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REVIEW

Advances in ORMDL Research in Malignant Tumors: A Review

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Abstract: ORMDL proteins (ORMDL1, ORMDL2, ORMDL3) are transmembrane proteins in the endoplasmic reticulum (ER) that regulate sphingolipid metabolism, maintain ER homeostasis, and modulate cellular stress responses. They influence cell proliferation, apoptosis, and metabolic balance. Recent studies have highlighted the altered expression and function of ORMDL proteins in various tumors, including breast cancer, DLBCL, colorectal cancer, and lung cancer. ORMDLs negatively regulate serine palmitoyltransferase (SPT), affecting ceramide and sphingolipid metabolism, which plays a key role in tumor cell proliferation, invasiveness, and resistance to therapy. The dysregulation of ORMDL expression may disrupt sphingolipid metabolism, trigger ER stress, and impair autophagy. Investigating ORMDL functions in cancer could lead to novel insights into tumor development and progression. ORMDL expression may serve as a potential biomarker for cancer diagnosis, prognosis, and therapeutic response prediction. Targeting ORMDL or its metabolic networks offers promising strategies for cancer therapy. Although research on ORMDLs is still in its early stages, further studies are needed to explore their roles in the tumor microenvironment, interactions with the immune system, and applications in personalized medicine. A deeper understanding of ORMDL proteins will enhance tumor diagnosis, treatment, and the development of new therapeutic approaches.

Keywords: malignant tumors, ORMDL, molecular targeted therapy, sphingolipid metabolism

Introduction

Cancer is one of the leading causes of death worldwide and ranks as the second most common cause of death across all countries. Despite notable progress in cancer screening and treatment, it remains a major public health challenge. Driven by factors such as population growth, aging demographics, and the widespread adoption of unhealthy lifestyles, the global incidence and mortality rates of cancer are expected to continue rising in the coming decades, further intensifying the global disease burden. Data from 2022 show nearly 20 million new cancer cases and approximately 9.7 million cancer-related deaths worldwide. It is estimated that about one in five men or women will develop cancer during their lifetime, and roughly one in nine men and one in twelve women will eventually die from it. These figures highlight the continuous escalation of the global cancer burden and demonstrate that countries worldwide are experiencing similar rising trends in cancer incidence and mortality.[1–3] For localized or non-metastatic cancers, surgery and radiotherapy are typically the primary treatments, while metastatic cancers are commonly managed using anti-tumor drugs such as chemotherapy, hormone therapy, and biological therapy.[4] Traditional chemotherapeutic agents work by targeting rapidly dividing cells, effectively killing cancer cells but also harming normal proliferative cells such as those in hair follicles,

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bone marrow, and the gastrointestinal tract, leading to side effects like hair loss, immunosuppression, and gastrointestinal disturbances. Additionally, the inherent toxicity of chemotherapy and the development of drug resistance in tumor cells further compromise treatment efficacy.[4] In recent years, with an improved understanding of tumor molecular mechanisms, novel targeted therapies have been developed that block specific signaling pathways, act on particular proteins, induce cancer cell death, activate the immune system, or deliver drugs precisely to tumor sites, thereby enhancing treatment effectiveness and minimizing damage to normal tissues.[4] Following the approval of multiple targeted therapies by the US Food and Drug Administration (FDA), these approaches have gained increasing prominence and brought new hope for cancer patients.[4] In esophageal cancer (EC), commonly studied biomarkers include RNA molecules (such as mRNA, miRNA, and long non-coding RNA), proteins, metabolites, immune-related molecules, and microbiome-associated markers.[5] Although proteomics holds great potential for biomarker discovery, its clinical application is still limited by high costs, whereas epigenetic markers, which can be easily detected in tissues and body fluids (such as blood, plasma, and urine), are considered to have promising prospects.[5] Currently, commonly used serum tumor markers such as squamous cell carcinoma antigen (SCCA) and carcinoembryonic antigen (CEA) still demonstrate limited specificity and sensitivity for the early diagnosis of esophageal cancer.[5]

