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Regulation of mitochondrial function by bioactive sphingolipids

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Abstract: Sphingolipids such as ceramide, sphingosine and sphingosine 1-phosphate [S1P] are key regulators of various cellular functions. Sphingolipids mediates of cell-stress responses and regulate mitochondrial function. Ceramide and its metabolites play an important role in the development and progression of mitochondria related disorders. Ceramide functions as an important second messenger in apoptosis signaling and is generated by de novo synthesis, sphingomyelin hydrolysis, or recycling of sphingolipids. S1P, a potent signaling sphingolipid exerts myriads of pathophysiological function, including lymphocyte trafficking, angiogenesis, vascular development and inflammation. This review is focused on the role of signaling sphingolipids, such as S1P, sphingosine, and ceramide-1 phosphate on mitochondrial function, particularly mitochondrial respiratory function, apoptosis and calcium homeostasis. Further, we discuss the role of sphingolipids in mitochondrial diseases and targeting them for drug development. This review article is a part of special issue on Mitochondria: Implications in human health and disease.

Keywords: Sphingolipid, Ceramide, Sphingosine-1-Phosphate [S1P], Mitochondria, Apoptosis

1. Introduction

Sphingolipids are a family of membrane lipids with important structural roles in the regulation of the fluidity and subdomain structure of the lipid bilayer, especially lipid rafts [1, 2]. Sphingolipid metabolites also act as second messengers in different cellular processes, such as cell differentiation, cell proliferation and cell growth arrest [2, 3]. In response to a wide range of stressful stimuli, membrane sphingomyelin and to a lesser extent other complex sphingolipids such as ganglosides are rapidly metabolized to the bioactive sphingolipid intermediate (Figure 1), ceramide and subsequently to sphingosine [1]. Phosphorylation of sphingosine by two sphingosine kinases namely SphK1 and SphK2 results in the formation of a highly potent signaling lipid, sphingosine-1-phosphate (S1P) [3, 4].

S1P has emerged as a potent second messenger that regulates diverse cellular processes, including cell proliferation, survival, and differentiation and migration [3-6]. S1P mediates its pathophysiological function through at least five G protein-coupled receptors, termed as S1PR1–5 [3, 4]. S1P can act in autocrine/paracrine manner to stimulate S1P receptors present at the cell surface [signaling "inside-out"] and initiates downstream G protein-mediated signalling pathways [3-6], leading to a variety of cellular responses such as increased Ca^{2+} mobilization, cell proliferation, cell

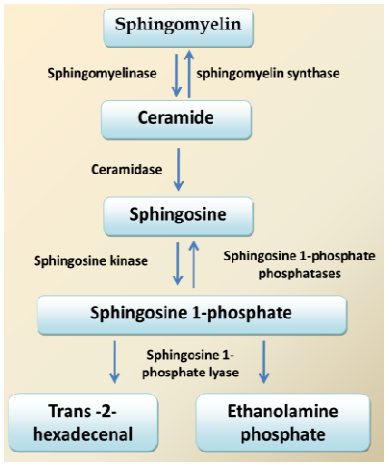

Figure 1. *Sphingolipid metabolic pathway in mammalian cells. Sphingomyelinase induces hydrolysis of sphingomyelin to ceramide which subsequently catabolized to sphingosine. Phosphorylation of sphingosine by two sphingosine kinases results in the formation of sphingosine-1-phosphate (S1P), which can be irreversible degraded in to trans-2-hexadecenal and ethanolamine phosphate by the action of S1P lyase.*

migration, inhibition of apoptosis, induction of stress fiber formation and up-regulation of adhesion molecules [3, 4]. S1P plays a pivotal role in numerous pathophysiological functions, including lymphocyte trafficking, inflammation, muscle regeneration and vascular development [5-8].

Mitochondria are highly dynamic organelles that undergo cycles of fusion and fission important for their function, maintenance and quality control [9]. Besides ATP synthesis, mitochondria are also involved in key cellular functions such as Ca^{2+} homeostasis, heme biosynthesis, nutrient metabolism], and signaling pathways for cell death and autophagy [9-11]. Mitochondrial dysfunction also leads to many human maladies, such as cancer [12-14], aging [15], neurodegenerative disease [16, 17], hepatic ischemia-reperfusion [18], diabetes [19], cardio-protection [20], and liver injury [21]. Multiple studies show intimate connections between ceramide signaling and the functioning of mitochondria, which play a central role in the integration of cellular signals to determine the outcome among apoptosis, necrosis, or proliferation [22-25]. Here, we review the recent literature on the role of bioactive sphingolipid metabolites such as ceramide, S1P, sphingosine and ceramide-1-phosphate [C1P] in various cellular processes particularly apoptosis regulated by mitochondria.

