deficiency: A Logical Causative Factor in Alzheimer's Disease and Dementia, *J. Lipid Res.*, *48*, 2485-2498.

[111] Fontech, A. N. & Chitton, F. H. (1992). Rapid Remodeling of Arachidonate from Phosphatidylcholine to Phosphatidylethanolamine Pools During Mast Cell Activation, *J. Immunol.*, *148*, 1784-1791.

[112] Snyder, F., Lee, T. C. & Blank, M. L. (1997). Plasmalogens: Their Metabolism and Central Role in the Production of Lipid Mediators, In : (R. W. Gross, Ed), *Advances in Lipobiology*, Jai Press, Stanford, CT, *Vol. 2*, 261-286.

[113] Glasser, P. E. & Gross, R. W. (1994). Plasmenylethanolamine Facilitates Rapid Membrane Fusion: A Stopped-Flow Kinetic Investigation Correlating the Propensity of Major Plasma Membrane Constituent to Adopt an HII Phase with its Ability to Promote Membrane Fusion, *Biochemistry*, *33*, 5805-5812.

[114] Thompson, D. H., Gerasimov, O. V., Wheeler, J. J., Rui, Y. J. & Anderson, V. C. (1996). Triggerable Plasmalogen Liposomes: Improvement of System Efficiency, *Biochim. Biophys. Acta*, *1279*, 25-34.

[115] Murphy, R. C. (2001). Free Radical-induced Oxidation of Arachidonoyl Plasmalogen Phospholipids: Antioxidant Mechanism and Precursor Pathway for Bioactive Eicosanoids, *Chem. Res. Toxicol., 14*, 463-472.

[116] Gerasimov, O. V., Schwan, A. & Thompson, D. H. (1997). Acid-catalyzed Plasmenylcholine Hydrolysis and its Effect on Bilayer Permeability: A Quantitative Study, *Biochim. Biophys. Acta, 1324*, 200-214.

[117] Rui, Y. J., Wang, S., Low, P. S. & Thompson, D. H. (1998). Diplasmenylcholine-Folate Liposomes: An Efficient Vehicle for Intracellular Drug Delivery, *J. Am. Chem. Soc, 120*, 11213-11218.

[118] Shin, J., Qualls, M. M., Boomer, J. A., Robarge, J. & Thompson, D. H. (2001). Efficient New Route to Plasmenyl-type Lipids: Synthesis and Cytotoxicity of a Plasmenylcholine Analogue of the Antitumor Ether Lipid ET-18-OMe, *J. Am. Chem. Soc., 123*, 508- 509.

[119] Boomer, J. A., Thompson, D. H. & Sullivan, S. M. (2002). Formation of Plasmid-based Transfection Complexes with an Acid- Labile Cationic Lipid: Characterization of *In vitro* and *In vivo* Gene Transfer, *Pharm. Res., 19*, 1292-1301.

[120] Boomer, J. A., Inerowicz, H. D., Zang, Z. Y., Bergstand, N., Edwards, K., Kim, J. M. & Thompson, D. H. (2003). Acid Triggered Release from Sterically-stabilized Fusogenic Vesicles: A Novel DePEGylation Strategy, *Langmuir, 19*, 6408-6415.

[121] Thompson, D. H., Inerowicz, H. D., Grove, J. & Sarna, T. (2003). Characterization of Plasmalogen Photooxidation Products, *Phytochem. Photobiol., 78*, 323-330.

[122] Zhang, Z. Y., Shum, P., Yates, M., Messersmith, P. B. & Thompson, D. H. (2002). Formation of Fibrinogen-based Hydrogels using Phototriggerable Diplasmalogen Liposomes, *Bioconj. Chem., 13*, 640-646.

[123] Rui, Y. & Thompson, D. H. (1996). Efficient Stereoselective Synthesis of Plasmenylcholines, *Chem. Eur. J., 2*, 1505-1508.

[124] Rui, Y. & Thompson, D. H. (1994). Stereocontrolled Synthesis of Plasmalogen-type Lipids from Glyceryl Ester Precursors, *J. Org. Chem., 59*, 5758-5762.