In breast cancer, the ERBB2 status has been confirmed to correlate with clinical characteristics,[6] and increasing evidence suggests that ERBB2 may also predict patient responses to chemotherapy and endocrine therapy.[6] Therefore, to improve cancer cure rates and survival outcomes, there remains an urgent need to discover novel molecular biomarkers and to develop more precise diagnostic technologies and more effective therapeutic strategies, enabling earlier tumor detection and better prognostic outcomes.[5,6] The ORMDL protein family (ORMDL1, ORMDL2, and ORMDL3) regulates the catalytic activity of serine palmitoyltransferase (SPT) through direct binding, thus maintaining normal SPT function. These proteins are highly conserved across different species; in prokaryotes, the interaction between SPT and ORMDL is regulated by phosphorylation, whereas eukaryotic ORMDL proteins lack these phosphorylation sites.[7] In mammals, ORMDL genes encode endoplasmic reticulum (ER) transmembrane proteins that sense ceramide levels, maintain sphingolipid metabolic balance, and participate in protein folding within the ER. Genome-wide association studies have identified ORMDL3 as a risk factor for ulcerative colitis, a disease with a certain risk of malignant transformation. In cancer-related studies, ORMDL family proteins have been found to interact with SPTLC1 and contribute to the progression of clear cell renal cell carcinoma. Moreover, in colorectal cancer, ORMDL1 expression is upregulated and has been associated with favorable patient prognosis.[8] Given their critical role in regulating sphingolipid metabolism, ORMDL proteins may serve as important targets for influencing tumor cell proliferation, apoptosis, and migration. Targeting ORMDL proteins could provide a novel strategy for modulating tumor biological behavior and developing innovative therapeutic approaches.

Sphingolipids, similar to glycerolipids, serve as crucial storage forms of bioactive metabolites and are widely involved in various cellular signaling pathways and pathophysiological processes. Their metabolic derivatives, including ceramide, ceramide-1-phosphate (C1P), and sphingosine-1-phosphate (S1P), have been shown to play key roles in regulating cell proliferation, survival, immune cell migration, and maintaining the integrity of vascular and epithelial structures—functions that are particularly critical in the development of inflammation and cancer.[9] S1P and C1P are recognized as key bioactive molecules in inflammation and tumor progression. Studies have indicated that S1P plays a central role in the development of inflammation-associated colorectal cancer, while C1P may be involved in tumor cell proliferation, migration, survival, and inflammatory responses; however, it remains unclear whether C1P directly contributes to the formation of inflammation-associated cancers.[10] In samples from Japanese patients, researchers utilized LC-ESI-MS/MS technology to compare sphingolipid metabolite levels between normal breast tissue and breast cancer tissue, revealing a significant elevation of sphingolipids such as S1P and ceramide in breast cancer tissues. This finding suggests that S1P may play a critical role in breast cancer and its tumor microenvironment.[10] Dysregulation of sphingolipid metabolism is a hallmark of various diseases. The biosynthesis of sphingolipids is initiated in the endoplasmic reticulum, where serine palmitoyltransferase (SPT) catalyzes the condensation of serine and palmitoyl-CoA to generate the first committed intermediate of sphingolipid synthesis, 3-ketodihydrosphingosine.[7]

In recent years, studies on ORMDL have revealed its key role in a variety of biological processes, especially in immune response, tumorigenesis and cardiovascular diseases.[11] ORMDL proteins are thought to play an important role in cellular stress responses, especially through the regulation of endoplasmic reticulum stress, inflammatory responses, and lipid

metabolic pathways.[12–15] Recent studies have shown that ORMDL is closely associated with the development of a variety of diseases, especially in diseases associated with immune system dysfunction, such as asthma and autoimmune diseases.[16,17]

In the field of cancer, ORMDL is considered to be an important factor in the regulation of the tumor microenvironment. ORMDL may affect tumor growth, metastasis, and immune escape by regulating the interaction of tumor cells with surrounding host cells (eg, immune cells, vascular endothelial cells, etc).[18,19] Recent studies have found that ORMDL expression is upregulated in a variety of cancers and that it may play a role in immune escape mechanisms, particularly in suppressing T cell function and promoting immunosuppressive cell activity.[8,20]

The aim of this review is to provide an overview of the potential of ORMDL proteins in tumor immunotherapy, focusing on their role in cancer immune escape and their research progress as potential therapeutic targets. By summarizing the existing research results, this paper hopes to provide insights into related studies and promote the development of ORMDL as a new target for the treatment of cancer and other immune-related diseases.

Literature Search Strategy

To ensure the comprehensiveness and relevance of this review, we performed a narrative literature search using databases including PubMed, Web of Science, and Google Scholar. The keywords used included "ORMDL" "ceramide" "sphingolipid metabolism" and "cancer" combined with specific terms such as "proliferation" "metastasis" and "drug resistance."

