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### Publication Date

2024-07-01

### DOI

10.1016/j.plipres.2024.101288

HHS Public Access

Author manuscript

*Prog Lipid Res*. Author manuscript; available in PMC 2024 August 27.

Published in final edited form as:

*Prog Lipid Res*. 2024 July ; 95: 101288. doi:10.1016/j.plipres.2024.101288.

# Leveraging altered lipid metabolism in treating B cell malignancies

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## Abstract

B cell malignancies, comprising over 80 heterogeneous blood cancers, pose significant prognostic challenges due to intricate oncogenic signaling. Emerging evidence emphasizes the pivotal role of disrupted lipid metabolism in the development of these malignancies. Variations in lipid species, such as phospholipids, cholesterol, sphingolipids, and fatty acids, are widespread across B cell malignancies, contributing to uncontrolled cell proliferation and survival.

Phospholipids play a crucial role in initial signaling cascades leading to B cell activation and malignant transformation through constitutive B cell receptor (BCR) signaling. Dysregulated cholesterol and sphingolipid homeostasis support lipid raft integrity, crucial for propagating oncogenic signals. Sphingolipids impact malignant B cell stemness, proliferation, and survival, while glycosphingolipids in lipid rafts modulate BCR activation. Additionally, cancer cells



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Author contributions

J.L wrote the first draft of the manuscript. J.L. A.M. M.J.S., and R.M.K. edited and wrote the final version of the manuscript. All authors have read and approved the final manuscript.

CRediT authorship contribution statement

**Jaewoong Lee:** Writing – review & editing, Writing – original draft, Visualization, Validation, Conceptualization. **Arya Mani:** Writing – review & editing, Validation. **Min-Jeong Shin:** Writing – review & editing, Validation. **Ronald M. Krauss:** Writing – review & editing, Visualization, Validation, Supervision, Conceptualization.

Declaration of Competing Interest

There are no conflicts of interest to be reported that are related to this manuscript.

enhance fatty acid-related processes to meet heightened metabolic demands. In obese individuals, the obesity-derived lipids and adipokines surrounding adipocytes rewire lipid metabolism in malignant B cells, evading cytotoxic therapies. Genetic drivers such as MYC translocations also intrinsically alter lipid metabolism in malignant B cells.

In summary, intrinsic and extrinsic factors converge to reprogram lipid metabolism, fostering aggressive phenotypes in B cell malignancies. Therefore, targeting altered lipid metabolism has translational potential for improving risk stratification and clinical management of diverse B cell malignancy subtypes.

**Keywords**

Lipid metabolism; B cell malignancy; Leukemia; Lymphoma; B cell receptor; Obese

## 1. Introduction

B cell malignancies are a highly heterogeneous group of over 80 malignant blood disorders [1]. Given their pathological complexity, treatment response and clinical outcomes are largely dependent on oncogenic signaling properties [2]. Several lines of evidence indicate metabolic reprogramming at the lipid level is one of the most relevant hallmarks of cancer including B cell malignancies.

The proliferation and survival signals from uncontrolled and persistent B cell receptor (BCR) signaling is a primary feature in B cell non-Hodgkin lymphomas (B-NHLs) [2]. Constitutive activation of BCR signaling relies on altered phosphorylation of phosphoinositide that is achieved by mutation on lipid kinase such as the phosphoinositide 3-kinases (PI3K) or lipid phosphatase such as PTEN in a subset of diffuse large B cell lymphoma (DLBCL) and mantle cell lymphoma (MCL). Excessive accumulation of phosphoinositides provides a local convergence site at the distinct liquid-ordered microstructure called lipid raft at the plasma membrane by recruitment of downstream oncogenic signaling complexes. The microstructure anchoring BCR-signalosome including Igα (also known as CD79A), Igβ (also known as CD79B), BTK (Bruton's tyrosine kinase), PDK1 (phosphoinositide-dependent kinase), and AKT (murine thymoma viral oncoprotein homolog) is further supported by the metabolism of cholesterol and sphingolipids, which are considered as fundamental components of lipid rafts.

Furthermore, oncogenic MYC aberrations, such as genomic translocations, are prominent characteristics of B cell lymphoma. Elevated MYC levels regulate the uptake of fatty acids to facilitate fatty acid oxidation (FAO), leading to accelerated proliferation by providing sufficient energy under conditions of limited nutrients and oxygen availability in lymphoma cells [3,4]. Notably, MYC aberrations alter lipid biosynthesis, leading to a marked increase in abundance of phosphatidylglycerol (PG) and cardiolipin (CL). The prominent elevation of PG serves as a precursor to CL, which is crucial for preserving the integrity of mitochondrial membranes [5]. This feature is consistent with the well-established observation that MYC aberrations induce mitochondrial biogenesis [6]. This distinctive lipid profile in MYC-driven lymphoma cells differs from that observed in RAS-driven lymphoma, which displays

a higher abundance of phosphatidylinositol (PI) relative to phosphatidylglycerol (PG). Consequently, RAS-driven lymphoma cells exhibit pronounced activation of the canonical RAS-PI3K pathway, which relies on the abundance of PI within lipid rafts on the cell membrane, in contrast to MYC-driven lymphoma cells [7]. This suggests that exploiting unique alterations in lipid profiles derived from distinct oncogenes could be employed to both identify and target diverse lymphoma subtypes.

In normal B cells, BCR and/or CD40 induces phosphorylation of AKT at T308 in the activation loop by PDK1 in a manner dependent on PIP3 production upon PI3K activation. Subsequently, AKT triggers the phosphorylation of tuberous sclerosis complex 2 (TSC2), an inhibitor of mammalian target of rapamycin complex 1 (mTORC1), at T1462 [8], causing the disruption of its interaction with TSC1 and destabilization of TSC2 [9]. This alleviates the GTPase-activating protein (GAP) activity of the TSC2 toward the small G-protein RHEB, thereby inducing the activation of REHB in its GTP-bound active state, in turn inducing the activation of mTORC1. mTORC1 consisting of mTOR, Raptor, and mLST8 promotes the nuclear accumulation of the mature form of sterol-response element-binding protein (SREBP), a master transcription factor for *de novo* lipid biosynthesis, thereby upregulating the level of the genes encoding enzymes driving this metabolic process [10]. Thus, mTORC1 integrates intricate signals from growth factors, oxygen level, energy, and nutrient status including levels of amino acids to orchestrate processes required for cellular growth by facilitating anabolic processes such as the synthesis of proteins, nucleotides, and lipids. mTORC1 also stimulates metabolic processes such as glycolysis and glutaminolysis for energy production while impeding catabolic processes such as autophagy. Therefore, mTOR serves as a central gatekeeper coordinating the balance between anabolic and catabolic processes [11].

In B cell malignancy, excessive activation of mTORC1 stimulates cellular metabolic pathways related to anabolic and energy-producing processes including *de novo* lipid and sterol biosynthesis as a consequence of constitutive activation of the BCR-PI3K-AKT pathway [12]. In line with this, aberrant activation of mTORC1 by deletion of TSC2 increases the expression of genes required for *de novo* lipid and sterol biosynthesis in an SREBP1 dependent manner. In addition, myristoylated AKT (myr-AKT), a modified form of AKT that is constitutively anchored to the membrane, aberrantly activates mTORC1 signaling, thus inducing expression of SREBP1 and SREBP2 for lipid and cholesterol biosynthesis [10]. Elevated lipid and cholesterol feed-forward to sustain activation of the BCR-PI3K-AKT pathway, enabling robust proliferation of malignant B cells.

MCL, representing about 5-10% of non-Hodgkin’s B cell lymphomas (B-NHL) with the poorest prognosis [13], is characterized by high Cyclin D1 expression and currently has no standard treatment. MCL cells exhibit enhanced metabolomic pathways of glycolysis, PPP, and lipid biosynthesis caused by constitutive activation of the PI3K/AKT/mTOR pathway to overcome constrained energy resources in the microenvironment [14]. Therefore, patients with MCL show promising clinical responses to mTOR inhibitors such as temsirolimus, everolimus, and deforolimus [15-18]. Collectively, lipid metabolism is intricately intertwined with the pathogenesis of B cell malignancies, exhibiting distinctive profiles contingent on the underlying oncogenic mutation-driven signaling pathways. This

insight can be leveraged for the diagnosis and treatment of various subtypes of B cell malignancies.

Lipid metabolism in malignant B cells is altered by both extrinsic microenvironment and mutant-driven intrinsic signaling. The secretome released from adipocytes in cases of obesity impacts lipid metabolism, providing malignant B cells with the necessary fuel for robust proliferation and survival in response to chemotherapy. Accordingly, oncogenic mutation-driven signaling pathways that adapt to the extrinsic microenvironment take advantage of imbalanced lipid metabolism homeostasis, further enhancing the fitness of malignant cells.

## 2. Cell extrinsic factors

A growing body of evidence indicates a significant correlation between obesity and adverse outcomes in patients diagnosed with B cell malignancies. Obesity not only significantly reduces event-free survival (EFS) and raises mortality rates but also increases the risk of relapse by approximately 50%. Notably, adipocytes play a central role in promoting the proliferation and drug resistance of malignant B cells (Fig. 1) [19-21].

The adipocyte secretome directly promotes chemoresistance of B-ALL cells against various chemotherapeutic drug including L-asparaginase (ASNase) and methotrexate (MTX) [22]. For example, asparagine and glutamine released from adipocytes provide a compensatory source for cellular metabolism including protein synthesis to B-ALL cells upon treatment of ASNase chemotherapy, a first-line drug for B-ALL that degrades asparagine and glutamine [23,24]. Consequently, adipocytes increase minimal residual disease and reduce survival of leukemia in response to treatment of ASNase in patients with obesity. In addition, aspartates released from adipocytes are imported into B-ALL cells through SLC1A3, and act as a key metabolite supporting the proliferation of B-ALL cells in low oxygen conditions, thus maintaining cellular fitness against robust proliferation under a hypoxic microenvironment [25]. In the presence of MTX, the adipocyte secretome induces activation of multiple metabolic programs in B-ALL cells including arginine biosynthesis and alanine, aspartate, glutamate, and glutathione metabolism, providing an alternative shield for B-ALL cells against oxidative stress to circumvent chemotherapy-mediated cytotoxicity [26]. Thus, adipocytes not only fuel malignant B cells but also serve as a shelter for malignant B cells to hide from chemotherapy in fat tissue. Adipocytes metabolize chemotherapeutic drugs such as daunorubicin to the less bioactive daunorubinicol by expressing enzyme Aldo-keto reductases (AKR) and carbonyl reductases, protecting B-ALL cells from chemotherapy-induced cell death in the tumor microenvironment [27].

