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Epigenetics and Sphingolipid Metabolism in Health and Disease

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Abstract

Sphingolipids represent one of the major classes of bioactive lipids. Studies of Sphingolipids have intensified in the past several years, revealing their roles in nearly all cell biological processes. In addition, epigenetic regulation has gained substantial interest due to its role in controlling gene expression and activity without changing the genetic code. In this review, we first introduce a brief background on sphingolipid biology, highlighting its role in pathophysiology. We then illustrate the concept of epigenetic regulation, focusing on how it affects the metabolism of sphingolipids. We further discuss the roles of bioactive sphingolipids as epigenetic regulators themselves. Overall, a better understanding of the relationship between epigenetics and sphingolipid metabolism may help to improve the development of sphingolipid-targeted therapeutics.

Keywords

Sphingolipids; Epigenetics; Therapeutics

Introduction

Sphingolipid Biology

Sphingolipids are bioactive lipids that contain a sphingoid base backbone, they are a class of aliphatic amino alcohols that include sphingosine, and are found in all cellular and subcellular membranes [1]. Sphingolipids can be formed by *de novo* synthesis or can be created through salvage pathways from existing sphingolipids via various enzymatic pathways, resulting in a large variety of sphingolipids including ceramides and dihydroceramides, phytoceramides, sphingosine and dihydrosphingosine (sphingaine), various phosphorylated sphingolipids, sphingomyelins, and many glycosphingolipids such as gangliosides, cerebrosides, and sulfatides (Figure 1). For example, ceramide can be deacetylated to form sphingosine, and subsequently phosphorylated to form Sphingosine-1-Phosphate (S1P), which can have dramatic impacts to cellular fate. Alternatively, ceramide can be glycosylated to form glycosphingolipids or acquire a phosphocholine group to form sphingomyelin. The synthesis and degradation of sphingolipids are finely tuned and closely regulated to maintain cellular homeostasis. On the cell surface, they can function as adhesion sites for extracellular proteins and serve both as structural lipids and signaling molecules [2]. In 1996, the "sphingolipid rheostat" model was proposed, hypothesizing that ceramide and S1P differentially regulate cellular signaling pathways involved in cellular death and proliferation/survival, respectively. Signaling molecules including growth factors, cellular stress and inflammatory mediators may alter the balance between ceramide and S1P to control cell fate [3].

Pathophysiological Roles of Sphingolipids

Structurally diverse Sphingolipids are bioactive and have roles in multiple biological processes, including cell growth, cell death, cell differentiation, inflammation, apoptosis and angiogenesis [4]. Consequently, abnormalities in sphingolipid homeostasis are implicated in aberrant pathophysiological processes such as metabolic disorders, cancers, inflammation, neurological syndromes and cardiovascular disease [4-8].

Metabolic disorders Sphingolipids influence glucose metabolism in a variety of tissues. Changes in sphingolipid levels have consequential pathophysiological effects in metabolic syndromes [6-8]. It has been observed that diabetic patients have elevated plasma ceramide levels, which improve following Roux-en-Y bypass surgery and correlates to weight loss and restoration of insulin sensitivity [6]. Furthermore, increased levels of ceramide results in attenuation of insulin action, most likely via inhibition of AKT [4,7,8]. In a similar manner, other sphingolipids, including sphingomyelin, glucosylceramide, and other glycosphingolipids, have been shown to inhibit insulin action [8-10]. Beyond its ability to blunt insulin signaling, ceramide