Structure and Function of ORMDL

The ORMDL protein family, comprising ORMDL1, ORMDL2, and ORMDL3, consists of highly conserved transmembrane proteins localized to the endoplasmic reticulum (ER) membrane (Table 1). The three ORMDL genes are located in

Table 1 Proteins of the ORMDL Family

Classification	Information
Family Members	ORMDL1, ORMDL2, ORMDL3
Gene Locus	ORMDL1: 2q31–32; ORMDL2: 12q13; ORMDL3: 17q21
Co-localized Genes	Co-localized with HOXD (2q), HOXC (12q), and HOXB (17q), respectively
Structural Features	Small endoplasmic reticulum (ER) transmembrane proteins with a conserved transmembrane domain; the N-terminus and C-terminus are positioned in the cytosol and ER lumen, respectively
Homology	Share approximately 80% amino acid sequence homology in humans and up to 95% in mice
Conservation	Highly conserved across species; eukaryotic ORMDL proteins lack the phosphorylation sites related to SPT regulation found in prokaryotes
Subcellular Localization	Primarily localized to the ER membrane; the cytosolic domain mediates signaling and protein–protein interactions, while the luminal domain may contribute to protein folding and metabolic regulation
Function 1	Inhibit serine palmitoyltransferase (SPT) activity, negatively regulating sphingolipid and ceramide biosynthesis to maintain ceramide homeostasis
Function 2	Regulate sphingolipid synthesis, calcium homeostasis, and the unfolded protein response (UPR)
Function 3	Facilitate protein folding within the ER
Function 4	Modulate mast cell functions and maintain the balance of inflammatory responses, with ORMDL3 playing a particularly prominent role
Effects of Deletion	Decreased ORMDL3 expression leads to increased production of pro-inflammatory cytokines and COX-2; deficiency of ORMDL1/2 further amplifies inflammatory responses
Pathological Significance	Dysregulation of ORMDL expression or function disrupts sphingolipid metabolism, impacts cell survival and apoptosis, and is associated with the development of cancer and other diseases

homologous regions on chromosomes 2q, 12q, and 17q, which also contain fragments from chromosomes 7 and 3,[21] including clusters of HOX genes and other protein family members. For example, ORMDL1 is located near the HOXD cluster on 2q31–32, ORMDL2 is near the HOXC cluster on 12q13, and ORMDL3 is adjacent to the HOXB cluster on 17q21.[22] The proteins encoded by the ORMDL genes are anchored in the ER membrane and constitute a three-member transmembrane protein family.[22,23] Their transmembrane domains embed them within the ER membrane, providing a structural basis for interactions with other ER proteins, such as SPTLC1. ORMDL proteins are a class of evolutionarily conserved ER membrane proteins whose primary known function is to inhibit the activity of serine palmitoyltransferase (SPT), thereby downregulating sphingolipid biosynthesis. In humans, ORMDL1–3 share approximately 80% amino acid sequence homology, while in mice, this homology reaches up to 95%.[12] In addition to their role in regulating sphingolipid metabolism, ORMDL proteins are also involved in the modulation of calcium homeostasis and the unfolded protein response (UPR).[23] Their subcellular localization and responsiveness to certain drugs in yeast suggest a potential involvement in protein folding processes within the ER.[22] Structurally, the N-terminus and C-terminus of ORMDL proteins extend into the ER lumen and the cytoplasm, respectively; the cytoplasmic portion may participate in signal transduction and protein–protein interactions, while the luminal domain may be associated with metabolic regulation or protein folding.

Although ORMDL proteins are conserved across multiple species, eukaryotic ORMDL1–3 lack the phosphorylation sites that regulate the interaction with SPT in prokaryotes.[7] ORMDL proteins, particularly ORMDL3, play a crucial role in regulating mast cell function and controlling inflammatory responses. Downregulation of ORMDL3 expression increases the levels of pro-inflammatory factors and COX-2, while the absence of ORMDL1 and ORMDL2 further enhances this response, causing mast cells to become activated and release inflammatory mediators even in the absence of antigenic stimulation. This suggests that ORMDL proteins are important negative regulators of inflammation, and their functional imbalance could lead to uncontrolled inflammation.[12] ORMDL proteins are key factors in regulating sphingolipid metabolism. By forming a conserved complex with SPT, they negatively regulate ceramide production. Ceramide is not only a pro-apoptotic signaling lipid but also a critical precursor for the synthesis of sphingomyelin and glycosphingolipids. Abnormal ceramide levels can impact cell growth, survival, and apoptosis. ORMDL proteins maintain stable ceramide levels through a feedback regulation mechanism, preventing excessive accumulation that may trigger apoptosis, or insufficient levels that could lead to metabolic disorders. Changes in ORMDL gene expression or mutations in phosphorylation sites may disrupt this balance, leading to sphingolipid metabolic disturbances with potential pathological implications in diseases such as cancer.[24,25]