Adipocytes provide free fatty acids to malignant B cells, providing an alternative energy source through β-oxidation (FAO) and contributing to chemotherapy resistance against anti-cancer drugs such as daunorubicin and vincristine. Conversely, malignant B cells stimulate lipolysis of adipocytes, leading to a robust release of fatty acids that feed-forward to disease progression [28]. Leptin, an obesity-derived pro-inflammatory adipokine, plays a central role in cellular energy consumption including induction of FAO [29]. Its binding to the leptin receptor (LEPR) activates signaling pathways including the Janus kinase

(JAK) signal transducer and activator of transcription (STAT), PI3K, mTOR and mitogen-activated protein kinase (MAPK) that mediates pro-inflammatory response in normal or malignant B cells [30,31]. Furthermore, adipocytes release a large panel of bioactive lipid metabolites, such as sphingosine-1-phosphate (S1P) and ceramide-1-phosphate (C1P), significantly modulating stemness, division, and survival of malignant B cells in cooperation with newly synthesized intracellular lipid metabolites driven by oncogenic translocation such as IGH/MYC, which is discussed below [32]. Elevation of FAO by dysregulation of lipid metabolism is the emerging hallmark of energy metabolism supporting anabolism, proliferation, and drug-resistance of malignant B cells [33,34]. Thus, the role of adipocytes associated with the alteration of lipid metabolism in malignant B cells needs to be further investigated for improving chemotherapy of B cell malignancies.

Collectively, obesity directly exacerbates the progression of B-ALL and is significantly associated with elevated risk of B-NHLs [35-37]. The secretome released by adipocytes acts as a biological switch, inducing alteration of cellular metabolism that allows malignant B cells to evade the cytotoxic effects of chemotherapy. This implies the role of the adipose-rich microenvironment in fostering a more aggressive phenotype of malignant B cells. Consequently, it is crucial to evaluate the potential detrimental impact of obesity on B cell malignancies to enhance the precision of diagnosis and prognosis in combination with integrative multiomic approaches.

## 3. Cell-intrinsic factors

In addition to the pro-tumorigenic effects derived from adipocytes, dysregulated homeostasis of lipid metabolism is critically associated with the development, treatment response, and clinical outcome of B cell malignancies. We here review the significance of altered metabolism of various lipid species, including glycerophospholipids, cholesterol, sphingolipids (sphingosine, ceramide, sphingomyelin (SM), glycosphingolipids), and fatty acids in the pathogenesis of B cell malignancies.

### 3.1. Glycerophospholipid metabolism

The plasma membrane plays a crucial role in the physiological function of the B cell-mediated adaptive immune response against potentially harmful foreign antigens through the process of antigen recognition, internalization, and presentation. Antigen recognition is mediated by the B cell receptor (BCR) or pattern recognition receptor (PRR) such as toll-like receptor (TLR) and triggers a series of intracellular signaling cascades leading to activation and differentiation of mature B cells. In B cell malignancy, the majority of key oncogenic mutants responsible for B cell transformation mimic constitutively active BCR signaling, causing uncontrolled proliferation and survival of malignant B cells. Since these initial signaling cascades indispensably rely on the microstructure of the plasma membrane constructed by different lipid species, lipid composition of the plasma membrane has a pivotal role in the physiological state of B cells in either normal or malignant conditions.

The plasma membrane is composed of phosphatidylcholine (PC), the most abundant phospholipid comprising 44-55%, followed by 15-25% of phosphatidylehanolomaine (PE), 10-15% of phosphatidylinositol (PI), 5-10% of SM, 2-10% of phosphatidylserine (PS), 1-2%

of phosphatidic acid (PA), 2-5% of cardiolipin, 2-5% of glycosphingolipid, and 10-20% of cholesterol [38].

On the other hand, despite the relatively small fraction of PI in the plasma membrane, it has indispensable roles in initial signaling cascades essential for normal B cell activation and malignant transformation, which has been highlighted by recurring oncogenic mutations of PI3K, PTEN, and other molecules involved in the PI3K-AKT signaling pathway in patients with B cell malignancies [39].

PI(3)P, PI(3,4)P2, and PI(3,4,5)P3 are generated from the phosphorylation of the inositol ring of phosphatidylinositol (PI), the monophosphate (PI(4)P) and the bisphosphate (PI(4,5)P2) phosphatidylinositol, respectively, by the action of phosphatidylinositol 3-kinase (PI3K) Class I [40]. These phosphate modifications of inositol enhance negative electrostatic force, thus enabling specific recruitment of proteins harboring phosphoinositide-binding domains such as Pleckstrin homology (PH), which includes basic amino acids that in the phosphoinositide binding pocket [41]. Consequently, the recruitment of phospholipid-binding proteins to the membrane facilitates the transmission of signaling cascades essential for B cell activation from the membrane to intracellular compartments.

In particular, PI(3,4,5)P3, referred to as PIP3, acts as a crucial secondary messenger transmitting the activation of PI3K signaling by recruiting PDK1, AKT, BTK, and PLC (Phospholipase C) gamma to the plasma membrane. The biological significance of PIP3 in B cells is well evidenced by studies using mice with deleted or mutated PI3K, which show reduced mature B cell numbers and impaired adaptive immune responses with defects in antibody production [39]. In B cells, the process of PIP3 formation is initiated upon antigen binding to the BCR, leading to PI3K activation and subsequent phosphorylation of phosphatidylinositol-diphosphate (PIP2) to generate PIP3 within seconds. Concentrated PIP3 at lipid rafts, cholesterol- and sphingolipid-rich microdomains in the plasma membrane, acts as a docking site for the rapid and transient recruitment of proteins containing PH domains to the cell membrane. These events lead to a signaling cascade involving PDK1, followed by AKT activation with phosphorylation on threonine 308. This, in turn, enhances the kinase activity of AKT, leading to the phosphorylation of its downstream targets, ultimately enabling B cell survival, proliferation, differentiation, and migration [42,43]. In the context of hematologic malignancy, the PI3K/AKT pathway has been implicated in disease progress of T-cell acute lymphoblastic leukemia (T-ALL), anaplastic large cell lymphoma, multiple myeloma, Hodgkin’s lymphoma, mantle cell lymphoma, and germinal center B cell-like diffuse large B cell lymphoma (GCB-DLBCL) [39,44-47].

The phosphorylation of phosphatidylinositol by PI3K is counteracted by the action of phosphatase and tensin homolog (PTEN), a phosphatase that removes the phosphate from PIP3. The phosphorylation of phosphatidylinositol leads to the hyperactivation of PI3K and downstream effectors, contributing to cancer cell proliferation, progression, and survival [48]. Thus, loss-of-function mutations in *PTEN*, found in approximately 55% of GCB-DLBCL cases, increase the level of PIP3 and enhance the activation of AKT [49,50]. Genetic lesions involved in the hyperactive PI3K-PIP3 pathway are present in approximately

92% of T-ALL cell lines and 81% of primary T-ALL cells [51], further highlighting the significance of phosphoinositide metabolism in hematologic malignancies.

Following the tight regulation of PIP3 generation, substantial function of PIP3 is further titrated by phospholipid-scaffolding proteins such as interferon-induced transmembrane protein 3 (IFITM3) (Fig. 2). In B cells, the endosomal membrane-localized antiviral protein IFITM3 translocates to cell surface upon activation of BCR signaling following antigen recognition. This results in the accumulation of IFITM3 as a part of the BCR-signalosome within lipid rafts. Consequently, the transmembrane proximal region of IFITM3, containing a basic amino acid patch, provides an electrostatic charge that facilitates the binding of IFITM3 to negatively charged PIP3. Thus, IFITM3 scaffolds PIP3, which is transiently produced upon BCR activation in close proximity to the active BCR signalosome, thereby amplifying PIP3-mediated signaling cascades, including PI3K/AKT, BTK, and PLCγ [39]. In line with this, IFITM3 has emerged as a prominent indicator of unfavorable clinical outcomes in B-ALL, MCL, AML, colon cancer, head and neck squamous cell cancer, hepatocellular carcinoma, and prostate cancer [52].

Simultaneously, the inositol lipid signaling pathway plays a crucial role in B cell activation. Upon BCR activation, lipid raft-anchored PLCγ hydrolyzes PI(4,5)P2, predominantly generated from PI(4)P through the action of PI(4)P 5-kinase (PIP5K), into diacylglycerol (DAG) and inositol-1,4,5-trisphosphate (IP3). The presence of DAG promotes the translocation of protein kinase C (PKC) from the cytoplasm to the lipid raft through specific binding of DAG to regulatory domain C1 of PKC. This binding induces a conformational change of PKC, exposing the catalytic domain for further kinase activity. Meanwhile, IP3 diffuses through the cytoplasm and binds to the IP3 receptor (IP3R) on the membrane of the endoplasmic reticulum (ER), triggering the opening of calcium channels on the ER membrane. This process promotes the influx of calcium ions ($Ca^{2+}$), which bind to the C2 regulatory domain of PKC. Consequently, this triggers the release of the catalytic activity of (PKC), leading to phosphorylation of CARD-containing MAGUK protein 1 (CARMA1; also known as CARD11) CARD11 inhibitory domain. The opened conformation of CARD11 induces assembly of a multienzyme complex consisting of CARD11, B cell lymphoma 10 (BCL-10), and mucosa-associated lymphoid tissue lymphoma translocation protein 1 (MALT1) that induces the nuclear factor-κB (NF-κB) activation signaling for B cell activation [53] (Fig. 2). Mutations eliciting constitutive NF-κB activation, such as CARD11-L232LI, and MYD88-L265P are found in approximately 50% of patients with activated B cell-like subtype (ABC) of DLBCL (ABC-DLBCL) [54].

In addition to the role of PI(4,5)P2 as the substrate of PLCγ2 for generating the crucial secondary messengers IP3 and DAG to transmit BCR signaling, PI(4,5)P2 is also a key regulator of the formation and stability of BCR microclusters by influencing actin dynamics. Specifically, PI(4,5)P2 binds to ERM (Ezrin-Radixin-Moesin) proteins, which link the actin cytoskeleton to the plasma membrane. A high density of PI (4,5)P2 attracts these ERM proteins to the plasma membrane, increasing tension and preventing microcluster formation. Conversely, a lower PI(4,5)P2 density allows the ERM proteins to be cleared from these regions, promoting the formation of microclusters [55,56].

PI(4,5)P2 is relatively enriched in the region surrounding the BCR microclusters, while it is efficiently depleted inside the BCR microclusters. As a result, the low density of PI(4,5)P2 within the BCR microclusters creates a favorable microenvironment with reduced interaction strength between the plasma membrane and the cortical actin, thereby promoting microcluster formation. On the other hand, a high PI(4,5)P2 density outside the microclusters supports actin polymerization, stabilizing the microclusters and thus aiding in B cell activation. Furthermore, high PI(4,5)P2 density outside the microclusters inhibits actin filament disassembly by regulating proteins such as Gelsolin and Cofilin, thereby stabilizing the actin network and supporting BCR microcluster stability [55,56].