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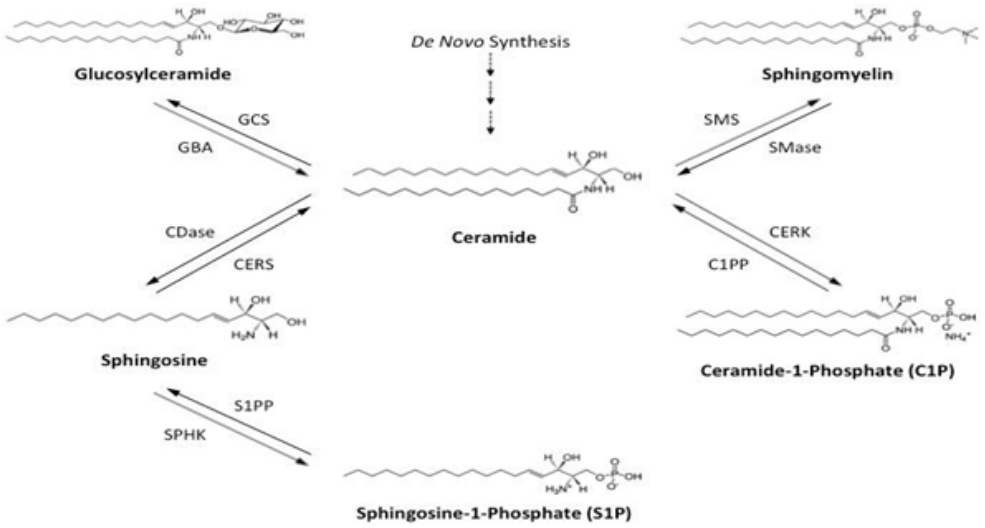

Figure 1: Ceramide is at a hypothetical center of Sphingolipid metabolism. *De novo* ceramide synthesis initially generates dihydro-sphingoid species prior to desaturation. Salvage ceramide synthesis, or turnover by the successive activities of acidic/lysosomal-localized catabolic enzymes, generates sphingosine that escapes the lysosome to be re-acylated to ceramide. Glucosylceramide synthase (GCS); cerebrosidase (GBA); sphingomyelin synthase (SMS); ceramide kinase (CERK), C1P phosphatase (C1PP); ceramidases (CDase); ceramide synthases (CERS); sphingosine kinases (SPHK); S1P phosphatase (S1PP).

has also been shown to cause beta islet apoptosis through a process known as lipotoxicity and to reduce the expression of the insulin mRNA transcript [6-8]. On the contrary, extracellular S1P carried by high-density lipoprotein can increase insulin levels by protecting pancreatic islet cells from apoptosis [11].

Cancer: Sphingolipids have a strong influence in the development and progression of cancer and are clearly implicated in cell death, proliferation, and multi-drug resistance. Ceramide can function as a tumor suppressor lipid by potentiating signaling events that drive apoptosis, autophagic responses and cell cycle arrest [12]. Increases in total plasma ceramide during a course of radiation therapy correlated with disease response in a phase II trial of metastatic colorectal cancer [13]. However, defects in ceramide generation and metabolism in cancer cells contribute to tumor cell survival and resistance to chemotherapy likely by neutralizing ceramide or generating pro-survival and mitogenic sphingolipids such as S1P [12]. Increased S1P signaling via S1P receptor (S1PR) 1 and 2 in endothelial cells are implicated in angiogenesis and inflammatory pathways, potentially contributing to tumor growth, invasion and metastasis [4,7].

Inflammation: During inflammation, immune cells are recruited to sites of infection or injury and produce a cytokine response necessary to protect the host. However, unchecked inflammation can lead to numerous pathophysiological states such as autoimmune disorders. Recently, it has been demonstrated that circulating S1P plays a critical role in lymphocyte egress [14,15]. S1P is enriched in lymph and blood compared to interstitial fluids. Furthermore, the majority (~65%) of plasma S1P is complexed with Apolipoprotein M (ApoM) [16]. ApoM–S1P is dispensable for lymphocyte trafficking yet restrains lymphopoiesis by activating S1PR1 on bone marrow lymphocyte progenitors. Thus, the signaling axis of ApoM–S1P–S1PR1 regulates the lymphocyte emigration from draining lymph nodes and adaptive immune responses [16]. High levels of S1P have also been found in patients with rheumatoid arthritis and with ulcerative colitis [17,18]. Altogether, these roles for S1P signaling in inflammatory and immune disease have led to clinical trials and approval of various S1PR modulators [17]. This is highlighted by approval of the S1PR1 modulator Gilenya™ (FTY720, fingolimod) for the treatment of relapsing-remitting multiple sclerosis, which works to sequester lymphocytes and prevent autoimmune-mediated damage to myelin in the central nervous system [19].

