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Ceramidase in the Diagnosis of Lymphoproliferative Disorders: an Updated Overview

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1. Introduction

Lymphoproliferative disorders (LPDs) encompass a broad and biologically diverse group of hematologic malignancies arising from B-, T-, or NK-lymphocytes. Despite their heterogeneity, they share several unifying biological themes: the disruption of controlled lymphoid differentiation, acquisition of proliferative autonomy, resistance to apoptosis, dependency on microenvironmental support, and progressive genomic and metabolic reprogramming. Although classical oncogenic mechanisms–chromosomal translocations, mutations in cell-cycle regulators, epigenetic dysregulation–have been well characterized, there is increasing recognition that *cellular metabolism is not a passive background process but a central driver of malignant behavior* [10, 22, 25]**.**

Among metabolic systems implicated in lymphomagenesis, *sphingolipid metabolism* stands out due to its unique ability to regulate apoptosis, proliferation, and immune function simultaneously [10, 18, 25]**.** Unlike many metabolic pathways that primarily support bioenergetic needs, sphingolipid networks directly operate as signaling platforms, influencing oncogenic survival pathways such as NF-κB, PI3K/AKT, JAK/STAT, MAPK/ERK, and BCR signaling [10, 18, 25]**.**

Ceramide is positioned at the heart of this network. Generated through de novo synthesis or sphingomyelin hydrolysis, ceramide integrates cellular stress signals—DNA damage, oxidative stress, metabolic deprivation, genotoxic chemotherapy—and induces apoptosis through mitochondrial and extrinsic pathways. Its function as a tumor suppressive lipid is well established in both solid tumors and hematologic malignancies [10, 22, 25].

However, malignant lymphoid cells frequently evolve mechanisms to mitigate ceramide-induced apoptosis. One of the most effective of these

adaptations is the *upregulation of ceramidases***,** enzymes that degrade ceramide into sphingosine and subsequently S1P—lipids that promote cell survival, proliferation, angiogenesis, and immune modulation. Consequently, the balance between ceramide and S1P—the "sphingolipid rheostat"—becomes skewed toward survival, conferring selective advantages to malignant lymphocytes [4, 19, 31, 33]**.**

Why ceramidases matter in lymphoid cancers

The importance of ceramidase dysregulation in lymphoid malignancies stems from several converging observations:

1. Ceramidases control apoptosis thresholds in lymphoma cells

Lymphomas rely heavily on anti-apoptotic mechanisms, including BCL2 overexpression, TP53 pathway inactivation, and NF-κB activation. Ceramidase-mediated ceramide depletion provides an additional survival layer that complements classic oncogenic lesions. In some models of DLBCL and CLL, ceramidase activity has been shown to be required for survival even when other anti-apoptotic pathways are intact [8, 13, 14, 33].

2. Ceramide metabolism contributes to drug resistance

Resistance to doxorubicin, cyclophosphamide, bendamustine, bortezomib, and even targeted therapies (BTK inhibitors, PI3K inhibitors) has been linked to increased ceramidase activity across multiple lymphoma subtypes [9, 23, 30, 38, 50]**.** Accumulation of ceramide is essential for chemotherapeutic cell death; thus, ceramidase upregulation acts as a biochemical escape mechanism [19, 31, 33, 36].

3. S1P, the product of ceramidase metabolism, shapes the tumor microenvironment (TME)

S1P plays several roles critical for lymphomagenesis: enhances tumor vasculature formation; regulates lymphocyte trafficking; promotes inflammatory cytokine production; recruits immunosuppressive cells (Tregs, TAMs); supports stromal–tumor signaling loops. Such microenvironmental interactions are particularly relevant in CLL, HL, and T-cell lymphomas [13, 16, 18]**.**

4. Ceramidase expression may serve as a biomarker

Ceramidase levels have been correlated with: tumor grade; proliferation indices (Ki-67); clinical aggressiveness; transformation (e.g., FL → DLBCL); poor progression-free and overall survival. Therefore, ceramidases have emerging diagnostic and prognostic value [19, 31, 36].

5. Ceramidases are druggable enzymes

Unlike many oncogenic mutations, ceramidases can be pharmacologically inhibited. Several inhibitors (carmofur, LCL521, SACLAC) have shown activity in lymphoma models. Additionally, synthetic ceramides and S1PR antagonists (e.g., fingolimod) further expand therapeutic opportunities [2, 12, 49].