Additionally, negatively charged PI(4,5)P2 provides a low threshold for IgG-BCR activation in isotype-switched memory B cells by mediating the tethering of the positively charged cytoplasmic tail of IgG to the plasma membrane. This partially explains the lower force requirement for activation and the rapid responses of memory B cells upon antigen re-challenge [57].

The most abundant negatively charged aminophospholipid, phosphatidylserine (PS), plays a role in immune processes such as effer-ocytosis, a process by which apoptotic or dying cells are efficiently cleared by phagocytes, through its asymmetric distribution on the lipid bilayer of the plasma membrane and its capacity to interact with membrane-bound proteins [58,59]. The majority of PS is typically found in the inner layer of the plasma membrane, with only small amounts present in the outer layer. In the early stages of apoptosis, PS becomes exposed on the outer layer due to the activation of phospholipid scramblases, including caspase-dependent Xk-related protein 8 (Xkr8) and $Ca2^{+}$-dependent transmembrane protein 16 (TMEM16) [60]. During the process of apoptosis, PS exposed on the outer surface of the cell membrane serves as a biomarker for the recognition of apoptotic cells by phagocytes through binding to receptors expressed on phagocytes, including TAM (Tyro3, Axl, and Mer) and TIM-1 (T-cell immunoglobulin and mucin domain 1). This process initiates phagocyte-mediated effer-ocytosis, contributing to immunosuppression by reducing the release of inflammatory signals from dying cells [61]. Therefore, delayed exposure of PS on the outer membrane of lymphocytes during apoptosis is associated with the development of autoimmune diseases such as systemic lupus erythematosus (SLE) through the accumulation of apoptotic lymphocytes, elevated inflammatory responses, and increased levels of autoantibodies [62]. Interestingly, in B cell lymphoma, inhibition of PS synthesis by the PTDSS1 inhibitor DS68591889 in the ER disrupts the lipid transport machinery responsible for the exchange of PS/PIP between the ER and the plasma membrane. This disruption leads to aberrantly increased levels of the PI4P pool, including PI(4,5)P2, at the plasma membrane. Consequently, it causes hyperactive BCR signaling characterized by extensive $Ca^{2+}$ influx and caspase-3-mediated cell death, which phenotypically resembles the clonal deletion of autoreactive B cells at autoimmune checkpoints [63,64]. Despite the known impact of PS on immune homeostasis, the exact role of PS synthesis in the autoimmune checkpoints during a series of developmental stages has not been elucidated yet.

The PI3K pathway, integral to glycerophospholipid metabolism, is often persistently activated due to various genomic abnormalities. [65]. These include activating mutations

and/or amplification of the catalytic subunit alpha (PIK3CA), PTEN loss, and mutations and/or amplification of AKT [66,67]. These genomic alterations in the PI3K pathway have been identified in hematologic malignancies and a range of solid tumors, such as colorectal, breast, lung, gastric, ovarian, prostate, bladder, pancreatic cancer, head and neck squamous cell carcinomas, melanoma, and glioblastoma [68-70]. The mechanisms of action by which these mutants drive tumorigenesis have been extensively investigated [66]. Interestingly, aberrantly elevated levels of IFITM3, which enhances the PI3K-AKT signaling pathway by serving as a PIP3 scaffold, also have been observed in diverse solid tumors, including colorectal, breast, lung, gastric, prostate, glioma, and liver cancers [52]. This upregulation predicts poor clinical outcomes, particularly in colon cancer, neck squamous cell carcinomas, implying a pivotal role of phospholipids in tumorigenesis [52].

In summary, the aforementioned process for propagation of signaling from BCR or its oncogenic mimicry highly relies on the microstructure of lipid rafts, where the IFITM3-BCR signalosome assembles. The geometry of lipid rafts requires the enrichment of cholesterol and sphingolipid. Cholesterol, with its amphipathic property, containing a hydrophobic steroid ring and a polar hydroxyl group, allowing for tight lipid packing through intercalation of cholesterol between the sphingolipids by electrostatic interaction to the polar head of sphingolipids and hydrophobic alignment of the steroid ring to acyl chains of sphingolipids. Unlike other phospholipids that possess unsaturated acyl chains, which tend to be bent and result in loosely packed liquid-disordered phases, sphingolipids in lipid rafts have predominantly saturated acyl chains. This straight acyl chain structure of sphingolipids enables them to compactly aggregate with cholesterol for the formation of distinct liquid-ordered microstructure in the plasma membrane [71]. This suggests that cholesterol and sphingolipid metabolism play a critical role in B cell-mediated normal immune response and B cell malignancies.

### 3.2. Cholesterol metabolism

Cholesterol, along with sphingolipids, constitutes a major component of lipid rafts. These provide a stable platform for the clustering of signaling molecules, including BCR and oncogenic BCR mimics. In line with this, treatment with simvastatin, a cholesterol lowering agent, leads to the inhibition of proliferation with increased apoptosis in B-, T-ALL cell lines, as well as patient-driven pre-B ALL cells. Simvastatin further exhibits synergistic effects when combined with cytotoxic agents, including vincristine, doxorubicin, and dexamethasone, resulting in reduced proliferation of human ALL cells. The effects of simvastatin against ALL cells are mediated by inhibition of 3-hydroxyl-3-meythlglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in the pathway leading to synthesis of both cholesterol and mevalonate (MVA)-derived metabolites. This inhibition is accompanied by down-regulation of the Raf/MEK/ERK signaling pathway [72]. In chronic lymphoblastic leukemia (CLL), a mature B cell neoplasm, simvastatin reduces leukemic cell survival, proliferation, and migration [73]. It also synergistically enhances the antitumor effects of BTK inhibitor targeting BCR signaling, and venotoclax, a selective BCL2 inhibitor [74]. Hence, it is imperative to assess the synergistic effect of statins and targeted therapies to facilitate the development of novel treatment strategies for CLL patients.

The scavenger receptor type B1 (SCARB1; also known as CD36), a high-affinity HDL receptor, is a potential molecular target as it mediates the delivery of cholesteryl ester from HDL to the target cell and activates PI3K-AKT signaling upon binding of HDL. Thus, targeting SCARB1 with HDL-like nanoparticles (HDL NPs) that induce cholesterol depletion results in profound cell death in GCB-DLBCL harboring oncogenic PI3K-AKT signaling. On the other hand, targeting SCARB1 is less effective for BCR-dependent DLBCL cells as constitutive BCR signaling increases cholesterol biosynthesis, compensating for acute depletion. Therefore, a combination of cholesterol depletion with inhibition of BCR signaling using an SYK inhibitor or BTK inhibitor, such as the ibrutinib, induces apoptosis of cholesterol depletion-resistant DLBCL cells, demonstrating the feasibility of targeting cholesterol homeostasis to treat B cell malignancies [75]. It is noteworthy that SCARB1 plays a role in cholesterol uptake by the liver and therefore its targeting may impair reverse cholesterol transport.

Additionally, statin treatment induces cytoprotective autophagic responses in ALL, CLL, and CML cells but not in normal human leukocytes by inhibiting AKT/mTOR signaling due to reduced cholesterol synthesis [76]. As a result, bafilomycin-mediated autophagy suppression synergistically induces statin-mediated leukemic cell death. Given that standard metabolic chemotherapeutics, such as L-asparaginase (L-asp) used to target ALL, evoke an autophagic response that compensates for the metabolic stress induced by the drug, combined treatment with statins and autophagy inhibitors might potentially restore the chemosensitivity of drug-resistant leukemic cells. These results provide a strong rationale for exploring the therapeutic effects of inhibitors targeting cholesterol metabolism, further underscoring the need to unveil intricate signaling mechanisms connecting cholesterol metabolism to disease progression that may point to new therapeutic approaches.

Cholesterol homeostasis is primarily regulated by transcription factors, including SREBPs and the liver X receptors (LXRs) [77,78]. As noted above, SREBP2 activates cholesterol synthesis by transcribing genes encoding enzymes, including HMGCR, the rate-limiting enzyme along the pathway leading to the synthesis of both cholesterol and mevalonate (MVA)-derived metabolite [78]. Under conditions of low cholesterol, the SREBP2 cleavage-activating protein (SCAP) escorts SREBP2 from the endoplasmic reticulum (ER) to the Golgi apparatus, leading to proteolytic cleavage of SREBP2 for its subsequent transcriptional activation of cholesterol synthesis. In addition to *de novo* biosynthesis, SREBP2 also promotes cholesterol uptake by upregulating the expression of the low-density lipoprotein receptor (LDLR) [79]. Conversely, excess cholesterol can be converted to cholesterol ester for storage in lipid droplets or excretion as lipoproteins [80]. High cholesterol conditions also block SREBP2 activation by interfering with its trafficking to the Golgi apparatus and inhibiting the detachment of Insulin-induced gene 2 (INSIG2). This also activates LXRs *via* formation of oxysterols, a derivative of cholesterol, promoting the elimination of excess cholesterol *via* upregulation of target genes such as ATP-binding cassette transporters A1 and G1 (ABCA1 and ABCG1). The activation of LXR in response to the binding of oxysterol to LXR leads to the upregulation of the inducible degrader of the LDL receptor (IDOL), which causes the redistribution of the LDLR from the plasma membrane to an intracellular compartment, along with the ubiquitylation and subsequent degradation of LDLR through the lysosome pathway [80].Thus, LXRs facilitate the process

of reverse cholesterol transport, which returns excess cholesterol to the liver for excretion and bile acid synthesis [81]. Interestingly, activation of T cells initiates the induction of the sulfotransferase family 2B Member 1 (SULT2B1), the oxysterol-metabolizing enzyme, leading to the subsequent suppression of the LXR pathway for cholesterol excretion, while facilitating the cholesterol synthesis *via* activation of SREBP pathway [82].

In line with this, LXR functions as a metabolic checkpoint to maintain cellular cholesterol levels in lymphocytes [83]. *Lxrb*-deficient lymphocytes undergo hyperproliferation in response to BCR and TCR activation, resulting in uncontrolled T and B cell expansion and the development of immunologic disorders characterized by splenomegaly and lymphadenopathy. In this study, gene sets linked to cholesterol, fatty acid, and phospholipid synthesis were upregulated in activated lymphocytes [83]. In particular, the SREBP2 target genes were markedly induced, whereas LXR target genes including ABCA1 and ABCG1 were rapidly downregulated during lymphocytic activation, indicating the tight regulation of cholesterol homeostasis in lymphocytic expansion. LXR is also known to inhibit NF-κB-dependent gene expression, which is crucial for lymphocytic activation, inflammation, and adaptive immune response [84]. LXRs counteract the action of NF-κB by suppressing the expression of inflammatory mediators such as inducible nitric oxide synthase, cyclo-oxygenase (COX)-2, and interleukin (IL)-6 in response to recognition of bacterial lipopolysaccharide (LPS) [85]. Consistent with these effects, the LXR agonist GW3965 has been shown to reduce the inflammatory response in models of irritant-induced contact dermatitis, atherosclerosis, sepsis, and autoimmune disease such as multiple sclerosis [86-89]. However, the detailed mechanism underlying the regulation of activation of LXR by the oxysterol and IDOL in both normal B cell and B cell malignancy has not yet been investigated.