Neurological Disease: In humans, sphingolipid concentrations are highest in the nervous system where their dysfunction contributes to neurological diseases. Key sphingolipid species are critical for the normal development and function of the brain. Gangliosides, which are heavily glycosylated sphingolipids, are major components of neuronal membranes and account for 10-12% of the lipid content in the nervous system [20]. There is evidence that gangliosides can contribute to the initiation and progression of Alzheimer's disease by facilitating plaque formation [21]. Conversely, defective ganglioside biosynthesis is associated with the development of epilepsy through a loss-of-function mutation in the monosialodihexosylganglioside 3 (GM3) synthase gene [22].

Cardiovascular Disease: Recent data suggests that specific ceramide species are linked to cardiovascular disease [23]. Higher plasma levels of sphingomyelin have been associated with increased atherosclerosis and have been proposed as independent risk factors for coronary heart disease in humans [24]. Similarly, plasma ceramides have found utilization in predicting cardiovascular death in patients with stable coronary artery disease and acute coronary syndromes [25]. Inhibition of *de novo* ceramide synthesis has been explored as a post-ischemic strategy to reduce myocardial reperfusion injury [26]. In contrast, plasma S1P is believed to be cardioprotective. Low S1P levels have been associated with impaired cell signaling and ischemic heart disease, although the exact relation between the two has not been conclusively addressed [27].

Sphingolipidoses: Several inherited disorders exist effecting sphingolipid catabolic pathways, and result in the aberrant cellular accumulation of sphingolipids. These disorders are often referred to as lipid storage disorders, and can result in severe pathological manifestations that may include developmental, neurological, hematological, cardiac, and immunological effects. Sphingolipid storage diseases can result from defects influencing