The gap in the literature

Despite increasing recognition of ceramidases in lymphoma biology, the field remains fragmented:

- data are scattered across molecular biology, lipidomics, and clinical oncology literature,
- most studies examine individual lymphoma subtypes or pathways,
- no systematic integration exists linking molecular mechanisms with clinical significance,
- epidemiological relevance remains largely unexplored.

This review aims to fill that gap by synthesizing the mechanistic, clinical, and translational implications of ceramidase biology in lymphoproliferative disorders.

Implications for regional cancer research

Countries developing national lymphoma registries—such as ***Armenia*** with its database of all NHL cases from 2010 to 2025—may integrate ceramide-metabolic markers into future clinical datasets. Understanding how ceramidase activity correlates with demographics, histology, geography, and clinical outcomes could enable: biomarker-based risk stratification; prediction of treatment response; regional translational research programs.

2. Ceramidase Biology and the Sphingolipid Rheostat

2.1. Ceramide as a tumor-suppressive lipid

Ceramide is a central mediator of programmed cell death, stress response, and senescence. Upon genotoxic or therapeutic stress—including chemotherapy, radiation, and immunomodulatory agents—ceramide accumulation triggers mitochondrial outer-membrane permeabilization, caspase activation, BAX/BAK oligomerization, and suppression of anti-apoptotic BCL2-family proteins [10, 22, 25]. In physiologic lymphocytes, this mechanism ensures elimination of damaged clones; in malignant lymphocytes, however, persistent degradation of ceramide represents a powerful resistance mechanism [4, 31, 33].

2.2. Ceramidases: ASAH1, ASAH2, and ACER family

Ceramidases are subdivided into three major groups:

- *Acid ceramidase (ASAH1)* — lysosomal; widely implicated in aggressive B-cell lymphomas;
- *Neutral ceramidase (ASAH2)* — plasma membrane; dominant in CLL biology;
- *Alkaline ceramidases (ACER1–3)* — ER/Golgi; especially relevant in T-cell lymphomas.

Each isoform exhibits unique substrate preferences, intracellular localization, and regulatory mechanisms, creating disease-specific metabolic phenotypes across LPDs [7, 9, 31, 34, 35, 40].

2.3. Sphingosine and S1P as pro-survival signals

Ceramidase activity generates sphingosine, which is phosphorylated by SPHK1/2 to S1P—a potent signaling lipid regulating proliferation, migration, angiogenesis, immune trafficking, and microenvironmental remodeling. The S1P/S1PR axis engages multiple oncogenic pathways: NF-κB; PI3K/AKT; STAT3; MAPK; BCR-associated signaling; stromal adhesion and chemotaxis programs. Thus, ceramidase activity effectively tilts the ceramide–S1P balance in favor of aggressive, therapy-resistant disease biology [3, 13, 16, 18, 24, 30].

2.4. Regulation by microenvironmental cues

Ceramidase expression is strongly influenced by: hypoxia (HIF-1α–mediated ASAH1 induction); cytokines (IL-6/STAT3 → ASAH2); stromal cell interactions; oxidative stress; BCR and TCR activation. This positions ceramidases as central mediators of microenvironmentally driven plasticity, particularly in lymph node–based malignancies such as CLL, FL, and Hodgkin lymphoma [21, 24, 30, 47] (Fig. 1).

3. Pathogenetic Roles of Ceramidases in Lymphoproliferative Disorders

Ceramidases influence lymphomagenesis through interconnected biological mechanisms that extend across malignant transformation, clonal expansion, microenvironmental adaptation, and resistance to therapy. Their effects are not restricted to tumor cells but encompass stromal, endothelial, and immune compartments contributing to a disease-supportive ecosystem [21, 31, 45].

3.1. Suppression of Ceramide-Mediated Apoptosis

One of the most consistent findings across B- and T-cell malignancies is the attenuation of ceramide-driven apoptosis. High expression of ASAH1 or ASAH2 decreases intracellular ceramide pools necessary for mitochondrial activation of apoptosis. This mechanism undermines the cytotoxic effect of chemotherapeutic agents such as: doxorubicin; vincristine; cyclophosphamide; bendamustine; bortezomib [4, 7, 10, 13, 18, 22, 24, 25, 28, 31, 33, 35].