Toll-like receptors (TLRs) play a pivotal role in recognizing conserved patterns that mark bacterial, viral, or fungal invasion, termed Pathogen-Associated Molecular Patterns (PAMPs). This serves as a key trigger of the innate immune response, inducing the release of pro-inflammatory mediators such as cytokines, chemokines, and type I interferon (IFN) through NF-κB activation upon antigen recognition. Notably, TLR4 is responsible for detecting LPS within the outer membrane of gram-negative bacteria [90]. The initial signaling cascades in part of the anti-bacterial immune response are induced by the clustering of TLR4 in lipid rafts, facilitating the recruitment of intracellular adaptor proteins such as myeloid differentiation primary response protein 88 (MyD88). This recruitment leads to the activation of NF-κB and Activated Protein-1 (AP-1) transcription factors.

The critical role of cholesterol in the initial immune response was observed in macrophages lacking the cholesterol efflux pump, ATP-binding cassette subfamily A1 (ABCA1). Accumulation of excessive cellular cholesterol in lipid rafts led to enhanced activation of MyD88-dependent signaling pathway by Toll-like receptors (TLRs) and thereby heightened proinflammatory response to LPS [91]. Importantly, human TLRs contain cholesterol-binding motifs called CRACs (defined as -[LV]-X(1,5)-Y-X(1,5)-[RK]-) and/or CARC (defined as -[RK]-X(1,5)-Y-X(1,5)-[LV]-) in their cytoplasmic domain near the transmembrane region. Notably, TLR4 features CARC-CRAC-CARC domains close to the cell membrane, which mediate interaction with cholesterol. This triggers a structural

change in TLR4, leading to efficient clustering at lipid rafts, followed by NF-κB activation [90]. The interaction between cholesterol and TLR4 is also promoted by the inhibition of cholesterol efflux, as TLR4 activation hinders the induction of LXR target genes, including *ABCA1* [89]. Accordingly, cholesterol depletion with treatment of statins leads to impairment of TLR4 recruitment into lipid rafts, thereby inhibiting NF-κB activation. Conversely, the supplementation of mevalonate restores TLR4 recruitment into lipid rafts and rescues the effect of statin [92]. Given the requirement of cholesterol for clustering of TLR4 in lipid rafts, the cholesterol binding capacity of CRAC and CARC motifs in TLR4 is vital for the LPS-TLR4 signaling pathway to elicit the initial inflammatory immune response against bacterial infection (Fig. 3).

In addition to the contribution of cholesterol to NF-κB activation, disruption of lipid rafts by cholesterol extraction with methyl β-cyclo-dextrin (MβCD) disrupts the -AKT-mTOR signaling cascade. Upon cholesterol depletion, AKT fails to localize into a lipid raft, leading to the abrogation of the binding of AKT to PDK1. Consequently, there is diminished AKT activity with reduced levels of AKT phosphorylation at threonine 308 and serine 473, resulting in the deactivation of mTOR and increased susceptibility to cellular apoptosis [93]. Given that aberrant activation of the PI3K/AKT/mTOR pathway leads to uncontrolled proliferation, fostering the transformation of lymphoblasts into a malignant form and contributing to disease progression, targeting the integrity of lipid rafts with manipulation of cholesterol metabolism may serve as a potential pharmacological strategy in the treatment of lymphoblastic malignancies. While the mechanism by which cholesterol in lipid rafts regulates cell signaling is increasingly evident, the mechanism of the predominant accumulation of cholesterol in lipid rafts for maintaining fundamental structure is not yet known. One possibility is that PIP3-binding protein IFITM3 acts as a barrier that prevents the diffusion of cholesterol, thus leading to cholesterol accumulation in the lipid raft. The amphipathic helix region close to the CRAC motif of IFITM3 directly interacts with cholesterol. As a result, IFITM3-mediated accumulation of cholesterol specifically *via* Phe63 and Phe67 in the late endosomal membrane increases membrane stiffness, which antagonizes viral-to-host membrane fusion, an essential event for the release of viral RNA into the host cytoplasm. Therefore, point mutations of two phenylalanines disable the antiviral function of IFITM3 against Influenza A virus (IAV) [94]. Hence, the interplay between two cholesterol-binding proteins, TLRs and IFITM3, which play a vital role in defending against harmful foreign antigens, is intriguing for gaining insights into the role of membrane-accumulated cholesterol in the immune response.

These findings suggest that cholesterol plays an essential role in facilitating the rapid proliferation of malignant B cells. It serves not only as a critical structural building block for the cell membrane but also functions as a platform for cellular signal transduction through lipid raft components. In addition to cholesterol, the intermediate byproducts generated during cholesterol synthesis also contribute to the regulation of post-translational prenylation of numerous proteins, including small GTPases [95].

Mevalonate (MVA) metabolism is not only essential for producing cholesterol and its related metabolites but also contributes to the progression of cancer, including CLL, by stimulating DNA synthesis during the cell cycle and promoting malignant proliferation [96].

Statins reduce proliferation and induce apoptosis of CLL cells *in vitro* and cytotoxicity is synergistically enhanced by the BCL2 inhibitor venetoclax and the BTK inhibitor ibrutinib [97]. This aligns with the clinical observation that blocking of the mevalonate pathway with statins, such as lovastatin and fluvastatin, reduces the risk of CLL[98,99]. More importantly, members of the RAS family, as small GTPases, require mevalonate-derived farnesyl or geranylgeranyl isoprenoid modifications for membrane localization. Disordered RAS signal transduction is a major contributor to hematologic malignancies, including B- and T-cell lymphoblastic leukemias. For example, zoledronate, which targets farnesyl diphosphate synthase (FPS), reduces the cellular intermediates of isoprenoid biosynthesis, including farnesyl diphosphate (FPP) and geranylgeranyl diphosphate (GGPP). Consequently, it induces cytotoxicity in malignant B cells, demonstrating anti-tumor effects with increased survival in patients with multiple myeloma, a terminally differentiated B cell malignancy [100]. Additionally, treatment with digeranyl bisphosphonate (DGBP), which targets geranylgeranyl diphosphate synthase (GGDPS), an enzyme in the mevalonate pathway, alters protein expression and membrane association of RhoA, Rac, and Rap1. This results in the activation of caspases and profound apoptosis in T lymphoblastic leukemia [101]. However, the role of the mevalonate pathway and the detailed mechanism underlying the therapeutic effect of DGBP in RAS-driven B cell malignancy has not yet been investigated.

Besides B cell malignancies, alterations in cholesterol and mevalonate metabolism have been implicated in promoting oncogenic mechanisms in various cell types, including those in breast, prostate, rectal, testicular, and colon cancers. For instance, dietary cholesterol has been shown to promote colon cancer by activating the NLRP3 inflammasome [102]. Furthermore, diet-induced hypercholesterolemia enhances the metastasis of prostate cancer cells by increasing the levels of metastasis-associated proteins IQGAP1 and caveolin-1 [103]. Cholesterol also activates the oncogenic G-protein coupled receptor Smoothened (SMO), thereby promoting Hedgehog signaling [104,105]. Additionally, cholesterol can directly bind to the PDZ domains of Na(+)/H(+) exchange regulatory cofactor (NHERF1), a key scaffolding protein assembling oncogenic Platelet-Derived Growth Factor Receptor, Beta Polypeptide (PDGFRβ), Epidermal Growth Factor Receptor (EGFR), PI3K/PTEN/ATK and Wnt/β-catenin signaling pathways [106]. It is shown that lysosomal cholesterol activates mTORC1 *via* the cholesterol-responsive motifs in SLC38A9, the lysosomal transmembrane, contributing to cancer development [107,108]. In breast cancer, mevalonic acid as a precursor of cholesterol activates YAP and TAZ mediators of the Hippo pathway that promotes tissue proliferation and organ growth [109]. These pathways can be utilized to investigate malignant B cells, further elucidating the role of cholesterol metabolism and its therapeutic potential.

In summary, cholesterol and related metabolites play critical roles as essential lipids in various cellular processes. Besides cholesterol's vital function in membrane structure, supporting BCR signaling, recent evidence has highlighted a strong link between cholesterol homeostasis, inflammation, and progression and relapse of hematological malignancies. This underscores the potential of targeting cholesterol homeostasis as a promising therapeutic approach for treating hematopoietic malignancies. This can be achieved by

modulating cholesterol homeostasis, either by disrupting its synthesis or by activating reverse cholesterol transport *via* LXRs.

### 3.3. Sphingolipid metabolism

Sphingolipids, which are synthesized from serine and palmitoyl-CoA, encompass ceramides, glycosphingolipids (such as cerebrosides and gangliosides), phosphatidylserine (PS), phosphosphingolipids (such as sphingomyelins), and sphingosine (Fig 4). These molecules play a crucial role in regulating hematopoiesis, migration of lymphocytes, immune responses, and the signaling pathways related to oncogenesis of B cell malignancies [110].

Sphingolipids are fundamental components of lipid rafts, along with cholesterol. Interestingly, TLRs, which harbor cholesterol binding motifs possibly mediating its insertion into lipid rafts, also include two consecutive sphingolipid binding-like motifs defined as [V/I/T/L]-X-[V/I/T/L]-[V/I/T/L]-X-X-[V/I/T/L]-[Y/F/W] in their transmembrane domain, implying the scaffolding role of sphingolipids in localization of membrane proteins within lipid rafts [111]. Additionally, macrophages lacking sphingomyelin synthase (SMS) 1 or 2 show attenuated NF-κB and MAPK activation upon LPS treatment due to reduced level of TLR4 at the cell surface, resulting from impaired receptor trafficking [112,113]. Macrophages with haploinsufficient *Sptl2*, which encodes serine palmitoyltransferase 2 (the first and rate-limiting enzyme of the *de novo* biosynthetic pathway of sphingomyelin), exhibit defects in TLR4 recruitment to a membrane microdomain, leading to impaired inflammatory responses triggered by LPS stimulation [114]. Conversely, stimulation by LPS activates SMS 1 and/or SMS2, which feeds forward to assembly and activation of TLR4 at the cell surface. As a result, the inhibition of SMS by treatment with tricyclodecane-9-yl xanthogenate (D609) disrupts LPS-induced pro-inflammatory responses with attenuation of TLR4 activation, indicating the therapeutic potential of regulating sphingolipid metabolism to treat inflammatory disease [115]. In B cells in the germinal center, antigen-stimulated BCR and TLR9 directly upregulate the expression of SMS2 on the surface yielding sphingomyelin at the expense of ceramide, and DAG as a by-product which further promotes the activation of PKC kinases [116].