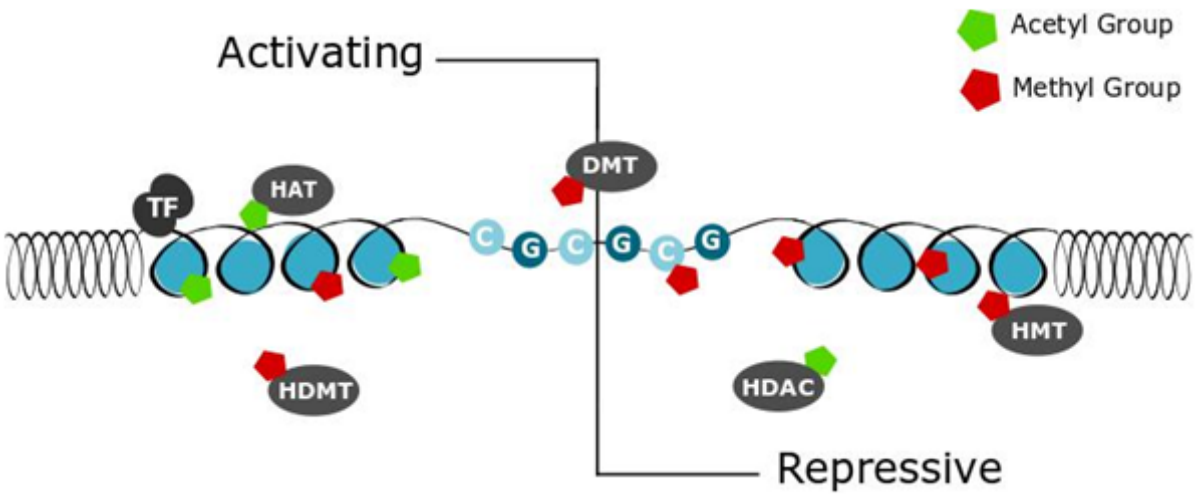

Figure 2: Epigenetic regulation is a dynamic process that occurs above the level of traditional base pair alterations. Common modifications include acetylation, methylation, phosphorylation, and ubiquitination. Chromatin remodeling events can be either activating or repressive and occur at the histone level. Common activating events at the chromatin level include acetylation of histone tails by Histone Acetyl Transferases (HAT) and removal of methyl groups by Histone Demethyltransferases (HDMT). However, addition of methyl groups by Histone Methyl Transferases (HMT) can also be activating. These modifications produce an open chromatin state, in which transcription factors can more easily access the DNA and facilitate gene expression. Common repressive events at the histone level include removal of acetyl groups by Histone Deacetylases (HDAC) and addition of methyl groups by HMTs. Epigenetic control can also be exhibited by direct modifications to nucleotides in certain sequences, such as CpG islands. Addition of methyl groups by methyltransferases is a repressive mark and reversal of methylation by Demethyltransferases (DMT) is frequently activating.

acid ceramidase (Farber) [28], acid sphingomyelinase or certain lipid transporters (Niemann-Pick) [29], acid glucocerebrosidase (Gaucher) [30], galactosylcerebrosidase (Krabbe) [31], alpha galactosidase A (Fabry) [32], beta-hexosaminidase A (Tay-Sachs) [33], or arylsulfatase A (metachromatic leukodystrophy) [34], as well as various other glycosphingolipid pathways. These sphingolipidoses are recognized as Mendelian disorders, and epigenetic influences have generally not been recognized or characterized. However, recent evidence suggests that epigenetic factors may account for some phenotypic differences that present between patients with the same disorders [35]. Current treatment approaches for many of these sphingolipidoses utilize either substrate reduction therapy or enzyme replacement therapy [28-35].

Epigenetic Regulation

The human genome is an expanse of genomic loci that contain protein-coding genes and their regulatory elements. Genes are only actively expressed when they are accessible to regulatory factors and transcriptional machinery, otherwise they are suppressed within compact and inaccessible structures [36]. Epigenetics describes inherited traits that are functionally relevant changes to the genome which cannot be identified by changes in the nucleotide sequence (Figure 2). Covalent modifications to histones and DNA without altering the DNA nucleotide sequence facilitate gene expression patterns [37]. These changes can be maintained through multiple cell divisions or may persist for multiple generations as non- genetic factors leading to quasi-permanent changes in gene expression [38]. Epigenetic regulation of gene expression is essential for normal development and cellular function. Changes in chromatin configuration may cause a wide range of diseases by altering the activity of specific genes [39]. Currently, three major mechanisms are involved in the epigenetic regulation of gene expression patterns: DNA methylation, histone modification and non-coding RNAs.

DNA Methylation

DNA methylation refers to methylation of cytosine at the 5'-position, converting it to 5- methylcytosine. DNA methylation is mainly catalyzed by three DNA methyltransferases (DNMTs): DNMT3A and DNMT3B primarily establish new sites of methylation whereas DNMT1 maintains existing methylation patterns [40]. Cytosine methylation within DNA sequences that serve as recognition sites for transcription factors can directly interfere with their binding or recruit transcriptional repressor complexes, which can repress transcription of genes. Most of our DNA is heavily methylated, thus DNA methylation is critical for silencing of transcription and resulting in changes to numerous cellular processes [41]. Abnormalities in DNA methylation play a role in pathological processes such as carcinogenesis and oncogenesis. As a result, DNMT inhibitors are being explored as potential cancer therapies. These inhibitors are cytidine analogues and work by incorporating into replicating DNA, covalently binding to the catalytic sites, and inhibiting the enzymatic activities of DNMTs [41].To date, two DNMT inhibitors — azacitidine (also known as 5-azacytidine) and decitabine (also known as 5-aza-2'-deoxycytidine), have been approved by the FDA for the clinical treatment of myelodysplastic syndrome [42].