2. Role of Ceramide in Mitochondrial Respiratory Chain

Ceramide from mammalian membranes is composed of sphingosine, linked to a fatty acyl chain, varying in length from 14 to 26 carbon atoms [1]. Ceramide functions as an important second messenger in apoptosis signaling and is generated by de novo synthesis, sphingomyelin hydrolysis, or recycling of sphingolipids [1]. Several sphingolipid-metabolizing enzymes have been found to be associated with mitochondria, including neutral ceramidase, neutral sphingomyelinase, and [dihydro] ceramide synthase, [1, 23, 24, 26]. Enzymatic reactions involved in the biosynthetic pathways of sphingolipids are dispersed throughout different cellular compartments [1]. The initial steps of sphingolipid synthesis, beginning from the activity of serine palmitoyltransferase to dihydro-ceramide desaturase, take place in the endoplasmic reticulum, mitochondria-associated membranes, but the further metabolism of ceramide to sphingomyelin and complex glycol-sphingolipids takes place mostly in the Golgi apparatus [1, 28].

Ceramide species differing in acyl chain length, with distinct biophysical properties, execute distinct functions and effects. Some of the ceramide species modulate mitochondrial function and oxidative phosphorylation [25]. C16-ceramide, sphinganine and sphingosine reduce the activity of the mitochondrial respiratory chain by direct inhibition of complex IV, resulting in enhanced generation of reactive oxygen species [ROS] and leading to oxidative stress [25, 28-30]. Lipid composition of mitochondrial inner membrane is of great importance for the stabilization of the respiratory chain complexes. However, the mechanism by which sphinganine, sphingosine, and C16-ceramide gain access to complex IV in mitochondria is not understood. Cerebral ischemia reperfusion-induces increases in the activity of mitochondrial ceramide synthesis resulting in elevated levels of ceramide in mouse brain mitochondria leading to mitochondrial respiratory chain damage [31]. Mitochondrial ceramide accumulation was abolished in c-Jun Kinase 3 [JNK3]-deficient mice, suggesting that ceramide synthase is under the control of JNK3 [31].

3. Mitochondria in Apoptosis

The ability of mitochondria to initiate apoptosis by releasing proteins into the cytosol is an established fact. Mitochondrial transmembrane potential [MTP] changes dynamically [9, 32], and these cellular dynamics are an important constituent for apoptotic initiation by providing pro-apoptotic factors that are involved in caspases activation, and Bcl-2 family proteins [32]. The Bcl-2 family proteins regulate the mitochondrial outer membrane [MOM] integrity [33] and contribute to the release of pro-apoptotic factors from their intermembrane space [IMS] to the cytoplasm by MOMP [34]. Pro-apoptotic members of Bcl-2 family proteins such as Bax or Bak tend to antagonize the function of anti-apoptotic members of the Bcl-2 family protein, eg. Bcl-2, Bcl-XL and permeabilize the MOM [51]. Mitochondrial apoptotic pathway also cross talks with death receptor mediated pathway of apoptosis. In response to apoptotic stimuli, caspase-8 activated by the death-inducing signaling complex cleaves the pro-apoptotic BH3-only protein Bid to the active truncated form [tBid]. In addition to cytochrome c, other inter-membrane space proteins such as SMAC/DIABLO, Omi/Htr2 are also mobilized and released into the cytosol where they promote caspase activation and hence cell death [34].

4. Regulation of Mitochondrial-Mediated Apoptosis by Ceramide

The involvement of ceramide in apoptosis induction is well established for quite some time [35, 36]. Ceramide-induced apoptosis is accompanied by release of pro-apoptotic proteins from mitochondria [37, 38], increased generation of mitochondrial ROS [39], discharge of mitochondrial transmembrane potential, $\Delta\psi$ [38, 40]. Further, Bak is required for generation of ceramide during apoptosis [35]. TNF-α-, ischemia/reperfusion or UV-induced apoptosis is associated with an increase in mitochondrial ceramide [29, 31, 41, 42].

Many enzymes required for sphingolipid catabolism are present in mitochondria [1, 28]. Mitochondrial SMase hydrolyses sphingomyelin present in mitochondrial-associated membrane, which subsequently metabolized to sphingosine and then to S1P [23]. S1P lyase, a S1P catabolizing enzyme present in mitochondrial-associated

membrane plays a crucial role in activation Bax [23, 43, 44]. S1P lyase causes irreversible breakdown of S1P and forms trans-2-hexadecenal and ethanolamine phosphate [45]. Trans-2 hexadecenal, an end product of S1P catabolism binds directly to Bax and leads to conformational changes in Bax, resulting in latter's activation [23, 43].