In B cell malignancies, there have been sustained efforts to leverage sphingolipid as a marker for diagnosis and prognosis [117]. This is because the activation of the cancer driver skews sphingolipid metabolism to favor the production of anti-apoptotic sphingolipids such as S1P while depleting pro-apoptotic sphingolipids such as ceramide and sphingosine. Sphingosine kinase (SPHK) 1 and 2, enzymes responsible for catalyzing the synthesis of S1P through the phosphorylation of sphingosine, are highly expressed by BCR-ABL1, a Philadelphia chromosome-derived fusion oncogene that mimics constitutively active BCR signaling. As the abnormal expression of SPHK1 and 2 is related to drug resistance to the BCR-ABL1 inhibitor imatinib in B-ALL, selective inhibition of SPHK1 with SK1-I, which reduces S1P production, induces death of imatinib-resistant B-ALL cells [118]. In addition to SPHK1, the S1P-bound form of SPHK2 directly interacts with and inhibits nuclear-located histone deacetylases 1 and 2 (HDAC1/2). Consequently, an increased level of acetylated histone H3 leads to enhanced MYC expression, which plays a pivotal role in development of BCR-ABL1-driven B-ALL and its resistance to imatinib [119]. In B-ALL

cells, SPHK2 inhibition with ABC294640 reduces MYC expression along with decreased levels of histone H3 acetylation, thus exerting a synergistic cytotoxic effect with imatinib [119].

Notably, leukemic cell death mediated by inhibition of SPHK is accompanied by the accumulation of ceramides, potent tumor-suppressing sphingolipids. The blockade of conversion of sphingosine to S1P through inhibition of SPHK leads to cytoplasmic accumulation of proapoptotic ceramides, which participate in the oxidative stress pathway, generating reactive oxygen species (ROS) [120]. The accumulation of cytoplasmic ceramides is also known to promote the inactivation of AKT signaling by either mediating AKT binding to its inhibitory protein, PKCζ, or facilitating the activation of the serine/threonine-protein phosphatase 2 A (PP2A), leading to dephosphorylation of AKT [121].

In CLL, stimulation of BCR and CD40 ligand (CD40L) induces depletion of proapoptotic ceramides *via* upregulating UDP-glucose ceramide glucosyltransferase (UGCG), which catalyzes the conversion of ceramide to antiapoptotic glucosylceramide. This process can be reversed by inhibiting PI3Kδ with CAL-101 (also known as idelalisib) and Bruton tyrosine kinase with PCI-32365 [122]. Interestingly, the BCL2 inhibitor Navitoclax, which targets CLL cells characterized by high levels of BCL2, is known to enhance enzyme activity of CerS, leading to an elevation of proapoptotic ceramides. Therefore, a combination strategy that induces ceramide accumulation using SPHK, UCGC, PI3K, and BTK inhibitors along with BCL2 inhibitors may exert a synergistic effect on CLL cells. These data suggest that manipulating sphingolipid metabolism with inhibitors of enzymes that block the conversion of ceramide to other pro-survival sphingolipids holds promise as a strategy to overcome drug resistance when combined with conventional chemotherapy, as described in detail below.

**3.3.1. Sphingosine metabolism—**Sphingosine (Sph), derived from ceramide cleavage by ceramidase, exerts cytotoxic effects by inhibiting the mitogen-activated protein kinase (MAPK) cascade, leading to the suppression of basal kinase activity of ERK1/ERK2. This, in turn, induces mitochondria-mediated apoptosis and reduces BCL2 expression at both the mRNA and protein levels in various cancer cells, including breast cancer and hematologic malignancies [123-125]. In DLBCL, Sph competes with phosphatidylserine (PS) for binding to the C1 domain of PKC, which is required for membrane recruitment and confirmational changes that expose its catalytic domain. Consequently, Sph induces cell death of DLBCL cells by interfering with pro-survival signals of PKC. This effect can be recapitulated by treatment with the synthetic stereoisomer L-*threo*-sphingosine Lt-Sph [126]. Accumulation of Sph can be achieved by pharmacological inhibition of the S1P-lyase, such as LX2931, which has passed Phase II clinical trials for the treatment of rheumatoid arthritis and other autoimmune diseases [127]. However, the therapeutic effects of LX2931 in hematologic malignancies have not yet been investigated.

While sphingosine is considered a pro-apoptotic sphingolipid, its metabolically active form, S1P, is known as a pro-survival factor and is involved in the pathogenesis of multiple cancers, including head and neck, breast, ovarian, colon, pancreatic, prostate, liver, and bile duct cancers [128-130]. Therefore, monoclonal antibodies targeting S1P, specifically neutralizing extracellular S1P, have promising therapeutic effects by preventing S1P-induced

proliferation, drug resistance, invasion, and angiogenesis in renal, breast, ovarian, and lung cancer models [131,132].

Intracellular S1P is synthesized from sphingosine through the action of an SPHK [133]. In mature B cell malignancies, PKC, a central kinase for NF-κB activation, induces the catalytic activity of SPHK2. Activated SPHK2 and its product S1Ps are localized in the nucleus and directly bind to histone deacetylases (HDACs) 1 and 2, thereby inhibiting histone deacetylation. As a result, enhanced histone acetylation by SPHK2 and S1Ps leads to the upregulation of transcription of genes such as that encoding c-fos [134]. In B cell lymphoma, resistance of DLBCL cells to the HDAC inhibitor (HDACi) dacinostat, is mediated by upregulation of the activator protein (AP)-1 complex, consisting of c-Fos and Jun. Conversely, the sensitivity of DLBCL cells to HDACi is enhanced by inhibition of the DNA binding capacity of c-FOS with T-5224, a c-FOS/AP-1 inhibitor [135]. This implies the relevance of a combined targeting strategy of AP-1 with S1P metabolism.

Besides SHPK2, the expression of SHPK1 significantly increases in DLBCL cells, showing a positive correlation with expression of genes associated with tumor angiogenesis. In line with this, S1P promotes angiogenesis and tumor growth, which is effectively reversed by employing the S1PR1 inhibitor Siponimod or the S1P neutralizing antibody known as Sphingomab *in vivo* [136]. In MCL cells, the enhanced activation of SHPK1 alters the intracellular balance of S1P to cardiolipin, allowing them to evade the surveillance of the Natural Killer T (NKT) cells that link the innate and adaptive immune responses against cancer by recognizing glycolipid antigens presented on CD1d. As a result, the blocking S1P production with SHPK1 inhibition results in an increased level of cardiolipin acting as an NKT agonist and promoting the cytotoxic activation of NKT cells against MCL cells [137].

In the context of the tumor microenvironment, S1P directly stimulates the phosphorylation of c-Abl1 at Y89, Y245, and Y412, which, in turn, activates the ERK, AKT, and NF-κB signaling pathways, promoting the growth, migration, and invasion of pancreatic cancer cells [138]. Interestingly, the c-Abl protein plays a crucial role in the normal development of pre-B cells and can also undergo constitutive activation through chromosomal translocation with the Breakpoint cluster region (BCR) gene, giving rise to BCR-ABL1, a key contributor to the pathogenesis of B-ALL. Nevertheless, the precise mechanisms through which S1P impacts the activity of c-Abl or BCR-ABL1 in B cell development and the progression of leukemia remain unclear.

Intracellular S1P is not only directly involved in various cellular signaling pathways but is also exported through the action of the protein spinster homolog 2 (SPNS2) or ABC transporters, thereby impacting its biological functions [139]. Extracellular S1P binds to the five G protein-coupled receptor (GPCR) family members, S1PR1 to 5, in an autocrine or paracrine manner, activating GPCR-mediated cellular responses [140]. The role of extracellular S1P as a chemoattractant in facilitating lymphocyte migration has been extensively studied. S1P receptors are expressed on the surface of lymphocytes, allowing them to respond to S1P gradients, which direct lymphocyte egress from low S1P-concentrated thymus or lymph nodes to high S1P-concentrated circulatory plasma and lymph. Consequently, this process plays a crucial role in the functional adaptive immune

response by facilitating the exit of newly formed T cells from the thymus and the exit of mature T and B cells from secondary lymph nodes. High concentration of S1P in the circulation is induced by the expression of Sphingosine-1-Phosphate Transporter, SPNS2, which mediates the export of S1P from endothelial cells, leading to a local S1P gradient for chemoattraction of lymphocytes [141-143].

Furthermore, the efficient exit of newly generated immature B cells from the bone marrow into the circulation relies on the S1P gradient in the circulation. This is supported by the observation that mice lacking S1PR1 in the B cell lineage exhibit reduced numbers of immature B cells in the circulation, while early B cell development in the bone marrow remains normal [144].

The immunomodulatory drug FTY720, also known as fingolimod, is a structural analog of sphingosine acting as a functional antagonist of S1P receptors, particularly S1PR1, which senses extracellular S1P. Therefore, FTY720 prevents S1P-mediated lymphocyte trafficking into the circulation or the central nervous system, providing therapeutic benefits in treating MS and autoimmune diseases by reducing the infiltration of autoreactive lymphocytes into target tissues [145].

S1P also plays a crucial role in the localization of marginal zone B cells (MZB) within the spleen. MZB cells are innate-like B cells responsible for the first line of immune defense against a broad spectrum of foreign antigens by rapidly differentiating into plasma cells that secrete self-and/or poly-reactive natural antibodies [146]. In the spleen, MZB cells shuttle between the marginal zone (MZ) and the follicle, delivering blood-borne antigens to follicular dendritic cells (FDCs) based on the balance of CXCL13 and S1P abundance. Thus, CXCR5 guides the migration of MZB cells to the follicle, whereas S1PR1 and S1PR3 promote the return of MZB cells back to the marginal zone. Given that the marginal zone serves as the primary entry point for blood-borne antigens, S1P metabolism in secondary lymphoid tissue is essential for efficient adaptive immune responses. This suggests the suppressive potential of immunogenicity by S1PR modulators such as FTY720, siponimod, ozanimod, ponesimod, KRP-203, and VPC44116 [147,148]. In the context of B cell malignancy, dysfunctional *S1PR1* mutations, which are present in approximately 7.8% of patients with MCL [149], mediate the retention of malignant cells in the supportive microenvironment, constituting a reservoir of minimal residual disease. Given that the adhesion of MCL cells to the surrounding stromal cells within the tumor microenvironment contributes to the resistance of ibrutinib, it is fascinating to explore the therapeutic potential of a combined treatment regimen involving ibrutinib and an immunomodulatory drug such as FTY720, which induces the release of lymphoma cells from the tumor site [150,151].

