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Anti-tumor activities of lipids and lipid analogues and their development as potential anticancer drugs

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ABSTRACT

Lipids have the potential for development as anticancer agents. Endogenous membrane lipids, such as ceramides and certain saturated fatty acids, have been found to modulate the viability of tumor cells. In addition, many tumors over-express cyclooxygenase, lipoxygenase or cytochrome P450 enzymes that mediate the biotransformation of ω−6 polyunsaturated fatty acids (PUFAs) to potent eicosanoid regulators of tumor cell proliferation and cell death. In contrast, several analogous products from the biotransformation of ω−3 PUFAs impair particular tumorigenic pathways. For example, the ω−3 17,18-epoxide of eicosapentaenoic acid activates anti-proliferative and proapoptotic signaling cascades in tumor cells and the lipoxygenase-derived resolvins are effective inhibitors of inflammatory pathways that may drive tumor expansion. However, the development of potential anti-cancer drugs based on these molecules is complex, with in vivo stability a major issue. Nevertheless, recent successes with the antitumor alkyl phospholipids, which are synthetic analogues of naturally-occurring membrane phospholipid esters, have provided the impetus for development of further molecules. The alkyl phospholipids have been tested against a range of cancers and show considerable activity against skin cancers and certain leukemias. Very recently, it has been shown that combination strategies, in which alkyl phospholipids are used in conjunction with established anticancer agents, are promising new therapeutic approaches. In future, the evaluation of new lipid-based molecules in single-agent and combination treatments may also be assessed. This could provide a range of important treatment options in the management of advanced and metastatic cancer.

Contents

Abbreviations: Akt, protein kinase B; ALP, alkyl phospholipid; CDK, cyclin-dependent kinase; COX, cyclooxygenase; CYP, cytochrome P450; DHA, docosahexaenoic acid; DISC, death-inducing signaling complex; EET, epoxyeicosatrienoic acid; EPA, eicosapentaenoic acid; ERK, extracellular signal-regulated kinase; FAK, focal adhesion kinase; HETE, hydroxyeicosatetraenoic acid; HPETE, hydroperoxyeicosatetraenoic acid; LOX, lipoxygenase; LT, leukotriene; MAPK, mitogen-activated protein kinase; PG, prostaglandin; PI3K, phosphoinositide 3-kinase; PPAR, peroxisome proliferator-activated receptor; PUFA, polyunsaturated fatty acid; ROS, reactive oxygen species; TTA, tetradecylthioacetic acid; TRAIL, TNF-related apoptosis-inducing ligand; VEGF, vascular endothelial growth factor; WM, Waldenström's macroglobulinemia.

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1. Introduction

In recent years cancer drug development has undergone fundamental changes in which there has been a shift away from non-specific cytotoxic agents in favor of more selective agents that target dysregulated pathways in cancer cells. By this approach a number of molecules that inhibit tyrosine and other kinases that are overactive in tumor cells have already become clinically indispensible. For example, imatinib targets the bcr-abl and c-kit tyrosine kinases that are aberrantly expressed in acute myelogenous leukemia and gastrointestinal stromal tumors, and sorafenib targets the Raf/MEK/ERK- and vascular endothelial growth factor (VEGF) receptor-linked cascades that are over-expressed in renal and hepatocellular carcinomas (Heinrich et al., 2003; Druker et al., 2006; Escudier et al., 2007; Llovet et al., 2008). In general, these agents are much better tolerated and exhibit fewer adverse effects than the more established, but non-specific, cytotoxic anticancer drugs. However, there is an ongoing need for the development of further well-tolerated targeted molecules to provide additional options in cancer chemotherapy. Whether used as single agents or in combination with other anticancer drugs, such agents can be used to develop novel cancer treatment regimen, especially in advanced disease.

There is accumulating evidence that many lipids and lipid analogues are critical regulators of tumorigenesis. Much of this information has emerged from investigations that have been undertaken in vitro in tumor cells or in vivo in experimental animals after dietary conditioning and using tumor cell xenografts. The exploitation of such molecules in cancer therapy is at an early stage, but some show considerable promise. In considering which lipid-based molecules might be developed it is important to derive mechanistic information that underpins their anticancer actions. However, there are also particular issues that arise with lipid-based drugs. Although the biological properties of certain molecules have appeared promising, and could be captured in novel cancer therapeutics, relatively few have made it through the drug development process because of chemical instability, rapid metabolism in vivo and, in some cases, the incidence of side effects. For example, a number of synthetic prostaglandin (PG) analogues have previously been developed as potential antiulcer, antihypertensive and fertility control agents (Collins & Djuric, 1993). Some have reached advanced trials or have even entered clinical use, but their application has been limited somewhat by adverse effects that are often extensions of the activity of the corresponding naturally-occurring prostanoids. Nevertheless, particularly in the area of cancer chemotherapy, several lipid-based agents have emerged that offer promise as effective antitumor agents. This review focuses on the roles of lipids and their analogues in the regulation of tumorigenesis. Existing lipid-based agents that are used in cancer chemotherapy and others that have the potential for development as clinically useful molecules are also discussed.