In addition, ceramide induces a transitory increase of intracellular pH [pHi] in relation to the permeability transition pore. This increase in pH lead to conformational changes in Bax and Bcl-2-antagonist/killer. Upon apoptosis induction, Bax and Bak oligomerize and at least partially inserted into the MOM [46-48], causing cytochrome c and other apoptogenic proteins in the intermembrane space to leak out. Leaked cytochrome c then initiates apoptotic caspase activation through a well-defined biochemical pathway, such as caspase-9 and 3 activation and PARP cleavage, resulting in apoptosis [48].

5. Ceramide Forms Channels in Mitochondrial Membrane

Ceramide can self-assemble in the mitochondrial outer membrane to form large stable channels capable of releasing apoptotic proteins from intermembrane space of mitochondria [49]. Ceramide channels are barrel-like structures whose staves are ceramide columns that span the membrane. The channels are in dynamic equilibrium with non-conducting forms of ceramide in the membrane. This equilibrium can be strongly influenced by other sphingolipids and Bcl-2 family proteins. Bax acts synergistically with ceramide to enhance membrane permeabilization both in the MOM and in phospholipid membranes. The Bax/ceramide channels are quite different from that formed by ceramide alone and Bax alone. However, it has been shown that proteins are not essential for channel formation by ceramide [49, 50]. Similar to ceramide, sphingosine also forms channels in membranes, but these differ greatly from the large oligomeric barrel-stave channels formed by ceramide. However, sphingosine channels, unlike ceramide channels, are not large enough to allow the passage of pro-apoptotic proteins from the intermembrane space of mitochondria in the cytoplasm [51].

6. Regulation of Apoptosis through Ceramide-1-Phosphate [C1P]

C1P is formed from ceramide by the action of a specific ceramide kinase [CerK], which is distinct from the sphingosine kinases that synthesize S1P [52]. CerK is specific for natural ceramides with the erythro configuration in the base component and esterified to long-chain fatty acids. C1P has opposite effects to ceramide, C1P exhibits mitogenic and pro-survival properties [53, 54]. CerK can be activated by different agonists, including interleukin 1-β, macrophage colony stimulating factor, or calcium ions [55]. C1P is also an important mediator of mitogenic effects implicated stimulation of the mitogen-activated protein kinase kinase [MEKK]/ extracellularly regulated kinases 1-2 [ERK1-2], phosphatidylinositol 3-kinase [PI3K] /protein kinase B [PKB, also known as Akt], and c-Jun terminal kinase [JNK] pathways [54]. Most of the effects of C1P so far described seem to take place in intracellular compartments; however, a plasma membrane receptor coupled to a Gi protein has been implicated in C1P action [24]. Therefore, C1P has the dual regulatory capacity acting as an intracellular second messenger to regulate cell survival, or as an extracellular receptor ligand to stimulate chemotaxis [52]. Usually ceramides and C1P exert opposing effects, [i.e. On PLD activation, adenylyl cyclase inhibition, or Ca^{2+} mobilization], however C1P is not able to reproduce the effects of S1P [53, 56]. Notably, no ceramidase capable of converting C1P directly into S1P have so far been reported in mammalian cells.

7. Ceramide and S1P Have Opposing Function

Ceramide and sphingosine mediate apoptosis, cell cycle arrest, and differentiation, whereas S1P promotes proliferation, survival, and inhibition of apoptosis. The ratio between the intracellular level of ceramide and S1P determines cell fate [3, 6]. The generation of S1P from ceramide requires the action of two enzymes, ceramidase which deacylates ceramide to form sphingosine, and Sphk, which phosphorylates sphingosine to S1P [8]. S1P has mitogenic effects, both as an extracellular signalling molecule and as an intracellular second messenger. In the cells, SphK1 is activated by growth stimuli and cytokines, increasing intracellular levels of S1P. One of the putative anti-apoptotic mechanisms of S1P is to prevent ceramide-induced mitochondrial events such as cytochrome c release (Figure 2) and caspase activation [57, 58]. Indeed, Cuvillier and co-workers reported that S1P prevents caspase-3 activation by inhibiting the cytochrome c and Smac/Diablo release from mitochondria induced by apoptotic stimuli [anti-Fas, TNF-α or C6-ceramide] [58].