In summary, it’s worthwhile to highlight that Sph can be finely regulated in two divergent directions because it undergoes two distinct pathways. Sph can be phosphorylated to form S1P, which binds and activates pro-survival S1PRs, or it can be acylated to ceramide, leading to pro-apoptotic effects as described below.

**3.3.2. Ceramide metabolism—**Ceramide (Cer) is the central molecule of sphingolipid metabolism frequently recognized as a proapoptotic sphingolipid due to its function as

a secondary messenger for apoptosis, senescence, and autophagy [152,153]. It is mostly produced by the hydrolysis of sphingomyelin *via* the action of sphingomyelinase in the plasma membrane or by the process of acylation and subsequent desaturation of sphinganine [154].

The accumulation of ceramide induces the clustering of Fas (also known as CD95) receptors through the aggregation of lipid rafts, subsequently amplifying the proapoptotic signaling initiated by Fas [155,156]. This aligns with the observation that ceramide triggers apoptosis by stimulating pro-apoptotic pathways through the activation of the stress-responsive protein kinase c-Jun N-terminal kinase (JNK) as a downstream effector of Fas [157]. On the other hand, the buildup of intracellular ceramides results in the formation of column-shaped ceramide channels in the mitochondria, which in turn augments the permeability of the mitochondrial outer membrane, heightening susceptibility to apoptosis [158,159].

In addition, ceramide promotes anti-apoptotic processes by counteracting the activity of AKT, which is a key enzyme implicated in the development of various B cell malignancies. Treatment with cell-permeable ceramide analogs effectively antagonizes cytokine-mediated activation of AKT by inhibiting phosphorylation at serine 473 on Akt. This process is achieved through ceramide-induced activation of protein phosphatases. Notably, okadaic acid, a known inhibitor of PP2A, impedes ceramide-induced phosphatase activity and restores AKT activation in response to cytokine stimulation in the presence of intracellular ceramide [160].

Remarkably, both AKT and PP2A share a critical downstream effector, BCL2, which plays a pivotal role in anti-apoptotic signaling in malignant B cells. In addition to the effect of ceramide-induced PP2A activation in dampening AKT activity, ceramide also triggers the activation of mitochondrial PP2A. This, in turn, promptly induces the dephosphorylation of BCL2, a critical step necessary for the complete and robust execution of the anti-apoptotic process [161]. The interference of mitochondrial function by the accumulation of ceramide also contributes to the rapid formation of ROS and ATP depletion, leading to the cell death of malignant B cells [162]. This may provide a partial explanation for the ceramide-induced apoptosis and cell cycle arrest observed in Fas-resistant Burkitt's lymphoma (BL) cells [163,164].

Intriguingly, chemotherapeutic drugs, in part, achieve cytotoxic effects by promoting the accumulation of ceramide within cancer cells [165]. For instance, drugs such as doxorubicin, which are used in the treatment of various cancers, including Hodgkin's lymphoma, induce apoptosis not only by directly targeting DNA synthesis but also by promoting the accumulation of ceramide through the activation of sphingomyelinase [166]. Etoposide, commonly used for the treatment of various cancers, including lymphomas, not only eliminates cancer cells by inhibiting DNA synthesis through the induction of breaks in double-stranded DNA, but it has also been reported to trigger *de novo* ceramide production by enhancing the activity of serine palmitoyl transferase in B-ALL cells [167]. This cytotoxic effect is also evident in other types of cancer cells. For example, ceramides serve as mediators in the process of etoposide-induced apoptosis by facilitating the release of cytochrome *c*, subsequently leading to the activation of caspase-9 and caspase-3 in glioma

cells [168]. Likewise, the microtubule-directed chemotherapeutic agent Paclitaxel, used in the treatment of lymphoma, triggers sphingomyelinase activation and subsequent ceramide production, which has a synergistic cytotoxic effect in T-ALL cells [169].

Besides the chemotherapeutic drugs, Rituximab, a chimeric human monoclonal antibody designed to specifically target CD20-positive malignant B cells, has demonstrated notable success in the treatment of B cell-derived lymphoid malignancies in combination with chemotherapy as part of R-CHOP (rituximab with cyclophosphamide, hydroxydaunomycin, vincristine, and prednisone) regimens. Beyond its primary anticancer effects, which involve antibody-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC), the binding of rituximab to CD20 initiates a pro-apoptotic signaling pathway by activating sphingomyelinase. This activation leads to an augmented production of ceramide, resulting in the selective induction of cell cycle-dependent kinase inhibitors such as p27(Kip1) *via* a mitogen-activated protein kinase (MAPK)-dependent mechanism [170].

The accumulation of ceramide can also be achieved by using sphingomyelinase inhibitors, such as D609. However, a notable challenge associated with sphingomyelinase inhibitors is their lack of selectivity. D609 is also a well-known inhibitor of phospholipase C, which is involved in DAG-mediated oncogenic BCR signaling. This indicates that its impact extends beyond the regulation of ceramide concentration [171]. Despite the remaining challenges, such as the specific regulation of ceramide synthesis or elucidating the detailed mechanisms underlying ceramide-mediated cytotoxic effects in B cell malignancies, it becomes evident that modulating ceramide metabolism holds significant promise in enhancing the efficacy of chemotherapeutic treatments in B cell malignancies.

**3.3.3. Sphingomyelin metabolism—**Sphingomyelin (SM) is predominantly located in lipid rafts in the plasma membrane and is essential for preserving both the structural integrity and functional significance of lipid rafts in regulating signal transduction. SM is generated through the condensation of ceramide with phosphocholine, a reaction catalyzed by SMS [172]. In fact, the concentration of SM in the membrane is required for the localization of K-RAS within inner plasma membrane rafts, which play a critical role in normal early B cell development at the pre-B cell stage, late B cell maturation, and the development of B cell malignancies such as multiple myeloma and hairy cell leukemia [173-175]. Therefore, the inhibition of sphingomyelinase with the avicin G, a family of natural plant-derived triterpenoid saponins from *Acacia victonae*, dissociates K-RAS from the plasma membrane and inhibits oncogenic K-RAS signal transduction [176].

Pharmaceutical interventions targeting SMS or sphingomyelinase can modulate the balance between two opposing bioactive lipids: ceramide and SM. Ceramide, with its pro-apoptotic properties, plays a vital role in processes such as apoptosis, necrosis, and autophagy-mediated cell death. In contrast, SM supports proliferative signal transduction within lipid microdomains. Hence, manipulating the ceramide/SM balance through the regulation of SMS or sphingomyelinase holds promise as a potential therapeutic strategy, particularly in the context of B cell malignancies, where it remains untested.

**3.3.4. Glycosphingolipid metabolism—**Glycosphingolipids (GSLs), including gangliosides (sialosylglyco-sylceramides), cerebrosides (monoglycosylceramides), and globosides (oligoglycosylceramides), are synthesized through sequential glycosylation of ceramide [177]. These GSLs, located on the outer leaflet of plasma membranes, play a crucial role in maintaining the structural integrity of the cell membrane and serve as bioactive compounds that modulate the activation of both innate and acquired immunity [178].

Gangliosides, sialic acid-containing glycosphingolipids, are amphiphilic lipids residing within membranes. Gangliosides are classified into four species, denoted as 0-, 1-, 2-, and 3-, which correspond to the number of sialic acids linked to the inner galactose residue, forming monosialogangliosides (GM), disialogangliosides (GD), trisialoganglio-sides (GT), and tetrasialogangliosides (GQ) [179,180].

Gangliosides not only influence membrane integrity and the functions of membrane-associated proteins but also act as receptors for various influenza viruses and bacterial toxins, such as the cholera toxin [181]. Therefore, gangliosides contribute to innate immunity by mediating interactions between hosts and pathogens. Gangliosides also play a critical role in adaptive immunity by modulating antigen presentation and the activation of BCR signaling in B cells. Monosialogangliosides (GM1) mediate antigen presentation, such as *Escherichia coli* enterotoxin (EtxB), a potent immunogen, in B cells and dendritic cells (DC), substantially amplifying the proliferation and cytokine production of EtxB-specific $CD4^+$ T cells [182]. The enrichment of GM1 within lipid rafts in B cells is crucial for the activation of BCR signaling. In the resting condition, BCR is excluded from GM1-enriched lipid rafts. Upon binding of foreign antigens to BCR, BCR colocalizes with GM1-enriched lipid rafts, which is essential for the activation of BCR and its downstream signaling for B cell activation in the context of adaptive immunity [183,184]. In the context of B cell malignancies, the mechanism of rituximab resistance is associated with the recruitment of CD20 to lipid rafts, a process influenced by the level of GM1 within lipid rafts. In line with this, patients with high GM1 expression in CLL and MCL cells exhibit a favorable response to rituximab as opposed to lymphoma cells with low GM1 expression [185]. Despite the significant role of GM1 in B cell activation and malignancies, the role of other species of gangliosides is poorly understood.

Cerebrosides, neutral compounds consisting of ceramide and a monosaccharide, are primarily found in myelin, which insulates and protects nerve fibers in the nervous system [186,187]. In the context of hematology, Gaucher disease is a rare inherited genetic disorder resulting from the accumulation of Gaucher cells, which are lipid-loaded tissue-resident macrophages characterized by the buildup of glucocerebroside in lysosomes due to a deficiency of glucocerebrosidase, in tissues such as the spleen and liver. This leads to chronic or fulminant infections in patients with Gaucher disease. Macrophages derived from individuals with Gaucher disease exhibit reduced superoxide anion production, potentially because glucocerebroside (GC) interferes with the activation of NADPH oxidase [188]. However, in contrast to ceramide, the mechanism by which cerebroside is involved in signal transduction in myeloid, B-, and T-cells remains largely unknown.

Altered sphingolipid metabolism is associated with various malignancies beyond B-cell malignancies. Altered levels of ceramide and sphingosine-1-phosphate (S1P) have been implicated in breast cancer progression and resistance to therapy [189], colon cancer cell proliferation and survival, liver cancer growth and metastasis, pancreatic cancer cell proliferation, invasion, and apoptosis resistance, ovarian cancer cell survival and chemoresistance [190]. Mechanistically, reduced ceramide production limits apoptosis, allowing for unchecked cell proliferation [191]. Additionally, the conversion of sphingosine to S1P by sphingosine kinases (SphK) promotes cell survival, angiogenesis, and metastasis. Increased SphK1 activity and decreased ceramide levels have been linked to poor prognosis and resistance to chemotherapy in breast cancer [192]. S1P can activate the PI3K/Akt pathway, further promoting cell survival and proliferation.

