Biochimica et Biophysica Acta 1859 (2017) 1657–1667

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbamem

Book Review

Alkylphospholipids: An update on molecular mechanisms and clinical relevance☆·☆☆

Pablo Ríos-Marco, Carmen Marco, Xiomara Gálvez, José M. Jiménez-López *, María P. Carrasco *

Department of Biochemistry and Molecular Biology I, Faculty of Sciences, University of Granada, Av. Fuentenueva s/n, Granada 18001, Spain

ARTICLE INFO

Article history:
Received 17 December 2016
Received in revised form 20 February 2017
Accepted 21 February 2017
Available online 24 February 2017

Keywords:
Alkylphospholipid
Antitumour lipid
Antitumour therapy
Antileishmanial activity

ABSTRACT

Alkylphospholipids (APLs) represent a new class of drugs which do not interact directly with DNA but act on the cell membrane where they accumulate and interfere with lipid metabolism and signalling pathways. This review summarizes the mode of action at the molecular level of these compounds. In this sense, a diversity of mechanisms has been suggested to explain the actions of clinically-relevant APLs, in particular, in cancer treatment. One consistently reported finding is that APLs reduce the biosynthesis of phosphatidylcholine (PC) by inhibiting the rate-limiting enzyme CTP:phosphocholine cytidylyltransferase (CT). APLs also alter intracellular cholesterol traffic and metabolism in human tumour-cell lines, leading to an accumulation of cholesterol inside the cell. An increase in cholesterol biosynthesis associated with a decrease in the synthesis of choline-containing phospholipids and cholesterol esterification leads to a change in the free-cholesterol:PC ratio in cells exposed to APLs. Akt phosphorylation status after APL exposure shows that this critical regulator for cell survival is modulated by changes in cholesterol levels induced in the plasma membrane by these lipid analogues. Furthermore, APLs produce cell ultrastructural alterations with an abundant autophagic vesicles and autolysosomes in treated cells, indicating an interference of autophagy process after APL exposure. Thus, antitumoural APLs interfere with the proliferation of tumour cells via a complex mechanism involving phospholipid and cholesterol metabolism, interfere with lipid-dependent survival-signalling pathways and autophagy. Although APLs also exert antiparasitic, antibacterial, and antifungal effects, in this review we provide a summary of the antileishmanial activity of these lipid analogues. This article is part of a Special Issue entitled: Membrane Lipid Therapy: Drugs Targeting Biomembranes edited by Pablo V. Escribá.

Contents

Abbreviations: 4E-BP1, eIF-4E-binding protein 1; APL, alkylphospholipid; CE, cholesteryl esters; CL, cutaneous leishmaniasis; CQ, chloroquine; CT, CTP:phosphocholine cytidylyltransferase; ER, endoplasmic reticulum; ErPC, erucylphosphocholine; ErPC3, erufosine; HePC, hexadecylphosphocholine; LDL, low-density lipoprotein; mTORC2, mTOR/rictor complex; myr-Akt, myristoylated form of Akt; NPC, Niemann-Pick type C; PC, phosphatidylcholine; PDK1, 3-phosphoinositide-dependent kinase 1; PE, phosphatidylethanolamine; PI3K, phosphoinositide 3-kinase; PIP2, phosphatidylinositol 4,5-bisphosphate; PIP3, phosphatidylinositol 3,4,5-trisphosphate; PTEN, phosphatase and tensin homolog deleted on chromosome ten; ROS, reactive oxygen species; RTK, receptor tyrosine kinase; S6K1, ribosomal protein S6 kinase; SM, sphingomyelin; SMase, sphingomyelinase; VL, visceral leishmaniasis.

☆ URL: http://www.ugr.es/~bbm1/.

☆☆ This article is part of a Special Issue entitled: Membrane Lipid Therapy: Drugs Targeting Biomembranes edited by Pablo V. Escribá.

* Corresponding authors.
E-mail addresses: jmajimen@ugr.es (J.M. Jiménez-López), mpazcj@ugr.es (M.P. Carrasco).

http://dx.doi.org/10.1016/j.bbamem.2017.02.016

1. Introduction

Synthetic alkylphospholipids (APLs) are new anticancer drugs with antiproliferative properties, which are chemically divided into two main classes: alkyl-lysophospholipids and alkylphosphocholines. The group of antitumour lipids also includes the glycosylated antitumour ether lipids and glycosidated phospholipids, the two distinguished by the presence of a sugar moiety. Molecular mechanisms of anticancer activity of these compounds have been described and extensively discussed in some recent reviews [1–7]. It is proposed that these chemotherapeutic agents interfere with lipid homeostasis due to their similarity with endogenous phospholipids, targeting membrane lipid rafts and altering lipid-linked signalling, hence leading to apoptosis.