The Role of ORMDL in Malignant Tumors

Under normal conditions, mammalian ORMDL proteins regulate ceramide synthesis and mediate a negative feedback regulation of exogenous ceramide synthesis through de novo synthesis, playing significant roles in sphingolipid metabolism and cancer (Table 2). Recent studies have shown that this feedback process involves the joint participation of all three ORMDL isoforms. In addition, previous studies have reproduced the feedback effect of exogenous ceramide on SPT enzyme activity in permeabilized cells, confirming that ORMDL proteins can directly regulate SPT activity.[25] ORMDL proteins are localized in the ER and were initially thought to be related to ER stress. Ceramide synthesis relies on the rate-limiting enzyme complex, SPT, which is negatively regulated by ORMDL proteins.[22] ORMDL proteins play a key role in maintaining sphingolipid homeostasis, a mechanism first discovered by Weissman, Chang et al through yeast studies, where they demonstrated a direct negative regulatory effect between ORMDL proteins and the SPT complex.[24,26] The co-expressed genes of ORMDL1 are involved in DNA damage response, nuclear localization, rRNA metabolism, and cell cycle checkpoints.[29] Furthermore, ORMDL1 may be a key factor connecting cholesterol and sphingolipid metabolic pathways in mammalian cells.[48] Deletion of ORMDL3 leads to a significant increase in pro-apoptotic markers in rat insulinoma cells, likely due to elevated ceramide levels.[30] Ceramide itself is a pro-apoptotic signaling molecule that inhibits tumor cell growth and induces cell death.[13] Under cellular stress conditions, ceramide and sphingosine generation can trigger tumor cell death through de novo synthesis, sphingolipid hydrolysis, or salvage pathways.[27,31] Further research into the interaction mechanisms of sphingolipid signaling within tumors and their microenvironment (such as stromal cells, endothelial cells, osteoclasts, and platelets) is essential for developing effective

Table 2 Roles, Mechanisms, and Research Advances of ORMDL Proteins and Sphingolipid Metabolism in Cancer

Themes and Mechanisms	Summary of Key Findings	Related Reference
Regulation of ceramide synthesis by ORMDL proteins	Under normal conditions, mammalian ORMDL proteins regulate de novo ceramide synthesis and provide negative feedback on exogenous ceramide. All three isoforms are essential, and ORMDL proteins modulate the activity of SPT enzymes.	[22, 24–26]
Potential roles of ORMDL proteins in cancer	The ORMDL family influences tumor cell growth, migration, invasion, and drug resistance by regulating the sphingolipid metabolic network.	[27, 28]
Association of ORMDL1 with the tumor microenvironment	ORMDL1 expression is significantly associated with B-cell infiltration in DLBCL, and gene gain mutations enhance this infiltration.	[29]
Pro-apoptotic role of ceramides	Ceramide is a pro-apoptotic molecule that can mediate cancer cell death, growth arrest, senescence, or inhibition.	[13, 27, 30–32]
Pro-survival role of sphingosine-1-phosphate (S1P)	Sphingosine-1-phosphate (S1P) promotes cancer cell survival, proliferation, and migration, acting in opposition to the effects of ceramide.	[13, 33–36]
Impact of metabolic pathways on anticancer therapy	Conversion of ceramide to S1P or GluCer leads to drug resistance, with key metabolic enzymes such as GCS, CERK, and SMS serving as critical targets.	[13, 37–39]
Relationship between endoplasmic reticulum stress and autophagy or apoptosis	Ceramide induces ER stress, which is associated with autophagy and can transition to apoptosis. For example, doxorubicin and methotrexate-induced stress leads to cell death.	[14, 40–43]
Immunomodulatory functions	Ceramide and S1P regulate immune cell functions, including enhanced CTL activity, suppression of MDSC function, and activation of the STAT3 feedback loop.	[44, 45]
Potential therapeutic value of sphingolipids in cancer treatment	Regulation of sphingolipid metabolic enzyme activity is a potential target for cancer therapy and resistance reversal, with both diagnostic and therapeutic implications.	[13, 46, 47]

anti-tumor strategies.[13] In addition, it is crucial to explore how to regulate sphingolipid signaling to enhance T cell anti-cancer activity while reducing the immunosuppressive effects of myeloid-derived suppressor cells or tumor-associated macrophages, thereby improving the efficacy of immunotherapy.[13]

The ORMDL family influences tumor cell growth, proliferation, invasion, migration, metastasis, and drug resistance in cancer by regulating the sphingolipid metabolism network.[27,28] In diffuse large B-cell lymphoma (DLBCL), the expression level of ORMDL1 is closely associated with the degree of B-cell infiltration, and gene gain mutations in ORMDL1 promote this infiltration.[29] Studies have indicated that sphingolipid metabolism is often dysregulated in various cancers.[29] Sphingolipids are essential components for maintaining the structure and function of cell membranes, and some metabolites, such as ceramide and sphingosine, act as signaling molecules to inhibit cell growth and induce apoptosis.[31,46] Phosphorylated products like sphingosine-1-phosphate (S1P) promote cancer cell survival, proliferation, and migration.[33,34] Ceramide and its metabolites often exert opposing effects in cell survival and death.[13] For instance, chemotherapy, radiation therapy, or oxidative stress induce ceramide accumulation, leading to cancer cell death or cell cycle arrest,[32] but its metabolic conversion to S1P or other forms can counteract these anti-tumor effects, resulting in treatment resistance.[35,36] At the same time, radiation-induced ceramide increases may also have toxic effects on normal tissues, highlighting the need to regulate its levels to reduce side effects.[13]

