Ceramide pathway: A novel approach to cancer chemotherapy

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Abstract

Apoptosis or programmed cell death applies as a protected way to remove unwanted cells and plays a determinative role in many important biological processes such as normal development and tissue homeostasis in multicellular organisms. The main purpose of studies in this field is to focus on understanding the related regulatory mechanisms and novel approaches to the discovery of anticancer drugs.

Among the apoptotic messenger molecules, the key roles of sphingosine and ceramide as the backbone of sphingolipids were considered in many pathways of apoptosis. It has been shown that ceramide plays an important regulatory role in apoptosis and its increased cytoplasmic levels lead to programmed cell death. Ceramide biosynthesis and biodegradation occur via several different enzymes they can be affected by many external factors. Instead, phosphorylated form sphingosine is an important biomarker for cell proliferation and differentiation. Phosphatases, kinases, and proteases are the main operators for ceramide messaging and they can affect different pathways of apoptosis directly or indirectly. Sphingosine is an extracellular ligand for G-protein receptors and an intracellular second messenger to promote cell survival. Many different types of current chemotherapy drugs and some understudy compounds for cancer can at least affect one of the ceramide metabolizing enzymes. Serine palmitoyltransferases, sphingomyelinase, ceramidase, and glucosylceramide synthase are the most important enzymes involved in sphingolipid metabolism have been the discussed in many studies. Consequently, sphingolipids and their related metabolizing enzymes introduced as new pharmacological targets will be helpful in anticancer drug development.

Keywords: Sphingolipids, Ceramide, Sphingosine, Apoptosis, Cancer

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Abbreviations: AIP, apoptosis-inducing factor; BAD, Bcl-2 associated death promoter; BAK, Bcl-2-antagonist/killer; BAX, bcl-2 associated X Protein; BID, BH3 interacting domain death; COX, cyclooxygenase; D-MAPP, dimethylallyl pyrophosphate; ERK, extracellular signal-regulated kinase; FADD, Fas-associated protein with death domain; FAK, factor associated neutral sphingomyelinase; GPCR, G protein-coupled receptor; IAP, inhibitor of apoptosis protein; IL-1, interleukin-1; MAPP, myristoylaminophenylpropanol; mTOR, mechanistic target of rapamycin; NF-κB, nuclear factor-kappa-B; PDGF, Platelet-derived growth factor; PI3K, phosphoinositide 3-kinase; PLC, phospholipase C; SMAC, second mitochondria-derived activator of caspases; SPT, serine palmitoyltransferase; TLR, toll-like receptor; TNF, tumor necrosis factor; TNFR, TNF receptor; TRADD, TNF receptor type 1-associated death domain; TRAIL, TNF related apoptosis-inducing ligand; TRAMP, TNF receptor-related apoptosis-mediating protein; UDP, uridine diphosphate.

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1. Introduction

In the past few years, lipids were mainly considered for their role in maintaining the structure of the membrane and protecting it from environmental stresses in cellular-molecular studies. The findings of the last two decades have greatly changed this concept, and today many lipids play a key role as secondary messengers in regulating different cellular processes, including inflammation, fever, survival, cell proliferation, cell division, differentiation, aging and cell death [1]. Sphingolipids have been considered as the most important profile of the lipid messengers, and the factors affecting them have been the subject of various studies [2]. They are a group of 18-carbon alcohol-based lipids, namely, sphingosine, and are made in an endoplasmic system [1].

The changes that sphingosine undergoes in the influence of various enzymatic systems will ultimately lead to the formation of sphingolipids with an important structural role in the cytoplasmic membrane as well as bioactive mediators in the regulation of cell homeostasis [2]. Contrary to the construction variability of the sphingolipids, functional enzymes in the fabrication, transformation, and destruction of these compounds are common systems in cellular metabolism [3].

The occurrence of apoptosis or programmed cell death as one of the most important processes for the preservation of homeostasis in multicellular organisms is commonly used to remove unwanted or unnecessary cells and interferes with many mechanisms of the immune system or diseases [4]. Apoptosis plays a vital role in important biological processes, such as natural development, homeostasis, removal of damaged or infected cells, or activated immune cells against self-administered antigens. The incidence of many autoimmune diseases, cancers, and viral infections are results of poor performance or inhibition of apoptosis [5]. The lack of equilibrium in the incidence of this phenomenon, both decreasingly and incrementally, causes cancer or neurodegenerative disorder such as Parkinson’s and Alzheimer’s disease [4,5].