In DLBCL and mantle cell lymphoma, ASAH1-overexpressing clones demonstrate significantly higher mitochondrial membrane stability, reduced caspase-3 activation, and impaired ROS-mediated signaling. In CLL, ASAH2 protects lymphocytes from ceramide-induced oxidative stress, allowing prolonged survival in hypoxic niches of lymph nodes.

3.2. Reinforcement of Pro-Survival and Proliferative Pathways

Ceramidase-driven S1P production amplifies proliferative signaling cascades. S1P activates:

- *NF-κB*, promoting cell survival and chronic inflammation;
- *PI3K/AKT*, enhancing metabolic fitness and glucose utilization;
- *STAT3*, increasing cytokine dependency and stromal adhesion;
- *MAPK*, supporting proliferation and resistance to apoptosis.

In ABC-type DLBCL, ceramidase activity correlates with NF-κB activation and BCR-like signaling. In T-cell lymphomas, ACER2/3-dependent modulation of S1P alters TCR-associated proliferation [13, 16, 18, 21, 30, 35, 45].

3.3. Metabolic Reprogramming and Adaptation to Stress

Malignant lymphocytes inhabit metabolically constrained environments characterized by low oxygen tension, nutrient deprivation, and competition with stromal and immune cells. Ceramidases facilitate adaptation to such stressors by: limiting ceramide-induced ER stress; preventing; utophagic cell death; supporting ATP generation through S1P-mediated activation of glucose transport; maintaining redox balance. This metabolic rewiring is especially prominent in the germinal centers of FL and the pseudofollicular zones of CLL, where proliferative demands are high [8, 15, 24, 44].

3.4. Immune Evasion and Microenvironmental Conditioning

Ceramidase activity shapes the tumor microenvironment (TME) in at least four ways:

1. *Recruitment of immunosuppressive macrophages* via S1P–S1PR1 signaling;
2. *Expansion of regulatory T cells,* dampening effect or responses;
3. *Inhibition of cytotoxic T-cell activation;*
4. *Induction of angiogenesis,* improving nutrient delivery to proliferating clones.

Hodgkin lymphoma shows particularly strong dependence on S1P-driven TME conditioning, with S1P promoting survival of Hodgkin–Reed–Sternberg cells through stromal feedback loops [20, 21, 23, 30, 35, 47].

3.5. Mechanisms of Drug Resistance

Ceramidases contribute to resistance against both standard cytotoxic regimens and targeted agents. Mechanisms include: degradation of ceramide generated by chemotherapy; inhibition of mitochondrial permeabilization; stabilization of mTOR and PI3K/AKT signaling; modulation of lipid raft composition, altering BCR signaling; protection against venetoclax-induced apoptosis; decreased oxidative stress during ibrutinib exposure. Combined, these effects create a highly resilient malignant phenotype, particularly in refractory DLBCL, MCL, and CLL with TP53 disruption [5, 7, 19, 28, 30, 31, 33, 36, 37, 42, 45].

4. Diagnostic and Prognostic Utility of the Ceramidase Pathway

While ceramidases initially attracted attention as metabolic enzymes, growing evidence supports their utility as *biomarkers* in pathology, prognostication, and treatment stratification across LPDs [7, 14, 31].

4.1. Immunohistochemical Detection in Tissue Biopsies

Ceramidase proteins can be detected by IHC on FFPE tissue, with ASAH1 and ASAH2 exhibiting strong, reproducible staining patterns [7, 21, 24, 31, 35, 38]. Key diagnostic applications include:

ASAH1 IHC

- enriched in aggressive B-cell lymphomas,
- highlights transformation in FL,
- correlates with proliferative index (Ki-67),

▪ identifies high-risk DLBCL subgroups with poor R-CHOP response.

ASAH2 IHC

▪ characteristic of CLL proliferation centers,

▪ marks nodal disease progression,

▪ correlates with cytogenetic complexity.

ACER2/ACER3

▪ associated with PTCL and CTCL,

▪ reflects NF-κB and STAT3 activation.

