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REVIEW

The Role of Lysosphingolipids in the Regulation of Biological Processes

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Abstract—This review summarizes data on the role of lysosphingolipids (glucosyl- and galactosylsphingosines, sphingosine-1-phosphate, sphingosine-1-phosphocholine) in the regulation of various biological processes in normal and pathological states.

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Sphingolipids are well known biologically active lipids that are involved in regulation of proliferation, differentiation, and apoptosis of cells; they also participate in some other biological processes. The main fragment of sphingolipids is a sphingoid base (usually, sphingosine – (2S,3R,4E)-2-amino-4-octadecene-1,3-diol). Sphingolipids can exhibit properties of second messengers or extracellular mediators. Numerous studies have recognized that ceramide (N-acylsphingosine, Cer) inhibits proliferation and stimulates differentiation and apoptosis of cells (see reviews [1-6] and the literature cited there), whereas products of ceramide glycosylation (glucosyl- and lactosylceramides and also some gangliosides) cause opposite effects; they stimulate growth and promote cell survival (see review [7] and the literature cited there). These sphingolipids contain an acylated amino group. However, there are sphingolipids with sphingoid base free amino group. These sphingolipids are lysosphingolipids. These include sphingosine-1-phosphate (S1P) and sphingosine-1-phosphocholine (S1PCh), often defined as sphingosylphosphorylcholine and glucosyl-, galactosyl-, and lactosylsphingosines. The presence of a free amino group in the sphingolipid molecules definitely influences their biological activity. The goal of this review is to consider properties of these compounds.

Lysoglycosphingolipids. It has been demonstrated earlier that lysosphingolipids, particularly lysoglycosphingolipids, induce apoptosis via a caspase 3 independent pathway in Neuro-2a cells; this involves accumulation of the lysosphingolipids but not their parent sphingolipids [8].

The first lysoglycosphingolipids were identified in patients with various diseases. For example, glucosylsphingosine was identified in patients with Gaucher's disease [9-11]. Galactosylsphingosine was found in patients with Krabbe's disease [12, 13]. Lactosylsphingosine was found in the brain [13], and antibodies against lactosylsphingosine were identified in blood plasma of cancer patients [14, 15]. Although lysoglycosphingolipids were found more than 30 years ago, the mechanisms of their action(s) under pathological conditions are still investigated.

It has been demonstrated that lysoglycosphingolipids mobilize Ca^{2+} from intracellular stores [16-19], and the mechanism of this phenomenon depends on lysoglycosphingolipid structure [18]. Lysoglycosphingolipids induce apoptosis [8], and the development of Krabbe's disease is accompanied by disappearance of myelin in the central nervous system and appearance of globoid cells accumulating psychosine (galactosylsphingosine) [20]. Treatment of MO3.13 cells (human oligodendrocyte) with psychosine caused their apoptosis. This was accompanied by activation of caspase 9 (but not caspase 8) [21]. Psychosine stimulates apoptosis in oligodendrocytes by inhibiting Akt and Erk1/Erk2 phosphorylation [22]. The authors suggested that apoptosis involves activation of caspases 3, 8, and 9 [23]. Psychosine also generates lysophosphatidylcholine and arachidonic acid in cells; this indicates that it activates phospholipase A2 (PLA2). It has been suggested that oligodendrocyte apoptosis

Abbreviations: S1P) sphingosine-1-phosphate; S1P(1), S1P(2), S1P(3)) receptors of sphingosine-1-phosphate; S1PCh) sphingosine-1-phosphocholine; Sphk) sphingosine kinase.

involves the PLA2-signaling pathway [24]. Gaucher's disease is also characterized by accumulation of glucosylsphingosine and neuronal apoptosis in the brain [25, 26].

Glucosyl- and galactosylsphingosines influence mitochondrial functions [21, 27, 28], for example, they inhibit activity of cytochrome *c* oxidase and electron transport [27, 28]. Lysoglycosphingolipids also inhibit generation of thrombin, a pro-inflammatory protease regulating the cascade of blood coagulation [29]. It should be noted that both lysoglycosphingolipid regulation of mitochondrial functions and thrombin inhibition require the free NH_2-group; its acylation causes either reduction [29] or disappearance [27] of the regulatory effect.

Lysophosphosphingolipids. Studies on the role of lysosphingolipids give much attention to the effects of lysophosphosphingolipids, S1P and S1PCh, on biological processes. Since the role of S1P in biological processes has been considered in several reviews [30-38], we will analyze here only publications that have appeared after 2000.

Sphingosine-1-phosphate was identified two decades later than lysoglycosphingolipids [39]. However, its role in cellular process has been (and is) investigated in numerous studies. S1P acts as a second messenger (inside cells) and as an extracellular modulator as well [7, 37, 38, 40-45]. Intra- and extracellular S1P play different regulatory roles.

Earlier it has been demonstrated that intracellular S1P stimulates cell proliferation and inhibits apoptosis (see the reviews mentioned above). Recent studies have been mainly focused on the involvement of S1P in biochemical and physiological processes and mechanisms underlying its action.