## 4. Fatty acid metabolism

The *de novo* synthesis or transporter-mediated uptake of fatty acids is essential to maintain the structural stability of cellular membranes [193]. Furthermore, fatty acids act as secondary messengers and as an energy source through FAO, especially in energy-limited environments [194]. While *de novo* fatty acid synthesis is highly active in dividing fetal cells during embryogenesis, the majority of normal cells in adults preferentially utilize dietary fatty acids and do not synthesize fatty acids under normal physiological conditions, except for hepatocytes, adipocytes, and hormone-responsive cells in lactating breast tissue, due to low expression of fatty acid synthase (FASN), which catalyzes acetyl-CoA to fatty acid palmitate [195]. In contrast, fatty acid metabolism is one of the most altered metabolic pathways in a multitude of cancer types, which ensures a steady supply of intermediate metabolites for the generation of energy and biomass, providing significant growth advantages to cancer cells and often correlating with a poor clinical outcome [196]. Recent studies have implicated altered fatty acid metabolism as a major oncogenic factor in aggressive B cell lymphomas, including BL, CLL, MCL, and DLBCL [3,33,197]. Thus, targeting *de novo* lipid synthesis is becoming a promising strategy to treat B cell malignancies.

BL is characterized by the chromosomal rearrangement of *MYC* to the immunoglobulin heavy chain (*IGH*) locus or light chain loci such as *IGK* or *IGL*, with the presence of lipid droplets in the cytoplasm of BL cells [3,198]. In contrast to other B cell lymphomas, the gene expression profile in BL cells reveals a significant overexpression of FASN and adipophilin, which is a member of the lipid droplet-associated PAT-proteins family involved in fatty acid transport and in preserving cellular triacylglycerols [199]. This is accompanied by marked upregulation of genes involved in lipid metabolism accommodating robust proliferation with an alternative fuel source for ATP generation, suggesting potential new markers for diagnosis and novel therapeutic strategies for BL treatment [2]. Following this, carnitine palmitoyl transferase 1 (CPT1), which acts as the rate-limiting enzyme catalyzing the transport of fatty acids into mitochondria for FAO, plays a crucial role in meeting the heightened energy demands in *MYC*-driven BL cells. Thus, disruption of CPT1 activity with ST1326 exerts a cytotoxic effect on BL cells by reducing FAO [200]. Furthermore, the inhibitory action of ST1326 extends to impede the function of carnitine-acylcarnitine translocase (CACT), a pivotal enzyme essential for shuttling long-chain fatty acids from the

cytosol into the intramitochondrial space for mitochondrial FAO, yielding acetyl-coenzyme A (CoA). Therefore, treatment with ST1326 causes compromised mitochondrial function, resulting in the progressive accumulation of lipid droplets within the cytoplasm, leading to the loss of the ability to utilize fatty acids as an energy source and to reconstruct cellular membranes. The cytotoxicity of ST1326 in BL cells is dependent on MYC levels, implying that pharmacological inhibition of fatty acid metabolism could offer a promising therapeutic avenue for targeting *MYC*-driven malignant B cells [4].

CLL, the most prevalent leukemia in adults, is characterized by the malignant accumulation of mature monoclonal B cells within the bone marrow, subsequently spreading to the bloodstream and lymphoid organs during disease progression. Interestingly, as observed in BL cells, cytoplasmic lipid droplets are found in approximately 95% of CLL cells in the bone marrow[201]. While the gene expression profile of CLL cells is similar to that of quiescent memory B cells, approximately 1% of CLL cells exhibit daily proliferation, leading to the pathological accumulation of malignant cells within the bone marrow. During this process, cancer-driving mutations, including *TP53* and *MYC* in CLL cells, rewire lipid metabolism, leading to the storage of lipids in cytoplasmic droplets for fatty acid metabolism. Concomitantly, constitutively activated STAT3 binds to the promoter of lipoprotein lipase (*LPL*), inducing aberrant upregulation of LPL, which catalyzes the hydrolysis of triglycerides into fatty acids. This suggests that lipid metabolism plays a crucial role in producing energy to ensure the survival and proliferation of CLL cells in the nutrient-limited environment of the bone marrow [202]. Therefore, targeting lipid metabolism is a promising strategy for treating CLL.

In addition to the overexpression of LPL in CLL cells, a high level of FASN, through enhanced stabilization *via* Wnt/β-catenin signaling, leads to *de novo* fatty acid synthesis in MCL cells. Therefore, orlistat, an FDA-approved FASN inhibitor primarily used for obesity, induces cell death and downregulation of cyclin D1 in MCL cells [203]. FASN has also been described as promoting the activation of SRC family tyrosine kinases and TLR/MYD88 inflammatory signaling by regulating its post-translational modifications, such as palmitoylation [204-206].

DLBCLs, the most common and genetically heterogeneous type of non-Hodgkin's lymphoma, are classified into two major subgroups that arise from different cells of origin with distinct transcriptional profiles, including germinal center B cell (GCB)-like and activated B cell (ABC)-like DLBCL [207]. The innovation of whole genome sequencing techniques has further identified four prominent subtypes that share a group of genetic aberrations, including BN2 (*BCL6* fusions and *NOTCH2* mutations) and EZB (*EZH2* mutations and *BCL2* translocations) that respond better to chemotherapy, while MCD (co-occurrence of MYD88$^{L265P}$ and *CD79B* mutations) and N1 (*NOTCH1* mutations) signify a worse prognosis [208]. In addition to the classification of DLBCLs based on either gene expression or genetic alteration, altered mitochondrial oxidative metabolism distinguishes two subsets, including BCR-DLBCL, which relies on the BCR signaling pathway, and BCR-resistant-DLBCL, which is insensitive to inhibitors of BCR signaling such as R406 and an ATP-competitive inhibitor of SYK [209]. BCR-resistant-DLBCL, also called OxPhos-DLBCLs, displays distinct lipid metabolism with an altered molecular signature marked by

concurrent activation of FAO and fatty acid synthesis, along with increased peroxisome proliferator-activated receptor gamma (PPARγ) activity [33]. Altered lipid metabolism leading to enhanced incorporation of fatty acid-derived carbons into the TCA cycle may serve as an alternative survival pathway in the presence of R406. Therefore, distinct lipid metabolism provides critical insight into the molecular heterogeneity of DLBCLs and a rationale to target the DLBCL subtype that is resistant to BCR signal blockade.

In addition to malignant B cells, cancer cells undergo lipid metabolic reprogramming to secure the material basis for their survival. Central to this reprogramming is fatty acid metabolism, which includes the uptake, synthesis, transport, and metabolites of fatty acids. Oncogenes or tumor suppressors often target these pathways, leading to altered expression of genes involved in these processes. This includes genes like acetyl-CoA carboxylases (ACC)1/2, ATP-citrate lyase (ACLY), CPT-1, CD36, elongation of very long chain fatty acids (ELOVL)-2/5/6/7, fatty acid binding protein (FABP)-1/3/4/5/7, fatty acid desaturase (FADS)-1/2, FASN, and SCD-1/5 [210]. Such alterations have been observed in hematologic malignancies and a wide range of solid tumors, including non-small cell lung cancer, lung adenocarcinoma, hepatocellular carcinoma, renal cell carcinoma, as well as breast, cervical, ovarian, colon, pancreatic, prostate, gastric, and esophageal squamous cancers to supply essential structural components and substrates for energy production [211,212].

## 5. Lipid metabolism in immunotherapy

Anti-cancer immunotherapy, including chimeric antigen receptor T-cell (CAR-T) therapy, marks a major breakthrough in treating B cell malignancies. However, despite promising initial response rates, resistance and relapse persist as significant challenges. Cancer cells, including malignant B cells, utilize various strategies to evade anti-cancer immunity. These strategies encompass nutrient competition, the production of bioactive metabolites, and the induction of tolerogenic immune cells within the immunosuppressive tumor microenvironment (TME), all of which directly undermine the effectiveness of anti-cancer immunotherapy.

In the development of immune tolerance, the roles of glucose and amino acid metabolism are well established. Increasing evidence indicates that tumor and immune cells compete for essential nutrients, such as glucose and amino acids, which are critical for immune cell function. In the TME, cancer cells consume glucose with a greater capacity to gain an advantage for faster energy generation, even though glycolysis is less efficient. This metabolic pathway additionally provides intermediates such as nucleotides, amino acids, and carbon sources for fatty acid and lipid synthesis, which are vital for cancer cell fitness. Consequently, glycolysis is predominantly observed in dividing malignant cells, contributing to a nutrient-poor environment [213]. This limits glucose supply to tumor-infiltrated M1 macrophages, NK cells, $CD4^+$ and $CD8^+$ effector T cells, causing impaired process of glycolysis with attenuated mTOR signaling that is necessary for their robust proliferation, cytokine release, and cytolytic function [214]. As a by-product of robust glycolysis, lactic acid impairs the cytotoxic activities of T- and NK-cells and drives PD-L1 expression in macrophages [215]. Additionally, lactic acid promotes PD-1 expression in Treg cells that can withstand high-lactate conditions in the TME, leading to immune tolerance

[216,217]. In addition to glycolysis, B lymphoma cells highly expressing MYC upregulate levels of glutamine transporters such as solute carrier family 1 member 5 (SLC1A5) and solute carrier family 7 member 5 (SLC7A5), resulting in increased consumption of glutamine and upregulation of glutamine catabolism to meet cellular demands for rapid proliferation [218]. Malignant B cells highly express indoleamine-2,3-dioxygenase (IDO), a rate-limiting enzyme that catalyzes the breakdown of the essential amino acid L-tryptophan into L-kynurenine, exerts immunosuppressive functions *via* inducing PD-1-mediated T-cell exhaustion [219], FOXP3-dependent development of Treg [220], Treg cell proliferation [221], inhibition of NK cell proliferation [222], and inhibition of NKp46- and NKG2D-activating receptors for cytotoxic NK cell function [223]. Consequently, high levels of either IDO [224] or L-kynurenine predicts poor clinical outcomes in patients with DLBCL [225].

Although the role of lipid metabolism in immune tolerance is relatively less understood compared to glucose or amino acid metabolism, emerging evidence indicates that lipid metabolism plays a pivotal role in the cytotoxic efficacy of immunotherapy and immune tolerance and in TME. Metabolic alteration in the TME is associated with lipid accumulation, leading to dysfunction of anti-cancer immune response. CD36 is highly expressed in $CD8^+$ cytotoxic T cells and promotes formation of terminally exhausted phenotype in TME. CD36 mediates uptake of oxidized low-density lipoproteins (OxLDL), induces lipid peroxidation and downstream activation of p38, leading to dysfunctions and ferroptosis of $CD8^+$ cytotoxic T cells [226,227]. On the other hand, lipid metabolism supports Treg survival and suppressive function to subdue anti-cancer immune response in TME. In addition to $CD8^+$ T cells, CD36 is also upregulated in Tregs and induces uptake of oxLDL. However, Treg cells protect themselves from lipid peroxidation-mediated mitochondrial dysfunction through the high expression of glutathione peroxidase GPX4. Furthermore, Treg cells upregulate SREBP signaling, and maintain the functional fitness of Treg by coordinating FASN-mediated *de novo* fatty acid synthesis and PD-1 expression in the TME [228]. Therefore, it suggests that treatment strategy targeting lipid reprogramming in TME could offer a new approach to cancer immunotherapy. Interestingly, Chimeric antigen receptor (CAR) containing the 4-1BB signaling domain metabolically reprogram CAR-T cells to obtain cellular energy by leveraging increased level of fatty acid oxidation. This metabolic reprogramming enhances the proliferation and persistence of 4-1BB CAR-T cells as a phenotype of central memory T cells compared to CAR-T cells with CD28 signaling domains [229]. Although the detailed mechanism needs further elucidation, these findings suggest that alleviating the metabolic burden of lipids in tumor-infiltrated CAR-T cells, combined with the selection of an optimal co-stimulatory domain and metabolic treatment strategies, can improve the current limitations of cancer immunotherapy.