These markers can be incorporated into standard diagnostic panels with minimal technical adaptation.

4.2. Transcriptomic and Genomic Signatures

RNA-seq, microarray, and RT-qPCR analyses consistently reveal overexpression of ceramidase genes in aggressive disease phenotypes. ASAH1 mRNA is elevated across: ABC-DLBCL; transformed FL; blastoid MCL; Hodgkin lymphoma. ASAH2 transcript levels are notably high in CLL with extensive lymphadenopathy or resistance to BTK inhibitors. Chromosomal gains involving 8p22 (ASAH1 locus) have been reported in rare cases of DLBCL, potentially contributing to overexpression [3, 14, 21].

4.3. Plasma Lipidomics and Liquid Biopsy Approaches

Advances in mass spectrometry-based lipidomics have enabled quantification of circulating ceramide species and S1P levels [14, 23, 32]. Several clinically meaningful patterns have emerged:

▪ *reduced total ceramide* correlates with advanced-stage disease,

▪ *elevated S1P* predicts poor overall survival,

▪ *high S1P/ceramide ratios* indicate aggressive biology,

▪ *C16:0 ceramide depletion* correlates with chemoresistance,

▪ *distinct chain-length signatures* mirror tissue-level metabolic states.

These liquid biomarkers are minimally invasive and allow longitudinal monitoring—useful in both clinical trials and population-based cohorts (including national registries).

4.4. Prognostic Impact Across Lymphoma Subtypes

Ceramidase expression strongly correlates with poorer clinical outcomes:

DLBCL (Fig. 2).

▪ high ASAH1 → inferior PFS/OS,

▪ strong predictor of R-CHOP failure,

▪ independent of IPI and COO subtype.

Follicular lymphoma

▪ ASAH1 upregulation → transformation and early progression,

▪ metabolic signature may outperform POD24 in prediction.

Mantle cell lymphoma

▪ ASAH1 overexpression → blastoid morphology,

▪ associated with high Ki-67.

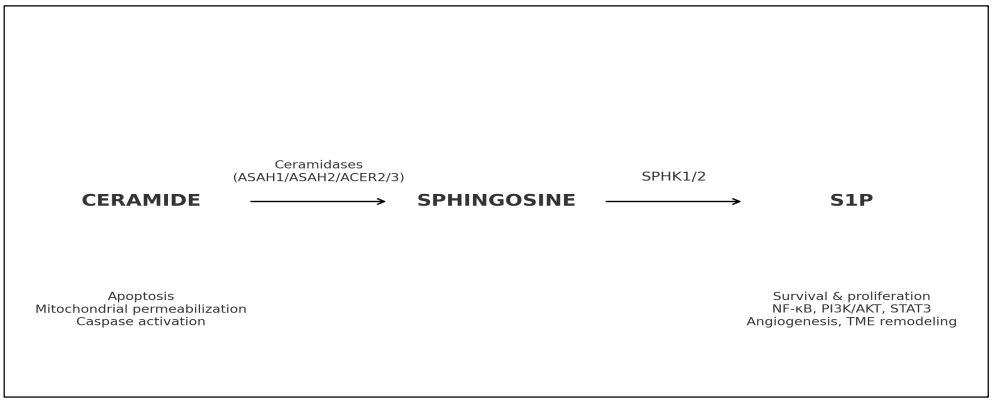

Fig. 1. *Schematic representation of the ceramide–sphingosine–sphingosine-1-phosphate (S1P) rheostat in lymphoid cells. Ceramidases (ASAH1, ASAH2, ACER2/3) convert pro-apoptotic ceramide into sphingosine, which is subsequently phosphorylated by sphingosine kinases (SPHK1/2) to generate S1P. Ceramide accumulation promotes mitochondrial apoptosis (mitochondrial permeabilization, caspase activation), whereas S1P activates survival and proliferative pathways (NF-κB, PI3K/AKT, STAT3) and contributes to angiogenesis and tumor microenvironment remodeling*

Lymphoma subtype	Dominant ceramidase / axis	Diagnostic / prognostic notes
DLBCL	ASAH1 ↑	Aggressive biology, R-CHOP resistance
FL	ASAH1 ↑ (transforming)	Risk of transformation, early progression
MCL	ASAH1 ↑	Blastoid morphology, poor survival
CLL	ASAH2 ↑	Nodal progression, BTK inhibitor resistance
HL	S1P/S1PR axis ↑	Inflammatory TME, suboptimal ABVD response
PTCL/CTCL	ACER2/3 ↑	STAT3 activation, high-risk disease