[125] Qin, D. H., Byun, H. S. & Bittman, R. (1999). Synthesis of Plasmalogen via 2, 3-Bis-*O*-(4'-methoxybenzyl)-*Sn*-glycerol, *J. Am. Chem. Soc., 121*, 662-668.

[126] Thompson, D. H., Shin, J., Boomer, J. & Kim, J. M. (2004). Preparation of Plasmenylcholine Lipids and Plasmenyl-type Liposome Dispersions, *Methods in Enzymol., 387*, 153-168.

[127] Bossche, J. V., Shin, J. & Thompson, D. H. (2007). Improved Plasmalogen Synthesis using Organobarium Intermediates, *J. Org. Chem., 72*, 5005-5007.

[128] Glass, C. K. & Witztum, J. L. (2001). Atherosclerosis: The Road Ahead, *Cell, 23*, 503-516.

[129] Butterfield, D. A. & Lauderback, C. M. (2002). Lipid Peroxidation and Protein Oxidation in Alzheimer's Disease Brain: Potential Causes and Consequences Involving Amyloid Peptide-associated Free Radical Oxidative Stress, *Free Radical Biol. Med, 32*, 1050-1060.

[130] a) Zoeller, R. A., Morand, O. H. & Raetz, C. R. H. (1988). A Possible Role for Plasmalogens in Protecting Animal Cells Against Photosensitized Killing, *J. Biol. Chem. 263*, 11590-11596. (b) Morand, O. H., Zoeller, R. A. & Raetz, C. R. H. (1988). Disappearance of Plasmalogens from Membranes of Animal Cells Subjected to Photosensitized Oxidation, *J. Biol. Chem., 263*, 11597-11606.

[131] Engelmann, B., Brauigam, C. & Thiery, J. (1994). Plasmalogen Phospholipids as Potential Protectors Against Lipid Peroxidation of Low Density Lipoproteins, *Biochem. Biophys. Res. Commun*, *204*, 1235-1242.

[132] Reiss, D., Beyer, K. & Engelmann, B. (1997). Delayed Oxidative Degradation of Polyunsaturated Diacyl Phospholipids in the Presence of Plasmalogen Phospholipids, *Biochem. J*, *323*, 807-814.

[133] Hahnel, D., Huber, T., Kurze, V., Beyer, K. & Engelmann, B. (1999). Contribution of Copper Binding to the Inhibition of Lipid Oxidation by Plasmalogen Phospholipids, *Biochem. J*, *340*, 377-383.

[134] Hahnel, D., Beyer, K. & Engelmann, B. (1999). Inhibition of Peroxyl Radical–mediated Lipid Oxidation by Plasmalogen Phospholipids and α-Tocopherol, *Free Radical Biol. Med*, *27*, 1087-1094.

[135] Zoeller, R. A., Lake, A. C., Nagan, N., Gaposchkin, D. P., Legner, M. A. & Lieberthal, W. (1999). Plasmalogens as Endogenous Antioxidants: Somatic Cell Mutants Reveal the Importance of the Vinyl Ether. *Biochem. J*, *338*, 769-776.

[136] Farooqui, A. A. & Horrocks, L. A. (2001). Plasmalogens: Workhorse Lipids of Membranes in Normal and Injured Neurons and Gila, *Neuroscientist*, *7*, 232-245.

[137] Nagan, N. & Zoeller, R. A. (2001). Plasmalogens: Biosynthesis and Functions, *Prog. Lipid Res.*, *40*, 199-229.

[138] Zieseniss, S., Zahler, S., Müller, I., Hermetter, A. & Engelmann, B. (2001). Modified Phosphatidylethanolamine as the Active Component of Oxidized Low Density Lipoprotein Promoting Platelet Prothrombinase Activity, *J. Biol. Chem.*, *276*, 19828-19835.

[139] Maeba, R. & Ueta, N. (2004). A Novel Antioxidant Action of Ethanolamine Plasmalogens in Lowering the Oxidizability of Membranes, *Biochem. Soc. Trans.*, *32*, 141-143.

[140] Sweely, C. C. (1991). In: (D. E. Vance, & J. E. Vance, Eds.), Biochemistry of Lipids, Lipoproteins, and Membranes, Benjamin/Elsevier, Amsterdam.