Sphingolipid metabolism in mammals is regulated by approximately 40 enzymes, which play crucial roles in cancer signaling and treatment.[13,46,47] In many tumors, the metabolism of ceramide is accelerated, with common mechanisms including enhanced activity of enzymes such as glucosylceramide synthase (GCS), sphingomyelin synthase (SMS), ceramide kinase (CERK), acidic ceramidase (AC), and sphingosine kinase (SPHK), which promote the generation of

sphingolipids with pro-survival effects.[37,38] After ceramide is hydrolyzed by AC, it generates sphingosine, which is then phosphorylated by SPHK1/2 into sphingosine-1-phosphate (S1P). S1P activates pro-survival signals via S1PR1-5 receptors.[9] Activation of ACER2 can enhance doxorubicin-induced cancer cell death, possibly related to sphingosine accumulation and oxidative stress signaling.[13] High expression of CERK, SMS, GCS, and other enzymes is closely associated with tumor development and represents potential targets for inducing cancer cell death or reversing drug resistance.[13] Additionally, sphingolipid metabolism can regulate the anti-cancer functions of immune cells, such as ceramide enhancing T cell activity and inhibiting myeloid-derived suppressor cells.[44] In contrast, S1P-S1PR signaling forms a positive feedback loop with STAT3 activation, promoting cancer progression.[45] Ceramide-induced endoplasmic reticulum stress can upregulate autophagy in glioma cells,[14] while certain treatments like doxorubicin and methotrexate activate cell death mechanisms by upregulating ceramide signaling.[40,41] However, in some cancers, such as oral cancer, C16 ceramide generated by CERS6 may have a protective role.[42,43]

Research Progress of ORMDL in Different Cancers

ORMDL proteins are key regulators of sphingolipid metabolism, primarily controlling the synthesis of ceramide by modulating the activity of serine palmitoyltransferase (SPT). They play a crucial role in maintaining cellular membrane lipid balance, responding to endoplasmic reticulum stress, and regulating various signaling pathways (Figure 1). A substantial body of research has demonstrated that ORMDL proteins are functional in multiple physiological systems and are closely associated with the development of malignancies in various organ systems (Table 3). Studies have also revealed that enzymes and metabolites involved in sphingolipid metabolism are often abnormally expressed in various cancers. For example, ceramide levels are elevated in head and neck cancer and breast cancer,[43,49] but decreased in ovarian cancer and colorectal cancer;[50,51] sphingosine is upregulated in endometrial cancer;[52] S1P is significantly overexpressed in glioblastoma;[53] while SPT expression is reduced in colorectal cancer.[54] These findings indicate that dysregulation of sphingolipid metabolism is closely linked to cancer onset, progression, and patient resistance to chemotherapy.