The importance of protecting cell processes from apoptosis as well as its inducing factors and, finally, the balance between these factors are so considerable. The evaluation of stimulor or inhibitor factors and messenger pathways in the occurrence of apoptosis regarded as one of the most attractive and applicable categories in various fields of biology [2,3].

Among the factors regulating this physiological (and sometimes pathologic) process, some of the sphingolipid molecules have played a determining role [2]. It has been shown that the phosphorylated sphingosine is one of the most potent inhibitors of apoptosis and mitogen stimuli, and the phosphorylated form of ceramide as a sphingosine precursor is a great inducer of apoptosis [1,6]. In addition, it has been demonstrated that the balance between the sphingosine and ceramide, as a determining factor in the fate of the cell, utilizes various operators in sending a message of life or death to the cell [3].

In the recent years, the factors enhancing or inhibiting ceramide operators and sphingolipids metabolizing enzymes, regarded as novel pharmacological targets for controlling apoptosis [6]. Other cellular processes dependent on these messengers have been the subject of discussion of various biological studies [7].

Considering the extent and complexity of ceramide and sphingosine operators and metabolizing systems as one of the most important apoptosis regulators and the introduction of some drugs affecting these pathways into clinical trials, further study in this area will be hope in treating many related disorders, including cancer [3,8].

2. The cellular apoptosis pathway

The inhibitors of apoptosis proteins (IAPs) and apoptosis-inducing proteins (AIPs) play important roles in the regulation of planned cell death. The occurrence or non-occurrence of a apoptosis, like any other physiological phenomenon, results from the balancing of a large number of messenger molecules with the effects on IAPs and AIPs [5,9]. These messenger pathways, by activating a large family of proteases called initiator caspases, have resulted in the activation of functional caspases, and ultimately functional caspases also by compacting and fragmenting the chromatin, cause the planed cell death [4].

Among the proteolytic enzymes, caspases are a group of proteins called cysteine proteases. The induction of initiating caspases, results in the breakdown of inactive dimer pre-caspases and their conversion into active and functional caspases [5].

Although two intrinsic (mitochondria-dependent) and extrinsic (dependent on cell death membrane receptors) have been identified as the main pathways for induction of apoptosis, other mechanisms, such as the endoplasmic and lysosomal pathway, have been recently reported [4,10]. The p53 molecule, as one of the most important tumor suppressors, plays a central role in stimulating the internal pathways of apoptosis and the damage to DNA is the critical factor in its action [11].

In the intrinsic pathway, factors such as environmental stress, heat, hypoxia, lack of growth factors, infections from intracellular masses and caspase-8 which activated in the external pathway of apoptosis results in increased expression of pro-apoptotic proteins of the B-cell lymphoma family such as BAX, BAK, BID, BAD and nitric oxide and attenuation of the anti-apoptosis proteins such as Bcl-2 and Bcl-XL [5,9,12]. The total of these events leads to increased permeability of the mitochondrial membrane and the formation of pores in its surface, resulting in the release of factors such as Cytochrome C and SMAC from mitochondria into the cytoplasm [13]. The release of these agents by generating the apoptosisome complex activates Caspase-9, and the activation of Caspase-9 induces caspase 3 which leads to apoptosis [14].

In the extrinsic pathway, the activation of receptors from the TNF family such as TNFR-1, CD95 (Fas), TRAMP, TRAIL-1 and 2 in the cell membrane resulted in the binding of these receptors from its intracellular sequences to ligands such as TNF-α, lymphotoxin, and Fas ligand finally, intermediaries like TRADD and FADD produce, which are Caspase-8 activators [4]. Caspase-8 also causes apoptosis with increased expression of pro-apoptotic proteins of the B-cell family and activation of functional caspases [9]. In the lysosomal pathway of apoptosis, the release of lysosomal proteases including cathepsin B, acid sphingomyelinase, acid ceramidase, etc., apart from being able to lead the cell to autophagy, will also stimulate the onset of apoptosis [10,15].