Mitochondria are key determinants of myocardial injury during ischemia-reperfusion [I/R] and a protective role of S1P has been shown by many investigators. In this context, the role of a SphK1 isoform of sphingosine kinase is well elucidated [59-61]. However, the contribution of SphK2 in cardio-protection is poorly understood. S1P produced by SphK2 isoform in the mitochondria interacts with prohibitin 2 to control the assembly and function of cytochrome oxidase in the electron transport chain [62]. In the baseline stage, SphK2 deficient mice exhibited decreased mitochondrial S1P content leading to dysfunction in mitochondrial respiration through cytochrome oxidase. Further, mitochondria from sphk2−/− mice exhibit decreased oxidative phosphorylation and increased susceptibility to permeability transition [63]. Furthermore, SphK2 is required for the downstream protective modulation of permeability transition as an effector of

preconditioning protection [63]. On the contrary, SphK2 generated S1P is detrimental in hepatic ischemia, and inhibition of SphK2 activity improves mitochondrial function and survival in mice after hepatic ischemia-reperfusion [64].

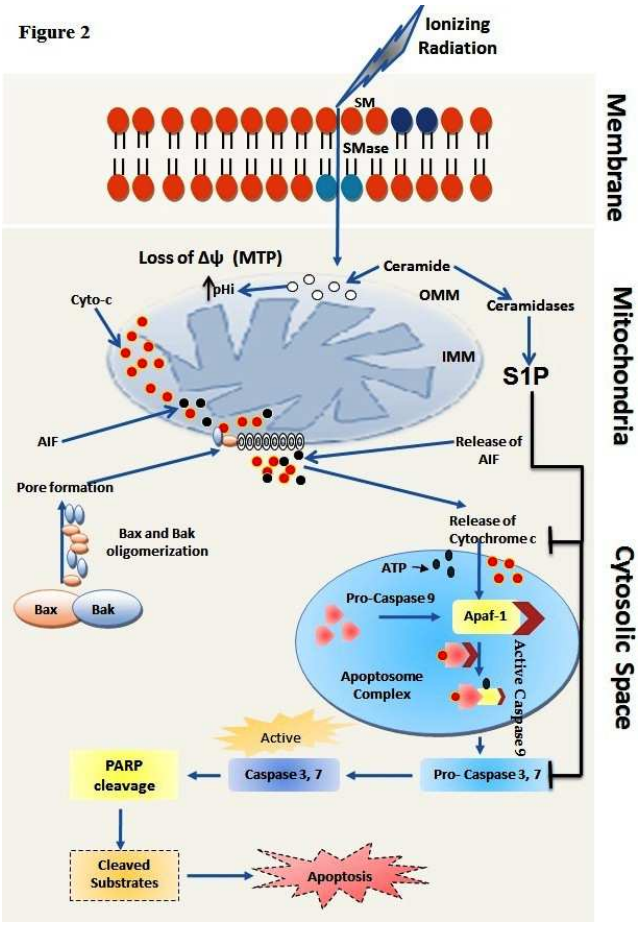

Figure 2. *Ionizing radiation activates sphingomyelinase (SMase) present in the plasma membrane, causing hydrolysis of sphingomyelin (SM) and forms ceramide. Latter causes loss of mitochondrial transmembrane potential (MTP) by targeting MTP-controlling proteins, resulting in the release of cytochrome c and apoptosis-inducing factor (AIF) from mitochondria to the cytoplasm. In addition, ceramide also induces a transitory increase of intracellular pH (pHi) resulting in conformational changes in BAX/BAK which is responsible for cytochrome c release, thereby causing caspase-9 activation, Poly ADP-ribose polymerase (PARP) cleavage. S1P prevents caspase-3 activation by inhibiting the cytochrome c and SMAC/Diablo release from mitochondria*

8. Role of Sphingolipids in Calcium Homeostasis

Ca^{2+} is the main second messenger that helps the biochemical machinery of cells particularly cardiomyocytes and neurons. The strict control of intracellular Ca^{2+} concentration is operated by Ca^{2+} binding proteins and by energy demanding Ca^{2+} transport proteins. The plasma membrane Ca^{2+} ATPase and the plasma membrane Na^{+}/Ca^{2+} exchanger extrude Ca^{2+} into the extracellular space. The Ca^{2+} pumps of the intracellular organelles, i.e., the ER/SR Ca^{2+}-ATPase and the Golgi Ca^{2+}-ATPase pumps accumulate Ca^{2+} in the intracellular store [65]. Mitochondria also contribute to the spatiotemporal tuning of the cytosolic Ca^{2+} concentration.