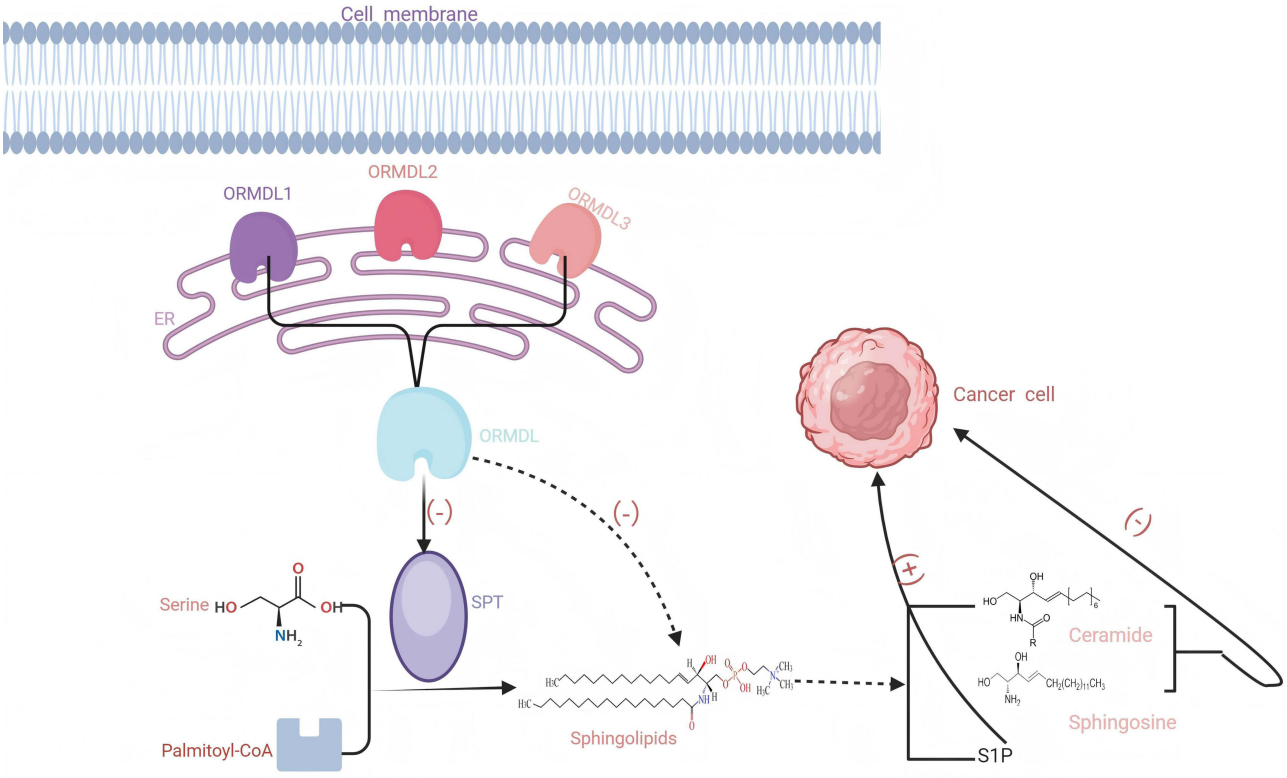

Figure 1 Endoplasmic reticulum and SPT-Orm complexes regulate sphingolipid metabolism. Created in BioRender. wang, h. (2025) https://BioRender.com/dpam01i.

Table 3 The Role of ORMDLs in Cancer

Cancer Types	Related Molecules/ Enzymes	Expression Changes	Functions or Roles	Reference
Head and Neck Cancer	Ceramide (Cer)	↑	Associated with chemotherapy resistance	[43, 49]
Breast Cancer	Cer↑, SPHK2↑, S1P↑, GCS↑, CERT↓	–	Ceramide induces neurotoxicity; CERT deficiency enhances EGFR signaling; S1P promotes cell migration; GCS maintains stem cell pluripotency	[43, 49, 55–58]
Ovarian Cancer	Cer↓, CERT↓	↓	CERT knockdown sensitizes paclitaxel treatment, inducing ceramide-dependent apoptosis/autophagy	[50, 51, 59]
Colorectal Cancer	SPT↓, CERS6↑, SPHK1↑, SPL↓, NCDase↑, AC↑	-	Disruption of sphingolipid metabolism promotes cancer; C16 ceramide enhances TRAIL sensitivity; Downregulation of SPL promotes miR-181b expression and cancer progression	[13, 50, 51, 54, 59–63]
Endometrial Cancer	Sphingosine↑	↑	Increased expression is associated with cancer development	[52]
Glioblastoma	S1P↑	↑	Associated with tumor cell proliferation and migration	[53]
Diffuse Large B-Cell Lymphoma (DLBCL)	ORMDL1↑	↑	High expression is associated with tumor recurrence and poor prognosis	[29]
Oral Cancer	GCS↑, Regulation of CERS6 C16 Cer	↑	GCS expression is associated with resistance; C16 ceramide prevents ER stress	[64]
Gastric Cancer	SGPP1↓	↓	S1P accumulation promotes migration; high SGPP1 expression improves overall survival (OS) in patients	[65]
Liver Cancer	ORMDL regulates ceramide metabolism, GCS↑	-	Upregulation of GCS is associated with chemotherapy resistance	[29, 66, 67]
Prostate Cancer	AC↑	↑	Consistent with upregulation in various cancers	[13]
HER2-Positive Breast Cancer	CERT↓	-	CERT knockdown sensitizes paclitaxel treatment	[59, 68]
Triple-Negative Breast Cancer (TNBC)	CERT↓	↓	Enhances EGFR signaling	[69]
Tp53 Deletion-Associated Thymic Lymphoma	Sphk1↓, Cer↑	↓	Upregulation of ceramide induces tumor cell senescence and cell cycle arrest	[70]

Note: ↑ indicates upregulated expression of the molecule/enzyme in the corresponding cancer type. ↓ indicates downregulated expression.