The endoplasmic reticulum is one of the major apoptosis regulating cellular organelles that plays the key role in this important biological event by making many apoptotic or antiapoptotic stimulants, including Bcl family proteins, death receptor ligands, and...
the release of calcium into the cytoplasm [2,5]. In addition, the newly synthesized (De Novo) ceramide, as one of the most important messenger phospholipids in cellular death, occurs in the endoplasmic reticulum. Golgi apparatus also plays a critical role in protecting cells from the apoptotic process by making glucosylceramides and P-glycoproteins [1].

3. Structure and role of sphingolipids in cellular physiology

Sphingolipids are a class of lipids with sphingosine as a complex amino alcohol core containing 18 carbons, which together with glycerolipids and sterols, form the major part of the cell membrane structure. Ceramide as ubiquitous sphingolipids is composed of a sphingosine, which is amide-bonded to a fatty acyl chain with different numbers of carbons, ranging from 14 to 26 [16]. Ceramides are one of the major components of the cell membrane and play a key role in protecting the cell from environmental stress [11]. The addition of phosphoethanolamine, monosaccharide or oligosaccharide together with sialic acid to ceramide leads to the formation of sphingomyelin, cerebrosides, and ganglioside, which, apart from the structural importance, they play a role as biological markers and the binding agent of extracellular ligands to the receptor [3,17].

However, over the past two decades, it has been shown that sphingolipids, especially ceramides and sphingosine, in their phosphorylated forms as messenger molecules, are crucial mediators of many physiological and pathological cellular processes, and the balance of their levels determines the fate of the cell [1,3]. Configuring processes of proliferation, cell division, fever and inflammation, aging, lipid, and sugar metabolism regulation, and many other things are also affected by these messenger molecules. In contrast, more complex sphingolipids have a constructional role and, except for a few cases, do not function as a secondary messenger [18].

Fig. 1 shows the molecular structure of important sphingolipids and compares their structural and messenger roles.

4. Sphingolipids as messenger molecules in cell survival

In recent years the results of numerous studies have shown the determinant role of ceramides and total cell sphingosine (in the phosphorylated form) in the formation of a death or cell survival message [3]. It has been shown that if this balance changes in any way towards increasing total cellular ceramide, the various pathways of the apoptosis occurrence, including the internal, external and common pathway, will be activated quickly and the cell will soon be directed to the planned death [2,18]. Conversely, the cleavage of ceramides in the cytoplasm by increasing the activity of various isoforms of ceramidase enzymes leads to an increase in the levels of intracellular sphingosine [19]. Sphingosine, by mediating environmental growth factors and stimulant cytokines of proliferation and division, is subjected to the action of the sphingosine-1-kinase. The phosphorylated sphingosine directly and indirectly (through the GPCR receptor) stimulates the factors involved in cell division, such as PI3K and PLC [6,20].

Fig. 2 shows a summary of the messaging paths of ceramide and sphingosine in determining the fate of the cell.

It has been shown that TNF induces apoptosis in tumor cells by increasing the production of ceramide, and in this way, ceramide does not require p53 [11]. The addition of exogenous ceramide also induces programmed cell death and ceramide generation is a key controller of apoptosis [7,21].

5. The main pathways of the sphingolipid metabolism as a new target for chemotherapy

The ceramide signaling pathway is known as a principal apoptosis-inducing factor in diverse tumor cells [6]. In recent decades, the elements contributing to the exogenous ceramide levels, their operators and the factors influencing its metabolism have been the subject of numerous studies [7]. Hence, consideration of enzyme systems which involved in the ceramide and sphingosine metabolism as main sphingolipids in the cell survival or cell death, and the mechanism of action of their effectors will be very helpful in this regard [17].

Many of the ceramide catabolism inhibitors, as well as its anabolism boosters, are passing clinical phases as tumor chemotherapy drugs [22]. In addition, the production of ceramide and the potentiation of its operators have been proposed as a secondary mechanism of anti-tumor activity of many chemotherapy agents and radiotherapy [19].

In Table 1, some examples of pharmacological agents which affect important enzyme systems involved in the sphingolipid metabolism are presented. Fig. 3 also shows a summary of different pathways of intracellular ceramide metabolism.