[141] a) Kolter, T. & Sandhoff, K. (1999). Sphingolipde-ihre Stoffwechselwege und die Pathobiochemie Neurodegenerativer Erkrankunge, *Angew. Chem.*, *111*, 1633-1670. (b) Kolter, T. & Sandhoff, K. (1999). Sphingolipids -Their Metabolic Pathways and the Pathobiochemistry of Neurodegenerative Diseases, *Angew. Chem. Int. Ed*, *38*, 1532-568.

[142] Hakomori, S. I. (1993). Structure and functions of Sphingoglycolipids in Transmembrane Signaling and Cell-cell Interactions, *Biochem. Soc. Trans.*, *21*, 583-595.

[143] Varki, A. (1993). Biological Roles of Oligosaccharides: All of the Theories are Correct, *Glycobiology*, *3*, 97-130.

[144] Hannun, Y. A. (1996). Functions of Ceramide in Coordinating Cellular Responses to Stress, *Science*, *274*, 1855-1859.

[145] Wertz, P. W. & Bergh, B. V. D. (1998). The Physical, Chemical, and Functional Properties of Lipids in the Skin and other Biological Barriers, *Chem. Phys. Lipids*, *91*, 85-96.

[146] Livingston, P. O. (1995). Approaches to Augmenting the Immunogenicity of Melanoma Gangliosides: From Whole Melanoma Cells to Ganglioside-KLH Conjugate Vaccines, *Immunol Rev.*, *145*, 147-166.

[147] Kopitz, J. (1997). In: (H. J. Gabins, & S. Gabins, Eds.). Glycosciences, Chapman & Hall, Weinheim, 153-189.

[148] Beutler, E. & Grabowski, G. (Eds.) (1995), *Gaucher Disease*, McGrawHill, New York, 2641-2670.

[149] Barton, N. W. (1990). Therapeutic Response to Intravenous Infusion of Glucocerebrosidase in a Patient with Gaucher Disease, *Proc. Natl. Acad. Sci. USA*, *87*, 1913-1916.

[150] Cox, T. M. (1994). Therapeutic Advances in Gaucher's disease: A Model for the Treatment of Lysosomal Storage Diseases, *Trends Exp. Clin. Med.*, *4*, 144-160.

[151] Grabowski, G. A., Barton, N. W., Pasteros, G., Dambrosia, J. M., Banerjee, T. K., McKee, M. A., Parker, C., Schiffmann, R., Hill, S. C. & Brady, R. O. (1995). Enzyme Therapy in Type1 Gaucher Disease: Comparative Efficacy of Mannose-terminated Glucocerebrosidase from Natural and Recombinant Sources, *Ann Intern. Med.*, *122*, 33-39.

[152] Hannun, Y. A., Luberto, C. & Argraves, K. M. (2001). Enzymes of Sphingolipids Metabolism: From Modular to Integrative Signaling, *Biochemistry*, *40*, 4893-4903.

[153] Kolesnick, R. N. & Kronke, M. (1998). Regulation of Ceramide Production and Apoptosis, *Annu. Rev. Physiol.*, *60*, 643-665.

[154] Pettus, B. J., Chalfant, C. E. & Hannun, Y.A. (2002). Ceramide in Apoptosis: an Overview and Current Perspectives, *Biochim. Biophys. Acta*, *1585*, 114-125.

[155] Ogretman, B. & Hannun, Y. A. (2001). Updates on Functions of Ceramide in Chemotherapy-induced Cell Death and in Multidrug Resistance, *Drug Resist. Update*, *4*, 368-377.

[156] Jarvis, W. D. & Grant, S. (1998). The Role of Ceramide in the Cellular Response to Cytotoxic Agents, *Curr. Opin. Oncol*, *10*, 552-559.

[157] Bittman, R. (2004). Applications of Novel Synthetic Lipids to Biological Problems, *Chem. Phys. Lipids*, *129*, 111-131.

CELL BIOLOGY RESEARCH PROGRESS

LIPIDS: CATEGORIES, BIOLOGICAL FUNCTIONS AND METABOLISM, NUTRITION AND HEALTH

PAIGE L. GILMORE
EDITOR

Nova Science Publishers, Inc.
New York