In mammals, the trimeric SPT complex consists of two large subunits (SPTLC1, SPTLC2, or SPTLC3) and a small subunit (SPT small subunit a or b), and is localized to the endoplasmic reticulum (ER).[71] Specific missense mutations in the human SPTLC1 gene are associated with type I inherited sensory neuropathy, which causes the SPT enzyme to use L-alanine instead of L-serine as a substrate, leading to the accumulation of toxic bases.[72] In cell models and the serum of breast cancer patients, elevated levels of 1-deoxysphingolipids catalyzed by SPT are associated with paclitaxel-induced peripheral neuropathy, a major side effect that limits the use of paclitaxel.[68] Using L-serine to metabolize 1-deoxysphingolipids into normal sphingolipids (such as dihydrosphingolipids or ceramides) may help alleviate paclitaxel-related neurotoxicity.[68,72] In triple-negative breast cancer (TNBC) cells, loss of CERT expression alters sphingolipid and sphingomyelin content in the plasma membrane, thereby enhancing EGFR signaling.[69] Furthermore, knocking down CERT may increase sensitivity to paclitaxel in ovarian cancer, colorectal cancer (CRC), or HER2-positive breast cancer cells by inducing endoplasmic reticulum stress triggered by ceramide, or by promoting autophagic flux through LAMP2 dependence.[59] After EGF signaling activation, ERK1 phosphorylates SPHK2 at Ser351 and Thr578, promoting breast cancer cell migration.[57] Additionally, estradiol can help release S1P from breast cancer cells through ABCC1 and ABCG2, activating S1PR signaling and promoting cell growth and survival.[58] Nuclear S1P produced

by SPHK2 can directly bind to HDAC1 and HDAC2, inhibiting their enzymatic activity and preventing histone H3 deacetylation in MCF7 breast cancer cells.[55] Moreover, glucose-ceramide accumulation via GCS dependency helps maintain the pluripotency of breast cancer stem cells, a process possibly related to the aggregation of the stem cell marker Gb3.[56]

Bacterial vesicles secreted by Enterobacteriaceae can induce intestinal epithelial cells to release exosome-like structures enriched with S1P. These structures promote the development of colon cancer driven by Th17 cells by activating the CCL20, PGE2, and MYD88 signaling pathways.[60] The discovery and cloning of CERS1–6 have laid the foundation for understanding the functions of CERSs with different fatty acyl chain lengths in cancer cell signaling.[13] For example, C16 ceramide synthesized by CERS6 can enhance the sensitivity of colon cancer cells to TRAIL-induced apoptosis, a process associated with the translocation of caspase 3 to the nucleus.[61] Research has also revealed a positive feedback loop between CERS6 and AC: CERS6 activates the JNK pathway, which in turn promotes the expression of AC.[62] In a mouse model of colon cancer induced by azoxymethane (AOM) and dextran sulfate sodium, the lack of alkaline sphingomyelinase NPP7 increased tumor number and size, possibly due to decreased ceramide levels.[73] NCDase is highly expressed in the intestines, and its inhibition promotes ceramide-mediated apoptosis and autophagy in colon cancer cells and xenograft tumors. Furthermore, NCDase-deficient mice are resistant to AOM-induced colon cancer.[74] SPHK1 is highly expressed in various cancers, including colon cancer, and SPHK1 knockout mice exhibit a lower likelihood of tumor formation after exposure to AOM compared to wild-type mice.[13] SPL terminates the sphingolipid metabolism pathway by rapidly degrading S1P. However, in colon cancer tissues, SPL protein expression is down-regulated, and SPL silencing promotes carcinogenesis by S1P accumulation or activation of S1PR signaling, which triggers the expression of miR-181b-1 and induces cancer.[63] In contrast, overexpression of SPL in colon cancer cells and xenograft tumors can inhibit S1P signaling, enhancing p53- and p38-dependent apoptosis.[75]

In hepatocellular carcinoma, ORMDL-regulated ceramide metabolism may influence the tumor microenvironment. ORMDL1 may promote the onset and recurrence of diffuse large B-cell lymphoma (DLBCL), and data from GSE10846 and GSE53786 also support the correlation between high expression of ORMDL1 and poor prognosis in DLBCL patients.[29] High expression of GCS is associated with poor prognosis in oral cancer patients.[64] Molecular or pharmacological inhibition of GCS can reduce chemotherapy resistance in head and neck cancer and liver cancer cells.[66,67] Additionally, inhibiting GCS can restore p53-dependent apoptosis in ovarian cancer cells with mutated p53, a process that depends on ceramide.[76]

Inhibition of SGPP1 leads to the accumulation of S1P, thereby enhancing the migration ability of gastric cancer cells.[65] In contrast, gastric cancer patients with higher SGPP1 expression (indicating weaker S1P signaling) have a longer overall survival.[65] Folic acid stress induced by methotrexate increases the formation of ER stress aggregates enriched with CERS6, which is associated with the activation of p53 in lung cancer cells.[41] Therefore, ceramide signaling may be involved in endoplasmic reticulum stress induction; however, at least in oral cancer, C16 ceramide synthesized by CERS6 appears to suppress the stress response.[42,43]