There is several Ca^{2+} transport mechanisms present in mitochondria by which they take up and release Ca^{2+} across their inner membrane. The transport of Ca^{2+} by these systems controls how much Ca^{2+} enters the cell, the Ca^{2+} concentration in cytoplasmic microdomains, the frequency of oscillatory cytosolic Ca^{2+} signals and the rate of propagation of a Ca^{2+} signal. In turn, mitochondria use their Ca^{2+} transporting activity to modulate the rate of ATP synthesis in a number of ways, i.e., by activating Krebs cycle dehydrogenases, by promoting the supply of oxidizable substrates and by regulating the activity of the ATP synthase [65].

Several sphingolipids, such as ceramide and sphingosine, and their phosphorylated derivatives C1P and S1P are directly involved in the Ca^{2+} regulation, are also recognized as signal messengers related to cancer processes [66]. Ca^{2+} overload is a common feature of all types of cell death [66]. During cellular Ca^{2+} overload, mitochondria take up cytosolic Ca^{2+}, which in turn induces opening of permeability transition pores and disrupts the mitochondrial membrane potential [$\Delta\Psi m$] [67, 68]. The collapse of membrane potential along with the release of cytochrome c from mitochondria is followed by the activation of caspases, nuclear fragmentation and cell death. Accordingly, C2-ceramide also stimulates mitochondrial network fragmentation in HeLa cells, which was linked to ER Ca2+ release and cell death [69]. Several reports have shown a rise in cytoplasmic Ca^{2+} at both early and late stages of the apoptotic process [70]. Ca^{2+} release from the ER and capacitative Ca^{2+} influx through Ca2+ release-activated Ca^{2+} channels have also been implicated in apoptosis [69, 71]. Ceramides have been shown to cause the release of Ca^{2+} from the ER, increasing Ca^{2+} in both the cytosol, and the mitochondrial matrix [67].

9. Sphingolipid and Mitochondria Associated Diseases

Mitochondrial dysfunction happens due to accumulation of mutations in the mitochondrial genome, the hypoxia-induced switch from mitochondrial respiration to glycolysis or the metabolic reprogramming resulting from the loss-of-function of enzymes which may responsible for different types of diseases. More than 300 pathogenic mtDNA mutations have been associated with various diseases [MITOMAP, 2011]. Mitochondria are one of the major sites for the generation of ROS as an undesirable side product of oxidative energy metabolism. Damaged mitochondria can augment the generation of ROS. Constant over production of ROS can adversely affect the functionality of lipids, proteins and DNA; particularly lipids are highly prone to free radical damage resulting in lipid peroxidation that can

lead to adverse alterations. Dysfunction of mitochondria increases the risk for a large number of human diseases; including cardiovascular diseases [CVDs] [14, 15, 28]. Mitochondrial dysfunction and oxidative stress are implicated in many neurodegenerative diseases [16, 17].With aging and as a consequence of some diseases, mitochondrial components may be rendered dysfunctional, and mtDNA mutations arise by the action of ROS [73].

Cancer cells accumulate defects in the mitochondrial genome, leading to deficient mitochondrial respiration and ATP generation [14, 74, 75]. In some cases, mitochondrial germline mutations have been shown to provide a genetic predisposition to cancer development [74]. In most cases, however, such mutations are acquired during or after oncogenesis. Cancer cells may adapt to decreased oxygen tension [hypoxia] that is characteristic of most, if not all solid tumors as the pre-malignant lesion grows progressively further from the blood supply. Thus, the way through which cells adapt to hypoxia would be to durably shut down mitochondrial respiration and to switch on glycolytic metabolism [76, 77].

Ceramide and S1P, two important bioactive sphingolipids, have been suggested as being key players in the pathology of Alzheimer's disease in inflammation and cancer. Niemann-Pick type C [NPC] disease is a neurovisceral atypical lipid storage disorder, which is caused due to mutation in sphingomyelinase gene. The pathogenesis of NPC is not clear, however oxidative stress has been observed in the livers and brains of NPC mice and in different NPC cellular models [78]. Several studies suggest that mitochondrial dysfunction and subsequent ATP deficiency may be responsible for the neuronal impairment in NPC disease [78, 79].

10. Conclusion

The bioactive lipids particularly ceramide and S1P are involved in multiple cellular signalling systems and has a pivotal role in the control of immune cell trafficking. Ceramide and S1P have been implicated in multiple mitochondria related diseases such as cancer, inflammatory diseases, neuro-degenerative diseases. Therefore, sphingolipids are attractive targets for drug development. Successful development of the sphingosine analogue FTY720, a pro-S1P mimetic, as a valuable drug has been established. FTY720 has been approved by FDA for the treatment of relapsing multiple sclerosis [80]. Inhibitors of S1P metabolism and its receptors have proven effective in many animal models of human diseases [81].

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