This review updates the main APL applications investigated so far and the ongoing evaluation of action mechanisms proposed in order to explain their broad spectrum of pharmacological effects. The unique mode of action of APLs on cell membranes gives these lipid analogues an advantage over conventional DNA-interacting chemotherapeutic agents. The action of the lipid analogues appears to be specific for tumour cells, and both cellular uptake and APL-induced apoptosis are increased in the malignant state of the cells [7], currently being explored in combination therapy to overcome or prevent resistance mechanisms during cancer treatment.

Initial efforts were made to synthesize metabolically stable lysophosphatidylcholine analogues that work as immune modulators with potential anti-neoplastic activity. Until now, compounds such as edelfosine, ilmofosine, miltefosine, and perifosine (Fig. 1) have been tested for their selective antitumour activity in phase I and II clinical trials for many types of advanced cancers. The ether lipid edelfosine (1-*O*-octadecyl-2-*O*-methylglycero-3-phosphocholine) is considered to be the alkyl-lysophospholipid prototype compound, whereas miltefosine (hexadecylphosphocholine, HePC) is the prototype of alkylphosphocholines. Ilmofosine (1-hexadecylthio-2-methoxymethyl-*rac*-glycero-3-phosphocholine) is a thioether variant of edelfosine, and in the drug candidate perifosine [octadecyl-(1,1-dimethyl-piperidinio-4-yl)-phosphate] the choline moiety of alkylphosphocholines is substituted by a heterocyclic piperidine group. Encouraging results have been found with all these compounds, and novel promising analogues such as erucylphosphocholine (ErPC) and its homocholine analogue erufosine (ErPC3) (Fig. 1) also hold promise as a single-agent (monotherapy) or in combination regimens.

2. Single-agent alkylphospholipid chemotherapy in advanced cancer

2.1. Edelfosine and ilmofosine

Edelfosine was initially considered a promising novel compound owing to its immunomodulatory properties and inhibitory activity on tumour-cell proliferation. However, its clinical application has been limited due mainly to its metabolic instability and lack of sensitivity, high hemolytic potential, and gastrointestinal toxicity [4]. Thus, intravenous and oral treatment with edelfosine has been used only for bone-marrow

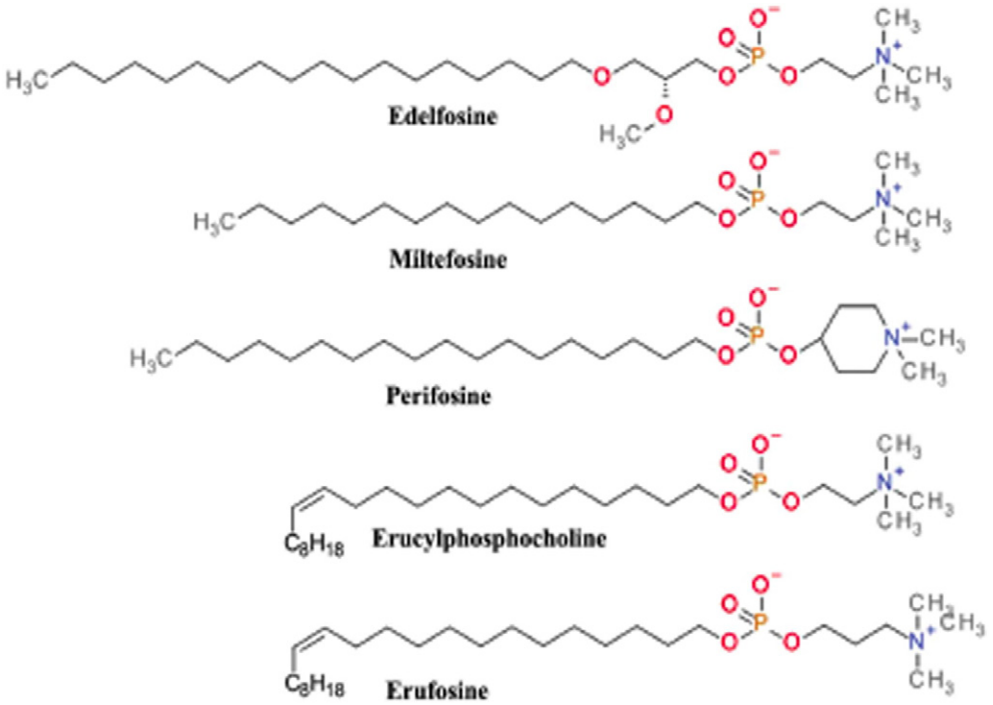

Fig. 1. Chemical structure of synthetic alkylphospholipids. The structures were taken from Nitulescu et al. [140].