Histone Modification

Histones are the chief protein components of chromatin that act as spools for DNA. Histones affect gene transcription by changing the accessibility of chromatin to transcription factors and gene expression machinery. They are subject to a wide range of modifications, including methylation, acetylation, phosphorylation, and ubiquitination [43]. Most studies regarding transcriptional changes with respect to histone modification have focused on acetylation and methylation [44]. Histone acetylation primarily occurs at lysine residues H3K18 and H3K27. The acetylation alters the net charge of the histone, weakening its interaction with DNA, leading to a more open chromatin state. The enzymes responsible for this type of modification are Histone Acetyl Transferases (HATs), and are antagonized by Histone Deacetylases (HDACs). Over expression of HDACs are observed in many cancer types, including prostate, gastric, and endometrial cancers [44]. Currently, three HDAC inhibitors are approved by the FDA: vorinostat (also known as Suberanilohydroxamic Acid or SAHA) for the treatment of cutaneous T cell lymphoma [44],

belinostat for the treatment of peripheral T cell lymphoma[45] and romidepsin for the treatment of both cutaneous and peripheral T-cell lymphoma [46].Histone methylation occurs on both lysine and arginine residues. Methylation of residue H3K4 acts to enhance gene expression whereas methylation of residues H3K9 or H3K27 represses gene expression. Methylations of histones are catalyzed by histone methyltransferases and are removed by histone demethylases. Specifically, methylation of H3K27 is regulated by Polycomb-group proteins (PcG), which are important in many aspects of development like homeotic gene regulation and X chromosome inactivation [47,48]. The catalytic enzyme in the PcG, EZH2, is upregulated in numerous cancers. Currently, inhibitors of several histone methyltransferases are in clinical trials, such as inhibitors of EZH2 and DOT1L, although none have been approved [49].

Non-coding RNAs

Non-coding RNA transcripts, including microRNAs (miRNAs), piwi-interacting RNAs (piRNAs), circular RNAs (circRNAs), and long noncoding RNAs (lncRNAs), have a profound epigenetic influence on transcriptional output of the genome [50]. Approximately 50% of miRNA genes are repressed by epigenetic methylation of their own promoter while other miRNAs are derived from spliced intronic sequences of coding mRNA [50]. After being processed into mature miRNA and incorporated into the RNA-Induced Silencing Complex (RISC) miRNAs bind to the 3'-UTR of target mRNAs for degradation. A single miRNA is capable of binding and degrading multiple mRNAs [51]. Like miRNAs, piRNA associate with the RISC complex and function as a gene silencing mechanism, especially by silencing transposons. Originally, piRNAs were thought to be expressed exclusively in germline tissue and only play a biological role in development. Recent evidence has implicated piRNA to be a functional epigenetic modifier in both germ and somatic stem cell self-renewal as well as tumorgenesis [51]. Conversely, ciRNA antagonize gene silencing by acting as miRNA "sponges" or as a decoy to miRNA's normal target genes, and therefore can play a key role in disease progression, especially cancer [52]. Lastly, lncRNA have the most dynamic range of epigenetic regulatory mechanisms that have been characterized to date. This includes functional roles in chromatin remodeling, X-chromosome inactivation, RNA splicing, genomic imprinting and DNA methylation [40,52-55].

Epigenetic Regulators of Sphingolipid Metabolism

Beyond being lipid components of cellular membranes, sphingolipids mediate signaling functions in both physiological and pathological processes. Multiple factors including development, environmental chemicals, drugs and diet affect sphingolipid homeostasis through epigenetic mechanisms [38,56].

Development

Gangliosides are a class of glycosylated sphingolipids with one or more sialic acids bound to a carbohydrate and are particularly abundant in the nervous system [57]. During brain development gangliosides shift from simple to complex species through a process mainly regulated by the staged expression of genes that encode the glycosyltrasferase enzymes [58]. In mice, developmental alteration of gangliosides is regulated through histone acetylation of the glycosyltransferase enzymes. Furthermore, HDAC inhibitors can effectively change the expression patterns of gangliosides and glycosyltransferases in neuroepithelial cells [59].

