Progress in Lipid Research 48 (2009) 62–72

Contents lists available at ScienceDirect

Progress in Lipid Research

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

Review

Metabolism of sphingolipids in the gut and its relation to inflammation and cancer development

Rui-Dong Duan [a,*], Åke Nilsson [b]

[a] Gastroenterology Lab, Biomedical Center B11, Department of Clinical Sciences, Lund University, S-221 84 Lund, Sweden
[b] Gastroenterology Division, Department of Clinical Sciences, University Hospital of Lund, S-22185 Lund, Sweden

ARTICLE INFO

Article history:
Received 31 March 2008
Received in revised form 8 April 2008
Accepted 8 April 2008

Keywords:
Ceramide
Ceramidase
Ceramide kinase
Colon cancer
Glucosylceramide
Inflammatory bowel disease
Intestine
Sphingolipid
Sphingosine
Sphingosine kinase
Sphingosine-1-phosphatase
Sphingomyelin
Sphingomyelinase

ABSTRACT

Sphingolipids are abundant in the microvillar membrane of intestinal epithelial cells where they are essential for structural integrity and may act as receptors for toxins, virus and bacteria. Metabolism of dietary and membrane sphingolipids in the intestine generates ceramide, sphingosine, sphingosine-1-phosphate, and ceramide-1-phosphate, via the action of alkaline sphingomyelinase, neutral ceramidase, sphingosine-1-kinase, and ceramide-1-kinase. These intermediary metabolites act as bioactive lipid messengers, influencing numerous cellular functions including growth, differentiation and apoptosis of both epithelial and immunocompetent cells in the gastrointestinal tract, and also the progress of inflammation and responsiveness of the mucosal cells to pathogens. This review summarizes background and recent progress in the metabolism of dietary and endogenous sphingolipids in the gut and its pathophysiological implications.

Contents

Abbreviations: Alk–SMase, alkaline sphingomyelinase; BSSL, bile salt stimulated lipase; C1P, ceramide-1-phosphate; *CerS*, ceramide synthase; COX, cyclooxygenase; CRC, colorectal cancer; GalCer, galactosylceramide; Glyco-SL, glycosphingolipid; IBD, inflammatory bowel disease; JNK, c-JUN *N*-terminal kinase; LPA, lysophosphatidic acid; LPS, lipopolysaccharide; Lyso-PC, lysophosphatidylcholine; MDR, multidrug resistance protein; N-CDase, neutral ceramidase; NPP, nucleotide pyrophosphatase phosphodiesterase; NSAID, nonsteroidal anti-inflammatory drugs; PAF, platelet activating factor; PC, phosphatidylcholine; PDGF, platelet-derived growth factor; PGE2, prostaglandin E2; PI3K, phosphatidylinositol-3 kinase; PLA2, phospholipase A2; pRb, retinoblastoma protein; S1P, sphingosine-1-phosphate; SM, sphingomyelin; SMase, sphingomyelinase; SphK, sphingosine kinase; TLR, toll-like receptor; TNF-α, tumor necrosis factor; VEGF, vascular endothelial growth factor.

* Corresponding author. Tel.: +46 46 222 0709.
E-mail addresses: Rui-dong.duan@med.lu.se (R.-D. Duan), Ake.Nilsson@med.lu.se (Å. Nilsson).

0163-7827/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.plipres.2008.04.003

1. Introduction

The interest in sphingolipids is increasing. A number of recent reviews have covered broad perspectives on sphingolipids, including metabolism [1,2], absorption and transport [3], roles in signaling pathways [4–8], enzymes involved [9–11], and relation to tumorigenesis [12] and inflammation [13]. Among the biologically active sphingolipid metabolites, ceramide and sphingosine-1-phosphate (S1P) are considered most important. Ceramide is a major lipid messenger that inhibits cell proliferation and induces apoptosis via dephosphorylation and inactivation of several proliferative and antiapoptotic molecules such as Akt, Bcl-2, PKCα and pRB. It also activates several kinases as Raf kinase and JNK depending on cell types [10,14,15]. S1P functions as a second messenger inside the cells, and as an extracellular signal via G-protein coupled receptors [5,16]. Increasing evidence indicates important roles of S1P in regulation of cell growth, angiogenesis, immune function and lymphocyte traffic, affecting downstream signaling molecules such as PLC, PI3K, Akt, VEGF, and COX 2 [16–18]. Recent studies have indicated that ceramide-1-phosphate (C1P) is also an important lipid signal that affects cell proliferation and inflammation through activation of PLA2 [19,20] (Fig. 1).