6. De novo pathway

The onset of the biosynthesis of cytoplasmic ceramide and a major part of other sphingolipids, also known as the De novo
Ceramide synthesis, is from the endoplasmic reticulum and results in the formation of ceramides from palmitoyl-CoA and serine in five steps [17]. The first step and the most important stage of ceramide biosynthesis, which is the limiting reaction speed, is the binding of serine and palmitic acid to coenzyme A, catalyzed by serine palmitoyltransferase (SPT) and results in 3-ketosphinganine generation [1]. After that, 3-ketosphinganine undergoes resuscitation, N-acetylation, and desaturation and eventually, after the addition of acyl-coenzyme A with a different number of carbons, ceramide is obtained with various numbers of carbons of the acyl group (6–24) [17]. It has been shown that inhibition of ceramide construction by suppression of this pathway with specific SPT inhibitors such as Fumonisin II, has reduced the response to tumor chemotherapy and, conversely, the mutation in this enzyme and its high basal activity, will result in an inherent discomfort of the sensory nerves [23]. Different biological agents such as nitric oxide, TNF, angiotensin II, the frequency of palmitic acid reserves, some conditions such as obesity, as well as the presence of pharmacological agents such as retinoic acid derivatives, camptothecin, daunorubicin have been introduced as the stimulus of SPT activity [1,17].

### 7. Sphingomyelinase pathway

The ceramide which made in the endoplasmic reticulum can be introduced into the Golgi apparatus by its own carriers and subject to different isoforms of the sphingomyelin synthase enzyme and convert to sphingomyelin with a similar number of carbons to that of the original ceramide. This happens by converting phosphoryl-
choline to diacylglycerol [31]. The product from this reaction is mainly used for the manufacture of myelin of the cell membrane of neurons or in the presence of the sphingomyelinase enzyme convert to ceramide [32].

The acidic form of sphingomyelinase is one of the most important isoforms of this lysosomal enzyme that performs the degradation and conversion of cytoplasmic membrane sphingomyelin to ceramide [26]. Therefore, its strengthening has become a target for anti-tumor drugs. The neutral and alkaline isoforms of sphingomyelinase are mainly present in the cytoplasm and are often magnesium and zinc-dependent, and the abundance of these heavy metals is also a factor in the enhancement of these enzymatic systems [33]. Suppression of this pathway in cancer cells has been introduced as a resistance mechanism to some chemotherapy agents [26].

Variety of sphingomyelin to ceramide converting enzymes leads to different biological responses from influential factors. Specific biologic factors such as interferon gamma, interleukin-1, heat, oxidative stress, ischemia/reperfusion stress, and factors associated with neutral sphingomyelinase (FAN) and pharmacological agents such as vitamin D3, doxorubicin, mitoxantrone and silibinin been proposed as an enhancer for varied numbers of sphingomyelinase isoforms [24,25,30]. These drugs either have anti-tumor effects, and increased ceramide production through induction of sphingomyelinase is a secondary mechanism for their effects or by enhancing the production of ceramide from this route, the probability of potential anti-tumor or tumor-preventative effects for them is posed.

On the other hand, in some studies, sphingomyelinase inhibitors also have protective effects on apoptosis in different cells. It has been demonstrated that antidepressants such as desipramine and amitriptyline, as inhibitors of acid sphingomyelinase, inhibit apoptosis, have a protective role in the heart cells and protect liver cells from fibrosis [26].

8. Ceramidase pathway

The ceramide present within the cytoplasm or in the lysosome can be broken down under the influence of various isoforms of the ceramidase enzyme and converted to the sphingosine and its free fatty acid [16]. So that not only the cell will be saved from the death mediated by ceramide, but its sphingosine base also converts to phosphorylated form, and the cells are directed to the survival and mitogenic condition [34]. Consequently, inhibitors of this enzyme can be considered as tumor suppressor agents [35].

Among the three types of ceramidase (acid, alkaline, and neutralized), the acidic form which presents in the lysosome also converts to sphingosine and sphingosine accumulation from this pathway. The mutation in this enzyme system and its lack of response to dacarbazine, have been introduced as a factor in the resistance of tumor cells to this drug [35]. We have previously shown that hesperidin derivatives
by inhibiting this enzyme are able to induce the ceramide-dependent apoptosis in HT-144 melanoma cancer cells [36].