In a Tp53 knockout mouse model, the knockout of Sphk1 reduces the occurrence of thymic lymphoma while increasing ceramide levels, enhancing the expression of cell cycle inhibitors, and promoting tumor cell senescence.[70] Additionally, AC is upregulated in various cancers, with the most significant increase observed in prostate cancer.[13]

The Potential of ORMDL as a Targeted Therapy

ORMDL is closely related to sphingolipid metabolism, playing a central role in regulating ceramide synthesis. Treatment with C6 ceramide inhibits SPT activity, suggesting that ORMDL may contain a domain that binds to ceramide, participating in ORMDL-dependent SPT regulation.[29] This interaction presents ORMDL as a potential therapeutic target, particularly in inhibiting ceramide synthesis, which could help induce cancer cell death or overcome resistance. The significant regulatory role of SMSr in ceramide homeostasis indicates that it affects ceramide levels through upstream metabolism, complementing the synthetic mechanisms regulated by ORMDL.[25] The cooperative effect of ORMDL and SMSr not only maintains ceramide balance but also contributes to sphingolipid metabolism regulation, which may play a role in cancer metastasis. For example, in melanoma, ceramide metabolism affects cell adhesion and migration, with ASMase activation promoting C16 ceramide formation and enhancing metastasis through α5β1 integrin activation.[13,77] Additionally, targeting ceramide transporters such as CERT may become a new strategy to induce cancer cell death and overcome resistance.[13]

Enzymes involved in ceramide metabolism play diverse roles in different types of cancer cells. For instance, HDAC1 and miR-574-5p can inhibit CERS1 expression, reducing C18 ceramide production, thereby suppressing apoptosis in head and neck cancer cells.[78] However, C18 ceramide synthesized by CERS1 can inhibit tumors in both in vitro and in vivo models.[79,80] The deletion of CERS2 leads to a reduction in long-chain ceramides (C22–24) and may result in pheochromocytoma due to apoptosis dysfunction.[81] C16 ceramide, generated by CERS6, is a transcriptional target of p53 and can induce cell death in lung cancer cells under folate stress.[82] It also enhances TRAIL-induced apoptosis and promotes Bax-mediated apoptosis in HeLa cells.[61,83] SPHK1 and SPHK2 metabolize ceramide into S1P, which regulates cancer cell proliferation, migration, and invasion through different S1PR subtypes.[13] ORMDL may indirectly influence tumor progression by modulating the S1P pathway. The function of ceramide and S1P depends on their subcellular localization and signaling targets, which may act as either pro-cancer or anti-cancer depending on the context and cell type.[13] The S1P pathway has become a research hotspot in cancer therapy. For example, enhancing CERK-C1P signaling can promote breast cancer recurrence after HER2 inhibition,[84] while the CERK inhibitor NVP-231 suppresses the proliferation of breast and lung cancer cells through ceramide-mediated cell cycle arrest and apoptosis.[85] Additionally, activating SPL or SGPP1 (or SGPP2) is also considered a promising anti-cancer strategy.[13]

Challenges and Future Directions

Due to the functional overlap within the ORMDL protein family, targeting them may lead to unclear therapeutic effects, and their roles can vary across different types of tumors. Furthermore, interfering with ORMDL could impact sphingolipid metabolism in normal cells, potentially leading to side effects.

Future research needs to further elucidate the specific mechanisms by which ORMDL regulates sphingolipid metabolism in tumors. Additionally, there is a need to develop highly selective small-molecule ORMDL inhibitors and systematically evaluate their safety and therapeutic efficacy in clinical applications.

Conclusion

The role of ORMDL in cancer suggests that it could be a promising therapeutic target, particularly in regulating ceramide metabolism, cell migration, metastasis, and drug resistance. Targeting ORMDL and its associated metabolic pathways holds potential for exploring new therapeutic strategies aimed at inducing cancer cell death, inhibiting tumor progression, and overcoming drug resistance. Future research that further elucidates the mechanisms of ORMDL and ceramide metabolism may lead to significant breakthroughs in cancer treatment.

Furthermore, gaining a deeper understanding of how sphingolipid signaling influences the interaction between tumor cells and host cells within the tumor microenvironment—such as stromal cells, endothelial cells, osteoclasts, and platelets—can provide valuable insights for creating innovative therapeutic approaches aimed at controlling cancer growth, spread, and metastasis.[11,18,19,86–88] By elucidating the molecular mechanisms underlying these interactions, researchers can identify key regulatory pathways that could be targeted to either disrupt tumor progression or enhance the immune system's ability to recognize and attack cancer cells. Additionally, this knowledge could lead to the development of therapies that not only focus on directly inhibiting tumor cell proliferation but also modulate the tumor microenvironment to make it less conducive to cancer cell survival and metastasis, ultimately improving patient outcomes and reducing the risk of relapse.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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