Sphingolipids, in particular glucosylceramide, are abundant in the apical membrane in the absorptive epithelium in the gut, and are considered important for the preservation of structural integrity during exposure to bile salts and enzymes [21]. The brush border sphingolipids may also support the insertion of transporters and receptors, necessary for the selective and effective transport of nutrients into the cells, although these aspects are poorly characterized. Sphingolipid composition changes when crypt cells differentiate to mature absorptive cells, reflecting the close connection between sphingolipid synthesis and mucosal regeneration and differentiation.

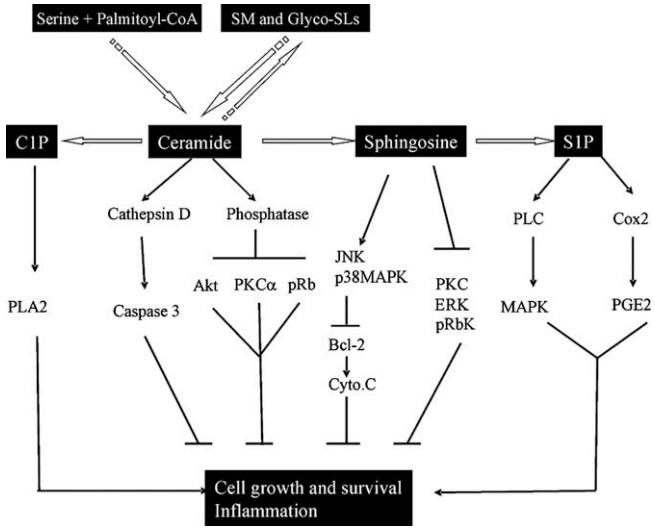

Fig. 1. Signaling effects of SM metabolites. Metabolism of SM generates signaling molecules including ceramide, sphingosine, ceramide-1-phosphate (C1P), and sphingosine-1-phosphate (S1P). Ceramide and sphingosine are major lipid messengers that inhibit cell growth and inflammation, whereas C1P and S1P are major molecules with proliferative and inflammatory properties, through various signal transduction pathways. The open arrow indicates the chemical pathways and the solid line indicates the biological effects. The lines with arrows indicate stimulation and those with a blunt line indicate inhibition.

Hydrolytic ectoenzymes, including those digesting sphingolipids, account for an important part of the proteins of the brush border [21]. Sphingolipid metabolites may thus be generated both by intracellular enzymes occurring in most cell types and by ectoenzymes acting on sphingolipids in the diet and in the outer leaflet of the absorptive cells. The generated ceramide, sphingosine, and S1P are intermediates in the conversion of sphingoid bases to chylomicron palmitic acid or in sphingolipid synthesis; they may reach signaling targets and act as messengers [3].

The relation of the sphingolipids in the gut to intestinal inflammation and colorectal cancer (CRC) is a novel and complex issue. Both CRC and inflammatory bowel diseases (IBD) are common diseases that result from gene - environmental interactions including a dietary influence. Current hypotheses for IBD pathogenesis emphasize a deregulation of the normal inflammatory response to the commensal bacterial flora [22]. Studies on gene targeted animals and in patients indicate that deregulation originating from defect barrier integrity, or from innate or specific immunity, may result in similar phenotypes [23]. Lipid signaling via eicosanoids, glycerolipid- and sphingolipid messengers is an important feature of IBD [24]. Most CRCs involves a stepwise series of mutations resulting in a progression to benign adenomas and eventually CRC, which can long be influenced by diet and drugs [25,26]. The role of lipid messengers is highlighted by the protective effect of cyclooxygenase inhibitors (NSAID, non steroid anti-inflammatory drugs) against CRC development [27] and by the fact that the same types of the drugs make ulcerative colitis worse [28].

This review focuses on the metabolism of sphingolipids in the gastrointestinal tract and the potential relation to mucosal protection, inflammation and carcinogenesis. Since the exposure to exogenous sphingolipids and the enzymes involved are unique features of the gastrointestinal tract, these aspects are covered in some detail.

2. Sphingolipid profile in the intestinal tract

Throughout the gastrointestinal tract sphingolipids are enriched in the apical membrane of the polarized epithelial cells. The sphingolipid profiles have been characterized by TLC, GLC and GLC–MS techniques with regard to sphingoid base, fatty acid and polar head group composition.

The stomach mucosa contains neutral glycolipid species with one, two, three or five sugars [29], acidic glycolipids of the sulphatide and ganglioside classes, and more complex neutral glycolipids with blood group reactivity. It also contains several molecular species of sphingomyelin (SM) [30]. The functions of the stomach sphingolipids are only partly known. Upon stimulation the parietal cells undergo a morphological transformation and membrane rearrangement. The secretory membrane containing the crucial K^+/H^+ ATPase was found to be rich in sphingolipids [31]. Glycolipids were later shown to interact with *Helicobacter pylori* [32], which produce