The importance of ceramides in the cancer biology is in the way that its selective inhibitors are developing and some of them, such as MAPP and B-13, enter the clinical phases of the treatment of some tumors, such as a malignant neoplasm of the prostate [22,37]. Regarding the presence of the most important isof orm of the ceramidase, namely acid ceramidase in the lysosome, access and change the structure-activity relationship of drugs in order to increase their efficacy have been challenging issues in related studies on this field [8,28].

9. Glucosylceramide synthase pathway

The entrance of ceramide to the Golgi apparatus is considered as the gateway for the manufacture of glycosphingolipids [29]. In this case, the first step is the addition of glucose from UDP-glucose to ceramide by glucosylceramide synthase enzyme and glucosylated ceramide production [17]. In the next steps, various products of glycosphingolipids, which are mainly structural and cellular markers, are derived from this mediator or additional glucosylated ceramides in the inverse pathway of the reaction are converted by cerebrosidase into its constructive ceramide [3]. Thus, the activity of glucosylceramide synthase is a cell rescuer from ceramide-induced apoptosis and a way to chemotherapy resistance [38].

Growth factors are mainly amplifying this pathway due to the cell's need for more bulking glycosphingolipids in the cell membrane construction [39]. However, the role of the inhibitors of this pathway to ceramide elimination has been low in cell death studies, and glucosylceramide synthase inhibitors such as G2667161 have been used in some neurological disorders [29]. The previous studies have been confirmed that some of the biofavanoid derivat ives such as silibinin and hesperidin by inhibiting this enzyme, allow the accumulation of ceramide in tumor cells [30,36,40].

10. Ceramide signaling pathways

Phosphorylated ceramides use multiple operators to announce the programmed cell death orders. In fact, the ceramide messaging route is located in the upstream of many other messenger molecules and is significant in this regard [21]. Of course, it should be noted that all three main pathways for apoptosis are directly induced by the ceramide pathway, although ceramide operators seem to play a more important role in terms of multiplicity and efficiency [41,42]. In some cases, ceramide has been shown to be capable of inducing programmed cell death without activating caspases.

Generally, the ceramide messenger path operators are divided into three categories of kinases, phosphatase, and proteases, which we will discuss each of them in the following [41].

Ceramide-activated protein phosphatases (CAPPs) are the most important mediator for ceramide signaling pathways, with two major elements: proteins phosphatase 2 A (PP2A) and protein phosphatase (PP1). PP2A deactivates the main cell survival and division mediators such as Akt, c-JUN, PKCα, and BCL2, thus shutting down the propagation engine and cellular life [1,42].

Akt or protein kinase B is located in the intersection of cell metabolism and is directly in a relationship with mTOR, which controls the metabolism and vitality of many of the cells throughout the body, especially the immune-system cells. Some studies point to the fact that the activation of caspase-9 and BAD is possible only with the Akt dephosphorylation [2].

The c-JUN phosphorylated form, together with cFos, is responsible for the construction of many cell cycle transcription factors and it has been shown that this mediator in association with NF-kB is able to save the cell from a planned death induced by TNF or UV waves [43]. It has already been revealed that ceramide prepares the cell for apoptosis by turning off c-JUN.

Among the various PKC subtypes, at least two of them are influenced by the ceramide messaging pathway: PKCα and PKCδ. PKCα is one of the common types of PKC family that requires calcium liberation in cytoplasm and diacylglycerol in a cytoplasmic membrane for signaling, in order to activate ultimately many cell survival factors, including p38 and MAP-kinase [42]. Ceramide by dephosphorylating this sub-group suppresses all related pathways. On the other hand, ceramide, by increasing the activity of PKCδ, delays the rearrangement of the Bcl-x gene family as one of the most critical apoptotic suppressors, thus causing cellular death [2].