Environmental Factors

Hypoxia occurs from stress at high altitude or an otherwise oxygen-depleted environment. In tissues and cells, hypoxia can occur when cellular oxygen demand exceeds that which can be supplied often during times of limited blood flow [60]. During hypoxia, hypoxia-inducible transcription factor-1α (HIF-1α) is expressed to enhance energy metabolism and autophagy. Recent studies found that hypoxia induces the expression of HIF-1α through increased activity of sphingosine kinase (SPHK). This effect can be blocked by administration of a SPHK inhibitor or S1PR antagonists [61]. Stabilization of HIF-1α further increases the expression of distinct histone lysine demethylases to promote gene expression [60]. Thus, sphingolipid metabolism is closely intertwined with epigenetic changes in chromatin during hypoxia. Similarly, cigarette smoke has long been proven to induce epigenetic modifications such as aberrant methylation [62]. It is also the major cause of chronic obstructive pulmonary disease (COPD) where alveolar macrophages are defective in their ability to phagocytose apoptotic cells [63]. Cigarette smoke extract significantly increases expression of S1PR5. In alveolar macrophages from COPD patients, the expression levels of S1PR5 is significantly increased and is correlated with defective efferocytosis [64]. Furthermore, this dysregulation of the S1P signaling system is caused by reduced DNA methylation of the S1PR5 gene. In this way, decreased promoter methylation releases gene transcription of *S1PR5*, which is essential for S1P-mediated clearance of apoptotic cells [64].

Drugs

Neutral Sphingomyelinase-2 (nSMase2) is a key ceramide-producing enzyme in cellular stress responses. Tretinoin, also known as All-Trans Retinoic Acid (ATRA), is used in the treatment of Acute Promyelocytic Leukemia (APL) [65,66]. Although the mechanism of action is still unknown, studies have demonstrated that tretinoin encourages progenitor cells in APL patients to differentiate terminally which thereby ameliorates the progression of the disease [65,66]. A recent study identified nSMase2 as an early ATRA-induced gene and implicated nSMase2 as having a role in growth arrest after ATRA treatment [67]. Furthermore, ATRA regulates nSMase2 directly through modulation of histone acetylation in a CREB-binding protein- and p300-dependent manner [67].

Mesenchymal stem cells (MSCs) are multipotent progenitor cells that can be used to improve tissue repair. Current MSC therapies are often primed with bioactive lipids such as S1P and ceramide-1-phosphate, which can enhance *in vivo* engraftment and survival of transplanted cells [68,69]. A recent study found that the HDAC inhibitor Valproic Acid (VPA) enforced the priming effect of S1P at a low dosage in human umbilical cord-derived MSCs through the activation of the MAPK and AKT signaling pathways [70]. This study indicates that the combinatory effects of epigenetic modulators and S1P-priming strategies can improve the therapeutic potency of stem cells. Similarly, VPA induces the generation of glycosphingolipid GM3, a known suppressor of epidermal growth factor receptor phosphorylation, to suppress cancer cell proliferation [71]. Additionally, another HDAC inhibitor, AR-42, exerts an anti-colon cancer activity partially through *de novo* ceramide production [72].

Toxins

Fumonisin B1 (FB1) is toxin that comes from the Fusarium family of molds, which commonly are found in maize- and wheat-based foods and feed products [73-76]. Hepatotoxicity, nephrotoxicity and carcinogenicity can occur following dietary exposure to FB1, which is a well-recognized inhibitor of *de novo* ceramide synthesis due to its ability to inhibit (dihydro) ceramide synthase activity [73-76]. Therefore, exposure to FB1 mostly results in the accumulation of dihydrosphingosine (sphinganine) and dihydrosphingosine-1-phosphate (dhS1P). Interestingly, it has been shown that FB1 exposure may lead to liver tumorigenesis by disrupting DNA methylation and chromatin modifications which causes chromatin instability in HepG2 cells [73,74]. This indicates that FB1 may act as an epigenetic regulator, or alternatively, either dihydrosphingosine (sphinganine) or dhS1P. Importantly, studies have shown that FB1-breakdown products do not exert the same toxicities or alterations to sphingolipid metabolism [75,76]. This reinforces that FB1, or the sphingolipids it regulates, are specifically involved in its mechanisms of toxicity.

Sphingolipids as Epigenetic Regulators

As mentioned, bioactive sphingolipids serve both as structural lipids and signaling molecules. Aside from prominent roles associated with localization at the plasma membrane, sphingolipids and their metabolizing enzymes are also found in the nucleus, and associated with the nuclear matrix and chromatin. Their metabolism in the nucleus is linked to the remodeling of chromatin and epigenetic regulation of gene expression [77].