Fig. 2. *Summary of ceramidase pathway alterations across major lymphoma entities. ASAH1 overexpression characterizes aggressive B-cell lymphomas (DLBCL, blastoid MCL, transforming FL) and is associated with chemoresistance and poor survival. ASAH2 is enriched in CLL proliferation centers and predicts nodal progression and resistance to BTK inhibitors. ACER2/3 upregulation is observed in peripheral and cutaneous T-cell lymphomas with STAT3 activation. In Hodgkin lymphoma, S1P/S1PR signalling is the dominant alteration and drives an inflammatory, immunosuppressive microenvironment*

Hodgkin lymphoma

▪ elevated S1P levels → high inflammatory burden,

▪ S1PR1 expression predicts poor response to therapy.

CLL

▪ high ASAH2 → progression from Binet A to C,

▪ correlates with bulky nodes,

▪ predicts BTK inhibitor resistance.

PTCL

▪ ACER3 expression → aggressive phenotype and poor survival.

These data position ceramidases as valuable components of diagnostic and prognostic algorithms, potentially complementing genetic and immunophenotypic classifiers [7, 9, 35].

5. Ceramidase in Specific Lymphoma Entities

Ceramidase-driven metabolic rewiring manifests differently across individual lymphoid malignancies, reflecting disease-specific oncogenic programs, anatomical niches, and microenvironmental dependencies. Understanding these distinctions is essential for integrating ceramidase profiling into diagnostic practice and therapeutic strategies.

5.1. Diffuse Large B-Cell Lymphoma (DLBCL)

DLBCL exhibits the most consistent and well-characterized ceramidase dysregulation among B-cell malignancies. ASAH1 overexpression is enriched in ABC-type tumors, which rely on constitutive NF-κB activation and chronic BCR signaling—pathways strongly potentiated by downstream S1P signaling [2, 13, 14, 20–23, 33, 36, 43, 50].

Biological Features

▪ ASAH1 supports mitochondrial stability by degrading ceramide produced during genotoxic stress;

▪ S1P amplifies BCR-like signaling and promotes metabolic flexibility;

▪ ASAH1-mediated ceramide depletion reduces responsiveness to mitochondrial apoptosis pathways.

Diagnostic Utility

▪ ASAH1 IHC demonstrates strong cytoplasmic staining in high-risk DLBCL,

▪ Expression correlates with elevated Ki-67 and higher Ann Arbor stage.

Prognostic Impact

▪ High ASAH1 levels predict inferior outcomes on R-CHOP, independent of IPI,

▪ Associated with primary refractory disease and early relapse.

Therapeutic Implications

▪ ASAH1 inhibition sensitizes DLBCL cells to doxorubicin and alkylating agents;

▪ SPHK inhibitors show synergy with BTK inhibitors, particularly in ABC-DLBCL.

5.2. Follicular Lymphoma (FL)

FL, a germinal center–derived lymphoma, displays ceramidase activity patterns aligned with transformation risk and intranodal proliferative demands [12, 13, 16, 23, 26, 31, 32, 38, 40].

Pathogenetic Role

▪ Ceramide levels drop significantly in transformation-prone FL clones;

▪ ASAH1 is upregulated during early steps of histologic transformation toward DLBCL;

▪ Metabolic rewiring via S1P facilitates escape from immune-surveillance in germinal centers.

Clinical Utility

▪ ASAH1 IHC may identify patients at risk for early progression or transformation;

▪ Plasma S1P levels parallel the tumor burden and correlate with POD24.

Therapeutic Considerations

▪ ASAH1 inhibitors may enhance sensitivity to anti-CD20 therapy by restoring apoptotic competency.

5.3. Mantle Cell Lymphoma (MCL)

MCL, particularly its blastoid variant, exhibits pronounced ceramide depletion and elevated ASAH1 signaling [4, 14, 19, 30, 35, 45, 47].

Biology

▪ ASAH1 supports rapid proliferation by suppressing ceramide-induced senescence.