2. The control of cell growth and cell death

2.1. The cell cycle regulates cell proliferation and mitogenesis

An appreciation of the mechanisms by which lipids and their metabolites regulate tumorigenic processes requires background information on the growth and dissemination of cancer cells. Cancer is a multistage process in which cells develop the capacity for unregulated proliferation, become resistant to proapoptotic stresses that kill normal cells, and acquire the ability to migrate to adjacent and distant tissues to establish secondary metastases.

The cell cycle describes the sequence of events between successive rounds of mitosis by which cells proliferate. Most mammalian cells are quiescent in G_0 phase but may re-enter the cell cycle in G_1 phase in response to mitogenic stimulation (Zetterberg & Larsson, 1985). During mitogenesis cyclins and their associated cyclin-dependent kinases (CDKs) are activated in a coordinated fashion to regulate gene transcription and cell replication. The activities of cyclin/CDK complexes are also modulated by interactions with antiproliferative CDK-inhibitors, including $p21^{Cip1}$, $p27^{Kip1}$ and the INK4 proteins ($p16^{INK4a}$, $p15^{INK4b}$, $p18^{INK4c}$ and $p19^{INK4d}$) (Malumbres & Barbacid, 2001). DNA synthesis occurs in S-phase, which is followed by G_2 phase, in which the cell prepares for mitosis (M phase). Cell cycle regulatory genes are subject to mutation in cancers and the amplification or dysregulation of cyclins, CDKs and CDK-inhibitors is common (Vermeulen et al., 2003). Over-activation of cyclin–CDK complexes results in unregulated gene transcription and increased rates of mitogenesis (Williams & Stoeber, 2012).

2.2. Signaling pathways and cell proliferation

Several signaling cascades have important roles in the regulation of cell growth and survival. The proliferative extracellular signal-regulated kinase (ERK), which is a member of the mitogen-activated protein kinases (MAPKs), is activated by growth factors, hormones and chemokines that are ligands for the corresponding growth factor, cytokine and chemokine receptors (Tilton et al., 2000; Roberts & Der, 2007; Fig. 1A). Mitogenic stimuli trigger the translocation of activated ERK from the cytoplasm to the nucleus, which then stimulates the formation of active cyclin D1–CDK4/6 complexes (Chambard et al., 2007).

The phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) pathway is also activated by growth factors and hormones and promotes cell survival (Fig. 1A). Indeed, full induction of cyclin D1 by mitogens requires the participation of both PI3K/Akt and ERK pathways (Sherr & Roberts, 1999). Other downstream targets for PI3K/Akt include kinases, such as glycogen synthase kinase-3, and transcription factors, like the NF-κB/IκB complex (Reddy et al., 2000). Akt regulates cell proliferation by targeting the CDK-inhibitors $p21^{Cip1}$ and $p27^{Kip1}$, and cell survival by direct inhibition of pro-apoptotic mediators like Bad, Bim and procaspase-9.

NF-κB is normally present in the cell cytoplasm as an inactive complex bound to inhibitory proteins of the IκB family, but IκB may be dissociated by a variety of stimuli, including infection, proinflammatory cytokines, mitogens and growth factors, and reactive oxygen species (ROS) (Viatour et al., 2005; Gloire et al., 2006). Dissociation of IκB activates NF-κB and modulates cell proliferation and survival by activating the expression of cyclin D1 and the anti-apoptotic bcl-xL and bcl-2 (Guttridge et al., 1999; Piva et al., 2006; Fig. 1A).

2.3. Cell death pathways

The most studied mechanism of programmed cell death is apoptosis, which occurs along the so-called intrinsic and extrinsic pathways. The intrinsic, or mitochondrial, pathway is activated by intracellular stress signals from DNA-damaging chemicals and ROS (Fig. 1B). These stimuli increase mitochondrial membrane permeability by modifying the interplay between Bcl-2 family proteins that interact with mitochondrial membrane voltage-dependent anion channels (Shimizu et al., 2000). Bcl-2 proteins have either proapoptotic (eg Bak, Bax, or Bok) or anti-apoptotic roles (eg Bcl-2, Bcl-XL, or Mcl-1); the BH3-only proteins (eg Bid, Bim, or Puma) also modulate pro- and anti-apoptotic Bcl-2 protein interactions. Apoptotic stimuli shift the balance between these proteins and promote mitochondrial membrane destabilization, cytochrome c release into the cytoplasm and activation of executioner caspases that cleave cytoplasmic and nuclear macromolecules and produce the morphologic features of apoptosis, like DNA fragmentation (Degterev et al., 2003).

ROS are not only mediators of damage to cell macromolecules but also modulate signal transduction. Major sources of ROS are mitochondrial complexes that mediate oxidative phosphorylation and enzymes, such as cyclooxygenases (COX), cytochromes P450 (CYP), lipoxygenases (LOX), and NADPH- and xanthine oxidases that operate