Formation of intra- and extracellular S1P involves various pathways. Intracellular S1P is formed by phosphorylation of sphingosine by kinases (besides the reviews mentioned above, see also [46, 47]). There are several sphingosine kinases (Sphk) in cells; they differ in intracellular localization and properties. For example, Sphk 1 promotes cell survival, whereas Sphk 2 stimulates apoptosis and inhibits cell growth [48]. It should also be noted that sphingosine kinases play an important role in the development of various pathological processes, especially, malignant growth [49-54]. Extracellular S1P is generated by activated platelets [55, 56]. Kidney cells secrete sphingosine kinases into the extracellular space, where it forms extracellular S1P followed by induction of angiogenesis [57].

As already mentioned, intracellular S1P stimulates cell proliferation and inhibits apoptosis. Study of the mechanism underlying this effect has shown that in cells of human acute leukemia S1P prevents apoptosis and caspase 3 activation by inhibiting cytochrome *c* release from mitochondria into cytosol [58]. In macrophages, it inhibited acidic sphingomyelinase, which converts sphingomyelin into ceramide; thus, inhibition blocks the proapoptotic effect of ceramide [59]. S1P causes release of Ca^{2+} from intracellular stores and entrance of extracellular Ca^{2+} into cells [60, 61].

Extracellular and intracellular S1P increases the concentration of Ca^{2+} in the cell [62]. The effects of extracellular S1P on cell processes are mediated by G-protein coupled receptors [32, 34, 41, 63-67]. Five types of S1P receptors [S1P(1-5)] have been recognized on the cell surface [41]. In various physiological and pathological conditions, S1P binds to different receptors [64]. Binding of sphingosine-1-phosphate to S1P(1) and S1P(3) activated proliferation and migration of cells, whereas S1P(2) inhibited these processes [68, 69].

S1P binding to its receptors at the cell surface plays a special role in the regulation of processes responsible for cell motility and migration [35, 62, 70, 71]. Inhibition or stimulation of these processes by S1P is determined by its binding to a certain type of receptors. Binding of sphingosine-1-phosphate to S1P(1) and S1P(2) stimulates [68, 69, 72] or inhibits [68, 69, 73] cell migration, respectively. For example, exogenous S1P inhibited migration of aorta smooth muscle cells [62]. Binding of S1P is especially important for migration of tumor cells and metastasis [68, 71-75]. This lysosphingolipid is also required for tumor angiogenesis [33, 38, 76-78].

S1P is also important for immune response [79-81], particularly in migration of dendrite cells, the inducers of immune response [81]. The ratio of Sphk/S1P is crucial for this process, and its modulation can be used in immune therapy [81]. S1P regulates immune cell motility, which ultimately requires S1P(1) [80]. S1P also inhibits T-lymphocyte proliferation [82], but regulates dendrite cell motility and promotes Th2 immunity [83].

S1P stimulates secretion of cortisol [84] and aldosterone, the hormone involved into control of electrolyte and water balance essential for cardiac homeostasis [85]. In the latter case, it was demonstrated that this regulation involves S1P receptors, extracellular Ca^{2+}, and protein kinase C.

Study of inhibition of apoptosis by S1P revealed that it protected endothelial cells against cell death by generating NO [86, 87], which involved the activation of NO synthase [88].

Extracellular S1P found in all types of blood lipoproteins plays a significant role in pathological processes. Its highest concentration was detected in high-density lipoproteins (HDL) [89]. Studies have shown that HDL S1P may protect patients with risk of myocardial ischemia, and this effect involves S1P(3) [90]. However, it was found that both exogenous and endogenous S1P protect myocytes [91]. Lipoprotein S1P protected venous endothelial cells [92] and induced the activity of some enzymes: serine protease matriptase [93] and extracellular kinases [94].

S1P is involved in development of some pathological conditions including inflammation [95], heart diseases [96, 97], and asthma [98, 99]. Certain attention is given to possible use of S1P for therapeutic treatment. In 2002, it was proposed that S1P could play a significant role in

therapy of pathological processes because it is a second messenger involved in regulation of homeostasis, angiogenesis, and maturation of vessels, and the ratio of Cer/S1P is crucial for these processes [100]. The putative target of S1P in tumor chemotherapy was associated with its role in induction of tumor cell proliferation, inhibition of apoptosis, and involvement in regulation of cell motility and angiogenesis of tumors [101-104]. Antibodies against S1P reduced tumor progression, blocked migration of tumor cells, capillary formation, and their protection against apoptosis [105]. Since S1P is actively involved in vascular processes, it has been suggested that agonists or antagonists of S1P receptors could be used in therapy of vascular diseases [106]. (It has already been mentioned that HDL S1P protected patients with risk of myocardial ischemia [90].) It is also suggested that S1P receptors may be potential targets for treatment of autoimmune diseases and unwanted effects during transplantation [107].

Sphingosine-1-phosphocholine (S1PCh). Lysosphingomyelin is also a lysosphingophospholipid. It shares similar functions with S1P, and their similarity and diversity has been considered in [108]. However, in contrast to S1P, there are fewer experimental studies and reviews [4, 109, 110] highlighting the biological role of S1PCh.