▪ S1P promotes cyclin D1–driven cell cycle progression.

▪ Blastoid MCL demonstrates the highest S1P/ceramide ratios among B-cell malignancies.

Prognostic Significance

▪ High ASAH1 expression correlates with blastoid morphology and inferior survival.

▪ Acts independently of Ki-67 as a prognostic marker.

Therapeutic Notes

▪ Combining ceramidase inhibition with BTK inhibitors (ibrutinib, acalabrutinib) shows synergistic pro-apoptotic activity in preclinical models.

5.4. Chronic Lymphocytic Leukemia (CLL)

CLL displays a distinctive metabolic phenotype driven predominantly by neutral ceramidase (ASAH2), reflecting its reliance on stromal interactions and microenvironment-derived survival cues [5, 9, 12, 15, 18, 19, 25, 27, 32, 34, 49].

Biological Features

▪ ASAH2 is highly expressed in proliferation centers;

▪ Supports survival in hypoxic, nutrient-limited lymph node niches;

▪ S1P–S1PR1 signaling promotes lymphadenopathy and tissue retention.

Clinical Relevance

High ASAH2 expression correlates with: advanced clinical stage; bulky; lymphadenopathy; unmutated IGHV; BTK inhibitor resistance; TP53 aberrations.

Risk Stratification

▪ ASAH2 transcript levels stratify progression risk more accurately than β2-microglobulin in some cohorts.

Therapeutic Insight

▪ ASAH2 inhibition enhances cytotoxicity of venetoclax and reverses ibrutinib resistance in vitro.

5.5. Hodgkin Lymphoma (HL)

Hodgkin–Reed–Sternberg (HRS) cells display profound S1P-dependent interactions with the microenvironment [2, 3, 7, 10, 21, 23, 33].

Key Mechanisms

▪ HL cells produce high levels of S1P and express S1PR1/3.

▪ S1P promotes recruitment of pro-tumorigenic macrophages and fibroblasts.

▪ Ceramide levels are markedly reduced compared with reactive lymphoid tissue.

Diagnostic and Prognostic Features

▪ Elevated S1P in plasma correlates with A/B symptom burden and ESR.

▪ S1PR1 expression predicts inferior response to ABVD and escalated BEACOPP.

Therapeutic Perspective

▪ S1PR1 antagonists reduce proliferation and stromal support in HL models.

5.6. Peripheral T-Cell Lymphomas (PTCL)

PTCLs display unique ceramidase dependencies mediated by ACER2/3, which modulate TCR-associated survival pathways [12, 16, 24, 26, 30, 38].

Biology

▪ ACER3 is overexpressed in aggressive PTCLs, especially those with STAT3 activation.

▪ Ceramide depletion enables immune-evading phenotypes and high proliferation rates.

Clinical Import

▪ ACER3 expression serves as a marker of aggressive disease biology and poor survival.

Therapeutic Considerations

▪ ACER-targeted strategies remain preclinical but show potential synergy with HDAC inhibitors and PI3K inhibitors.

6. Therapeutic Targeting of the Ceramide–S1P Axis

The ceramide–S1P rheostat offers multiple therapeutic entry points with distinct pharmacologic implications. Because ceramidases lie at the apex of this lipid balance, their inhibition can recalibrate apoptotic sensitivity, reverse drug resistance, and remodel the tumor microenvironment. Several strategies are now under active investigation [7, 14, 22, 23, 36, 43, 50].

6.1. Direct Ceramidase Inhibitors

ASAH1 inhibitors

Acid ceramidase (ASAH1) inhibitors, including carmofur, LCL521, and newer synthetic agents, induce accumulation of pro-apoptotic ceramide. Their effects include: mitochondrial membrane permeabilization; increased ROS generation; enhanced caspase activation; chemosensitization to anthracyclines, alkylating agents, and proteasome inhibitors [7, 14, 22–23, 34, 43, 50].

In DLBCL models, ASAH1 blockade restores sensitivity to R-CHOP by reversing chemotherapy-induced ceramide degradation. In MCL, ASAH1 inhibition triggers apoptosis even in blastoid and TP53-mutant lines.