S1P

S1P is the first identified endogenous nuclear regulator of HDACs [78]. In human MCF-7 breast cancer cells, nuclear S1P was found to specifically bind to HDAC1 and HDAC2 and inhibited their enzymatic activity [78]. Another study in dystrophic mice revealed that expression of S1P increased histone acetylation of specific genes, in which inflammatory genes are down regulated while metabolic genes are upregulated, helping muscle cells maintain energy metabolism [79]. Additionally, in a *drosophila* model of Duchenne muscular dystrophy, S1P was found to increase the capacity of the muscle cell to use fatty acids as an energy source by inhibiting the acetylation of specific histone residues [79]. Thus, nuclear S1P is directly involved in epigenetic regulation of gene expression by modulating histone acetylation. In a somewhat contrasting manner, the degradation of S1P by the S1P lyase has been attributed to the regulation of sepsis-mediated inflammation. This is attributed to S1P degradation products serving as regulators of histone acetylation [80].

Ceramide

Inhibitor 2 of Protein Phosphatase 2A (I2PP2A) is a biological inhibitor of the cellular serine/threonine protein phosphatase PP2A [81,82]. I2PP2A has been suggested to be oncogenic and is overexpressed in many tumor cell types. I2PP2A also has other targets besides PP2A, e.g., DNA exonucleases and the modification of histone acetylation [82]. Ceramide could potentially disrupt the association between PP2A and I2PP2A. Additionally, ceramide inhibits I2PP2A's upregulation of c-Myc and its downregulation of histone acetylation in prostate cancer cells, blocking the epigenetic action of I2PP2A [82]. Conversely, in Madin- Darby canine kidney cells, sphingomyelin-derived ceramide has been shown to inhibit the deacetylation of microtubules which induces formation of a ciliogenic lipid-protein complex that can sustain primary cilia [83]. This may not be directly epigenetic in nature, but involves the regulation of a post-translational modification that also plays a role in epigenetics.

Gangliosides

Gangliosides are expressed primarily on the outer leaflet of the plasma membrane of cells in all vertebrates, and are most abundant in the nervous tissues [84]. The ganglioside GM1 is associated with gene regulation in neuronal cells through an interaction with active chromatin via acetylated histones, binding acetylated histones H3 and H4 on the promoters of the *GalNAcT* and *NeuroD1* genes [84,85]. This interaction activates neuronal differentiation in neural stem cells, and can be promoted by exogenous supplementation of ganglioside GM1 [84,85].

Sulfatide

Sulfatide also is a galactosphingolipid mostly known for its role in the myelin sheath. In hepatocellular carcinoma cells, it suppresses miR-223 expression in association with reduced recruitment of acetylated histone H3 and C/EBPα to the pre-miR-223 gene promoter [86]. Furthermore, sulfatide also stimulates the expression of histone deacetylases HDAC9 and HDAC10, and enhances their recruitment to the miR-223 gene promoter [86].

Concluding Thoughts

Sphingolipid metabolism and epigenetic modulation are closely intertwined with one another. Epigenetic regulation is an important regulatory mechanism for controlling the expression pattern of sphingolipids. Conversely, sphingolipids in the nucleus can directly modify transcriptional activity via epigenetic modulation. An understanding of both processes is critical. Sphingolipids are integral in both normal development and the pathological processes leading to disease [4]. A deeper investigation in the context of the pathophysiology of disease development of the sphingolipid metabolic influence on epigenetic regulation, and the reciprocal relationship, can potentially lead to new diagnostics and therapeutic targets. Future studies of the relationships between epigenetics and sphingolipid metabolism should address the following questions: 1) what other sphingolipids directly influence epigenetic regulation, 2) how aberrant epigenetic regulation and sphingolipid metabolism directly contribute to the development of cancer and other diseases, and 3) what are the mechanisms that dictate the interplay between epigenetic and sphingolipid metabolic regulation? Investigation of these questions will undoubtedly yield results that inform a new generation of molecular and sphingolipid-targeted therapies.

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