PP1, The second group of downstream phosphatases which are dependent on the ceramide pathway, play an important role in controlling of the two families of cell cycle regulator, SR and Rb proteins [3]. SR proteins (proteins with repetitive sequences of arginine and serine) in their non-phosphorylated form facilitating the phosphorylation of the Ran-sarcoma protein (RAS) [3]. Subsequently, extracellular signal-regulated kinases (ERK) pathways are inhibited as one of the main pathways for DNA replication. On the other hand, the rapidly accelerated fibrosarcoma (Raf) Factor is also activated by another group of CAPKs, which carries the message of ceramide in inflammation induced by Interleukin-1 [1].

Proteases are the third main group of ceramide-1-phosphate operators, among which cathepsin B is the most prominent member of this group. After activation of cathepsin B by ceramide, BID is broken, and truncated BID (tBID) by releasing cytochrome C from the perforations created in the mitochondria will act as an activator of caspases in apoptosis [2,14].

Fig. 4 shows the summary of cellular pathways affected by ceramide operators in apoptosis.

11. The cell signaling pathway of sphingosine

The sphingosine derived from the decomposition of ceramide by stimulating external factors such as growth promoters and some cytokines, as well as the downstream activation of the TNF receptor, is affected by the phosphodiesterase 1-kinase and acts as a bioactive mediator [18]. Phosphorylated sphingosine, by affecting some of the regulatory factors in the cytoplasm and with its intrinsic effect on related G protein-coupled receptors (GPCRs) as a cell membrane surface receptors, (mainly in opposition to the pathway of ceramide) will direct the cell to proliferation and differentiation. Hence, more expression of sphingosine 1-kinase in high-proliferation cells such as immune and mucosal cells is expected [1].

The key role of the sphingosine and its receptors have been identified in many biological phenomena such as angiogenesis, vascular permeability, and chemotaxis of B and T lymphocytes, as well as TLR receptor-dependent immunosuppression, have been identified [6]. Moreover, the reinforcement of this messaging pathway has been introduced as a mechanism for resistance to some chemotherapy agents in cancer cells.
Phosphorylated sphingosine by directly activating COX II, ERK, and NF-κB, and deactivating BAX and Caspase-3, leads to inhibition of apoptosis and induction of cell division [15]. This mediator can also withdraw from the cell and act as an autocrine or paracrine on its GPCR and depending on the type of receptor, activates various messaging paths. They include G12/G13, Gq/G1, Gs and Gi/Go and the multiplicity and diversity of these receptors justify some of the contradictory effects observed from the sphingosine in cellular life [6].

12. The role of other sphingolipids in apoptosis

As noted above, glycosphingolipids with a complex sugar structure mainly play a composition role for the cell membrane, and apart from this, they act as cellular markers and receptors. For example, the toxin of some microbial agents uses gangliosides as a pathogen binding agent to enter the cell [44].

In accordance with the subject, it has been seen that in some regions of the brain during development, Ganglioside GM3 and GD3 were significantly more pronounced than other regions, which indicates their potential role in the development of the nervous system [45,46].

While monoclonal antibodies against ganglioside GD2 had beneficial effects in the treatment of melanoma, it has been shown that GD3 as one of the downstream products of glycosylation of ceramide induces apoptosis and plays an essential role in the removal of unwanted cells during evolution [39,47], whereas high levels of GM3 associated with Parkinson’s disease with unknown origin, some studies have exhibited that this factor, by following neurotrophic agents, has a protective and increasing role for neuronal plasticity, and its derivatives are known as effective agents for the treatment of Alzheimer’s and Huntington’s Disease [48–50]. In addition to the above, in many studies, glycosphingolipids played a regulatory and pivotal role as a secondary messenger in the process of insulin resistance and fatty liver induction [51–53].

13. Conclusion

The occurrence of apoptosis is one of the main protective methods for porcelain organisms in eliminating excess cells and/or avoiding cell cycle regulatory processes and preventing them from entering the neoplasm phase. The subcellular balance of the sphingosine/ceramide cytoplasm as the most significant apoptotic regulator determines the fate of the cell, and drug interventions on the enhancing or facilitating factors of each of them will control the transform of the cell to death or life. Increasing the knowledge of molecular biology in the context of metabolic enzyme systems, Intracellular downstream operators, as well as their external influential factors, will provide a new insight in the treatment of diseases resulting from apoptosis disorders, such as cancer, diabetes, Parkinson’s and Alzheimer’s disease.

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