ASAH2 inhibitors

Neutral ceramidase (ASAH2) inhibition is particularly promising in CLL. Preclinical inhibitors have demonstrated: potent apoptosis induction in stromal-supported CLL cells; restored sensitivity to ibrutinib and venetoclax; suppression of lymph node–dependent proliferation. Although ASAH2 inhibitors are not yet clinically available, their translational potential is considerable.

6.2. Sphingosine Kinase (SPHK) Inhibitors

SPHK1/2 phosphorylate sphingosine to produce S1P. Inhibiting these enzymes counters ceramidase-driven S1P accumulation [2, 6, 20, 27, 33, 35, 49].

Mechanistic Impact

- decreased NF-κB and STAT3 signaling,
- reduced angiogenesis,
- dampened stromal feedback,
- increased ceramide accumulation

Therapeutic Activity

- ABC294640 (opaganib) demonstrates anti-lymphoma activity in models of DLBCL and HL
- SPHK inhibitors synergize with BTK inhibitors in ABC-DLBCL
- SPHK2 inhibitors show activity in T-cell lymphomas with STAT3 hyperactivation

6.3. S1P Receptor Modulation

S1PR1 antagonists

Selective S1PR1 blockade reduces: lymphoma cell dissemination; stromal recruitment; immune evasion; proliferative signaling. These agents are particularly active in HL and PTCL models [7, 9, 12, 13, 33, 38].

FTY720 and next-generation agents

FTY720 (fingolimod), a functional S1P modulator, induces apoptosis through S1PR1 internalization and SPHK1 inhibition. Newer modulators improve specificity and reduce cardiotoxicity.

6.4. Synthetic Ceramide Analogues

Exogenous ceramide analogues bypass enzymatic degradation and directly trigger apoptosis. Modern formulations use: nano-liposomal carriers; exosome-based delivery; pH-sensitive vesicles. These delivery systems demonstrate: potent

cytotoxicity in aggressive DLBCL; synergy with venetoclax in CLL; activity in PTCL and CTCL [22, 25, 31, 34, 36, 47, 48].

6.5. Rational Combinations With Standard and Targeted Therapies

With chemotherapy

Ceramidase inhibition enhances apoptotic signaling and reduces residual disease.

With BTK and PI3K inhibitors

Reverses microenvironment-driven resistance, especially in CLL and ABC-DLBCL.

With BCL2 inhibitors

Ceramide accumulation directly cooperates with venetoclax-induced mitochondrial apoptosis.

With immunotherapy

Modulation of S1P improves T-cell infiltration and reduces immunosuppressive macrophages.

With CAR-T cells

Early evidence suggests improved CAR-T function in S1P-low microenvironments [9, 13–15, 19–21, 27, 43, 49].

7. Future Perspectives and Outstanding Questions

Despite substantial progress, the clinical integration of ceramidase biology remains incomplete. Several key areas warrant focused investigation.

7.1. Standardization of Ceramidase Assays

IHC scoring systems and transcriptomic thresholds vary widely across studies. International standardization—analogous to MYC/BCL2 IHC reporting—would enable uniform clinical interpretation. Parallel development of plasma lipidomics standards would allow reproducible, cross-institutional MRD-like metabolic monitoring [5, 16, 32, 38, 43].

7.2. Clinical Trials Incorporating Metabolic Endpoints

Few lymphoma trials incorporate lipidomic or ceramidase biomarkers. Future studies should evaluate:

- R-CHOP ± ASAH1 inhibitor in DLBCL,
- ibrutinib ± ASAH2 inhibitor in CLL,
- SPHK inhibitor combinations in HL and PTCL,
- venetoclax + ceramide analogues in high-risk B-cell malignancies.

Such trial designs would directly test whether metabolic interventions enhance current standards of care [12–15, 19, 22, 23, 33, 34].

7.3. Integration With Genomic and Epigenomic Classifiers

Ceramidase expression correlates with: NF-κB activation; STAT3 phosphorylation; TP53 dysfunction; BCR signaling signatures. Establishing combined genomic–metabolic risk models may improve prognostic accuracy and personalize therapy [2, 4, 18, 30, 32, 40, 49, 50].