Sphingosine-1-phosphocholine is both an intra- and extracellular mediator, which usually acts at G-protein coupled receptors [111]. It is the major lipid component of HDL [112]. Several types of its receptors have been found on the cell surface: OGR1 [113, 114], GPR4 [113-117], GPR12 [118], and also a new type of proton-sensitive receptors [119]. However, the existence of intracellular receptors for S1PCh has also been postulated [120].

Studies have shown that S1PCh is a signal molecule stimulating mitogenesis and DNA synthesis [121-123]; S1PCh was more potent in cell proliferation that S1P [122]. S1PCh may also influence apoptosis, but this effect depends on cell type. For example, HDL S1PCh inhibited apoptosis of endothelial cells [124], whereas treatment of human adipocytes with S1PCh stimulated cell death, and this process involved cytochrome *c*, caspase 3, and also ERK activation [125]. However, activation of JNK stimulated proliferation of these cells [126]. These authors also demonstrated that S1PCh stimulated differentiation of mesenchymal stem cells into smooth muscle cells; this was accompanied by secretion of transforming growth factors TGF-β1 and TGF-β3 [127].

S1PCh is involved in many pathological processes. For example, its receptors coupled to G-proteins are involved in the development of kidney disease [128, 129]. S1PCh inhibited functions of human platelets [130] and decreased thrombin generation. It should be noted that acylation of the NH_2-group of sphingosine-1-phosphocholine decreased its anticoagulation activity [131]. Accumulation of significant amounts of S1PCh [132, 133], stimulating cell proliferation [132], was found in the brain of patients with Niemann–Pick disease. Certain experimental evidence exists that S1PCh influences intracellular Ca^{2+}, and this accompanies some pathological states [134-136].

S1PCh plays a significant role in pathology of the cardiovascular system. In 2001, it was found that S1PCh, a lipid mediator of blood plasma, is involved in receptor-mediated regulation of cardiac functions [137]. An anti-atherogenic role of HDL lysophosphosphingolipids (S1P and S1PCh) has been considered in review [138]. Recently, it has been demonstrated that the anti-atherogenic and anti-inflammatory effects may be attributed to the S1PCh receptor mediated activation of Akt protein kinase and decrease in E-selectin and mRNA expression; this reduces translocation of NF-κB into the nucleus of vascular endothelial cells [139].

S1PCh is also involved in the development of skin diseases. For example, atypical dermatitis is accompanied by an increase in sphingomyelin deacylase and S1PCh [140]; the latter is a potential inducer responsible for impairments of intercellular keratinocyte adhesion [141], a stimulator of DNA synthesis and keratinocyte proliferation [142], and also a stimulator of connective tissue growth factor expression in cultured human skin fibroblasts [143].

As stated above, S1PCh is a component of HDL; its increased content was detected in both lipoproteins and ascites of patients with ovarian cancer [144, 145]. S1PCh was shown to increase cell elasticity and promote their protrusion through membrane pores (i.e., formation of metastases) [144]. The increased level of ascites S1PCh might be a sensitive marker for detecting ovarian cancer [145].

Sphingosine-1-phosphocholine influences vascular tone. In 2000, it was found that S1PCh as well as S1P is an endogenous regulator of vascular tone [146]. S1PCh either interacts with G-protein coupled receptors or acts via intracellular mechanisms. This results in activation of cyclooxygenase-2, the enzyme forming vasoconstrictor and vasodilator prostaglandins. Thus, changes of S1PCh concentrations influence vascular functional state [61].

Sphingosine-1-phosphocholine plays a key role in angiogenesis; it coordinates migration of vascular endothelial and smooth muscular cells [147, 148]. It may induce angiogenesis *in vivo*; this involves its interaction with GPR4 receptor followed by activation of phosphatidylinositol 3-kinase and Akt [116]. It was also demonstrated that S1PCh action in vascular smooth muscle cells involved mitogen activated protein (MAP) kinase phosphorylation and cell migration [149].

Sphingosine-1-phosphocholine stimulates some enzymes. It activates phosphatidylinositol 3-kinase [116] during induction of angiogenesis. S1PCh also stimulates transglutaminase activity [150, 151]. It influences pigmentation by coordinating expression of melanogenic molecules [152]. It has recently been demonstrated that S1PCh inhibits melanin biosynthesis and tyrosinase activity (the rate limiting enzyme of melanogenesis) and thus decreases pigmentation [153]. It activates extracellular signal reg-

ulated ERK kinase, and this also suppresses melanin synthesis [153]. As mentioned above, sphingosine-1-phosphate activates MAP kinases; S1PCh also activates these enzymes, but this involves a different mechanism [154].

Considering signaling functions of lysoglycosphingolipids and lysophosphosphingolipids, one can conclude that they are involved in numerous biochemical processes in cells. These molecules regulate enzyme activity, proliferation, differentiation, and apoptosis; they promote cell migration, metastasis, and angiogenesis. Lysoglycosphingolipids and lysophosphosphingolipids are also involved in immune response, etc. Studies of these effects suggest that lysosphingolipids may be employed in therapy of various diseases.

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