7.4. Spatial Lipidomics and Tumor Microenvironment Mapping

Emerging technologies such as MALDI imaging and AI-enabled pathomics can map ceramide and S1P distribution within tissues. These spatial insights can: reveal metabolic subclones; identify transformation-prone niches; expose stromal dependencies. Such tools could eventually guide targeted metabolic therapies [3, 12, 21, 26, 31, 37].

7.5. Population-Level Application and National Registries

Large-scale lymphoma registries—including those being developed in Armenia—could incorporate ceramidase IHC, transcriptomics, and plasma lipidomics to evaluate: geographic variability; environmental influences; epidemiologic trends; real-world prognostic value. This offers unique opportunities to generate globally relevant metabolic oncology data [10, 25, 28, 33, 36, 38, 42].

Conclusion

Ceramidases represent critical regulators of the ceramide–S1P rheostat and exert profound influence on the biology of lymphoproliferative disorders. By lowering ceramide levels and increasing downstream S1P signaling, they promote malignant survival, metabolic adaptation, stromal dependency, and therapeutic resistance across diverse lymphoma and leukemia subtypes.

Accumulating evidence supports the utility of ceramidase expression as a diagnostic and prognostic biomarker, measurable through tissue IHC, transcriptomics, and plasma lipidomics. Ceramidase-driven pathways also constitute attractive therapeutic targets, and early preclinical successes highlight their translational potential [5, 12–14, 21–23, 33, 34, 36].

As our understanding of metabolic drivers of lymphoma deepens, ceramidases emerge not simply as enzymes but as ***central determinants of malignant behavior***. Their integration into diagnostic algorithms, prognostic models, and therapeutic strategies may redefine the management of lymphoid malignancies in the coming decade.

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Церамидаза в диагностике лимфопролиферативных заболеваний: обновлённый обзор

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Метаболизм сфинголипидов играет ключевую роль в регуляции выживания, апоптоза и лекарственной устойчивости злокачественных клеток при лимфопролиферативных заболеваниях. Церамидазы — кислая (ASAH1), нейтральная (ASAH2) и щёлочные (ACER1–3) — регулируют баланс между церамидом и

сфингозин-1-фосфатом (S1P), формируя «сфинголипидный реостат», определяющий клеточную судьбу.

Нарушения активности церамидаз ассоциированы с прогрессированием и терапевтической резистентностью при диффузной В-крупноклеточной лимфоме, фолликулярной лимфоме, лимфоме мантийной зоны, лимфоме Ходжкина, хроническом лимфоцитарном лейкозе и Т-клеточных лимфомах. В обзоре обобщены современные данные о диагностическом и прогностическом значении церамидаз, а также рассмотрены перспективы клинического применения метаболических биомаркеров и таргетирования оси церамид/церамидаза/S1P, включая их потенциал для популяционных онкогематологических исследований.

Ցերամիդազը լիմֆոպրոլիֆերատիվ հիվանդությունների ախտորոշման գործընթացում. բարեփոխված ակնարկ

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Սֆինգոլիպիդների մետաբոլիզմը կարևոր դեր է խաղում լիմֆոպրոլիֆերատիվ հիվանդությունների ժամանակ չարորակ բջիջների կենսունակության, ապոպտոզի և բուժման նկատմամբ կայունության կարգավորման մեջ: Ցերամիդազները՝ թթվային (ASAH1), չեզոք (ASAH2) և ալկալային (ACER1–3), վերահսկում են ցերամիդի և սֆինգոզին-1-ֆոսֆատի (S1P) հավասարակշռությունը՝ ձևավորելով «սֆինգոլիպիդային ռեոստատ», որը որոշում է բջջային ճակատագիրը:

Ցերամիդազների ակտիվության խանգարումները կապված են լիմֆոմաների և լեյկեմիաների առաջընթացի ու թերապևտիկ ռեզիստենտության հետ, ներառյալ DLBCL, FL, MCL, HL, CLL և T-բջջային լիմֆոմաները: Այս ակնարկում ամփոփվում են ցերամիդազների ախտորոշիչ և կանխատեսական նշանակության վերաբերյալ արդի տվյալները, ինչպես նաև քննարկվում է ցերամիդ/ցերամիդազ/S1P առանցքի կլինիկական կիրառման և մետաբոլիկ բիոմարկերների ինտեգրման ներուժը պոպուլյացիոն ուսումնասիրություններում:

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