Tumor-associated macrophages (TAMs), which are characteristically similar to the pro-tumorigenic M2 macrophage, promote angiogenesis, facilitate cancer cell invasion, and inhibit anti-cancer immune activities of T cells [230]. In contrast to M1 macrophages, which compete with cancer cells for glucose to sustain glycolysis, TAMs adapt to glucose deprivation by increasing FAO in response to fatty acids secreted by cancer cells within the TME [231,232]. TAMs express elevated levels of CD36, which enables high levels of FAO, leading to the production of ROS and the activation of the JAK1-STAT6 signaling pathway required for polarization toward the pro-tumor function of TAMs [233].

Additionally, elevated cholesterol levels in the TME and high levels of cholesterol in tumor-infiltrating $CD8^+$ T cells are positively associated with the upregulation of PD-1, 2B4, TIM-3, and LAG-3 expression, leading to $CD8^+$ T-cell exhaustion in the TME.[234]. While lipid accumulation in the TME impairs the cytotoxic function of tumor-infiltrated lymphocytes, expression of the PPAR in TAMs and $CD8^+$ T cells mitigates the burden of fatty acid catabolism, partially restoring their cytotoxic effects under harsh TME conditions [235,236]. Therefore, several lines of PPAR agonists show promising anti-tumor effects in combination with PD-1 blockade or CAR-T therapy in colon cancer, Lewis lung carcinoma, breast cancer, head and neck squamous cell carcinoma, pancreatic cancer, and melanoma [237-242]. Given its role in modulating anti-tumor immune responses and overcoming resistance to immunotherapy, the therapeutic potential of PPAR agonists warrants investigation in B cell malignancies. Additionally, a recent study identified that lipid metabolism-associated genes predict poor clinical outcomes with immunosuppressive TME by analyzing the gene expression profiles combined with prognostic risk-scoring model for DLBCL. In particular, mitochondrial trans-2-enoyl-CoA reductase (MECR) was negatively correlated with activated $CD8^+$ T-cells and NKT cell-mediated cytotoxicity. MECR is an oxidoreductase that catalyzes the last step of mitochondrial fatty acid synthesis. Interestingly, the oxidoreductase function of MECR is crucial for the proliferation and survival of cancer cells [243], suggesting that novel therapeutic approaches disrupting this pathway, in combination with immunotherapy, could be a promising target.

## 6. Conclusions and perspectives

Lipid metabolism is defined as a complex process involving multiple steps, including the dietary intake of lipids, transport, cellular lipid uptake, synthesis of lipid species, and degradation [244]. Cancer cells reprogram lipid metabolism to meet abnormal demands for their accelerated proliferation rate and survival [245]. Therefore, dysregulated lipid metabolism has been implicated in cancer development and resistance to cancer therapies. Since the 1960s, seminal studies have illuminated the dynamic nature of lipid metabolism in cancer cells [246,247], revealing active lipid synthesis and uptake as fundamental to their accelerated proliferation. Subsequent research has delineated the complex landscape of lipid metabolism in cancer, underscoring its critical role in tumor growth [248,249], oncogenic signaling [250,251], and modulation of the tumor microenvironment (TME) [252]. Notably, the metabolic intricacies extend beyond mere lipid utilization to encompass the synthesis, accumulation, and regulation of specific lipid species, including short-chain fatty acids (SCFAs) [253]. These lipids intersect with pathways central to inflammation [254], glucose metabolism [255], and lipid homeostasis [256], thereby contributing to the multifaceted nature of cancer biology.

As these systemic and integrative alterations in lipid metabolism reflect their indispensable role in onset and progression of cancer, targeting lipid metabolic pathways has emerged as a viable strategy for therapeutic intervention. This approach encompasses a diverse range of compounds, each targeting specific elements within lipid metabolism to inhibit cancer growth and metastasis. Even though most of them are still under pre-clinical developmental stage, some of them are showing promising data. For example, CD36 monoclonal antibodies have shown promise in preclinical models by significantly reducing

metastasis in various cancer types without adverse effects, highlighting their potential in targeting lipid uptake mechanisms. In addition, targeting de novo fatty acid biosynthesis with inhibitors such as TOFA (5-tetradecyloxy-2-furoic acid), and acetyl-CoA carboxylase (ACC) with Soraphen A have demonstrated efficacy in preclinical studies across lung, colon, and prostate cancers by disrupting fatty acid synthesis and inducing oxidative stress. Betulin and Fatostatin which target the SREBP pathway of lipid synthesis have shown benefit in hepatocellular carcinoma (HCC) and prostate cancer models by enhancing the sensitivity of cancer cells to conventional therapies. Stearoyl-CoA desaturase (SCD) inhibitors, including A939572 and the novel compounds CVT-11127 or CVT-12012, have been investigated for their effects on membrane lipid saturation and signaling, offering new avenues for combating chemoresistance in cancer cells. The therapeutic strategy extends to inhibiting FAO where compounds like etomoxir have shown promise in preclinical studies for slowing tumor growth, particularly in gliomas. In addition, omeprazole, commonly known for its role as a proton pump inhibitor, exhibits the capacity to inhibit the thioesterase activity of FASN, demonstrating the potential for drug repurposing in cancer therapy (NCT02595372). Similarly, everolimus (NCT03580239) and other inhibitors of the PI3K/AKT/mTOR pathway, such as PF-05212384 (NCT01347866) and PF-04691502 (NCT01658176), disrupt critical pathways involved in lipid synthesis and signaling, thereby impeding cancer cell proliferation. AKT inhibitors such as vistusertib/AZD2014 (NCT02208375), MK-2206 (NCT01251861) and capivasertib/AZD5363 (NCT02525068) further illustrate the effectiveness of inhibiting lipid signaling pathways for cancer therapy. On the other hand, cholesterol biosynthesis and transport are also critical targets. Statins, such as lovastatin (NCT03358017), atorvastatin (NCT03324425), rosuvastatin (NCT02569645), and simvastatin (NCT03275376), which target HMG-CoA reductase to reduce cholesterol synthesis, and LXR agonists such as GW3965 and LXR623 that enhance cholesterol efflux, have shown benefit in preclinical cancer models. These treatments not only affect cholesterol homeostasis but also impact the composition and functionality of cancer cell membranes, suggesting a broad application of lipid metabolism modulation in oncology. ATR-101 (NCT01898715), which targets acyl-CoA cholesterol acyltransferase (ACAT) to disrupt cholesterol esterification, highlights the strategy of obstructing lipid storage mechanisms to induce stress and apoptosis in cancer cells. In the context of angiogenesis inhibition, compounds such as ABT-510 (NCT00602199) and natural agents such as Sibilin (milk thistle) expand the scope of lipid-targeted therapy to include modulation of the tumor microenvironment and suppression of tumor-induced angiogenesis. GPR119 agonists (GSK1292263; MBX-2982) and metformin intersect lipid metabolism with glucose regulation, offering a combined approach against the metabolic vulnerabilities of cancer. Inhibitors of prenylation (lonafarnib and tipifarnib) and phospholipase D (FIPI and EI-05) interfere with critical post-translational modifications and signaling processes, further underscoring the importance of targeting lipid-related pathways in cancer cells. Other agents, such as 2-bromopalmitate, Fluphenazine, and Nelfinavir, along with thiazolidinedione and GW9662, diversify the strategies against cancer by targeting fatty acid synthesis, signaling, and storage. This comprehensive targeting of lipid metabolism in cancer, from lipid uptake to biosynthesis and signaling pathways, represents a promising therapeutic avenue. The use of these compounds, tested across various cancer types including hepatocellular carcinoma, prostate, lung, colon, and melanoma, underscores the

broad applicability of lipid metabolism as a therapeutic target. For more detailed information on the stages of development and studies covering these drugs, other publications provide excellent explanations and insights into the potential of targeting lipid metabolism in cancer therapy.

In addition to non-hematologic cancers, lipid metabolism also plays a multilayered role in triggering the pathogenesis and progression of B cell malignancies. Both extrinsic factors from the tumor microenvironment and intrinsic oncogenic events rewire lipid homeostasis to meet the demands of accelerated proliferation and survival of malignant B cells. In the tumor microenvironment, adipocytes secrete free fatty acids, metabolites, and bioactive lipids that fuel B cell lymphomas, augment pro-survival signaling, and bestow resistance to chemotherapy. This adipocyte-tumor crosstalk enhances the aggressiveness of B cell malignancies, underscoring the need to target the adipose niche. On the other hand, intrinsic oncogenic events including MYC translocations, BCR pathway mutations, and anomalous NF-κB activation reprogram lipid metabolism through transcriptional, post-transcriptional, and post-translational mechanisms. This leads to widespread alterations encompassing almost all major lipid species.

In normal B cells, the binding of foreign antigen to the BCR prompts the translocation of BCR complex into the lipid rafts enriched with sphingolipids and cholesterol. This translocation initiates BCR signaling cascades by activating key kinases, including SYK, SRC, and PI3K. Within the lipid raft, PI3K facilitates the generation of PIP3, which in turn recruits BTK, AKT, and PLCγ to the cell membrane surface. Membrane-translocated PLCγ catalyzes the hydrolysis of PIP2 to generate DAG and IP3 as secondary messengers that subsequently activate PKC and trigger the NF-κB signaling pathway, inducing B cell activation, proliferation, and differentiation. Concurrently, the PI3K/AKT signaling axis, in conjunction with NF-κB signaling, triggers the activation of MYC and mTOR pathways, leading to alterations in lipid metabolism, including changes in the levels of fatty acid, ceramide, PG, CL, sphingolipids, phospholipids, and cholesterol, further supports B cell activation and contributes to the immune response (Fig. 5). In malignant B cells, constitutive BCR signaling, achieved by mutations in genes encoding BCR-ABL1 in early B cell leukemia or PI3K, MYC, PTEN, CD79B, CARD11, MYD88, and RAS in mature B cell lymphoma, reprogram lipid metabolism, contributing to uncontrolled cell proliferation, survival, and drug resistance. Phospholipids play central roles in propagating oncogenic signaling cascades that mimic constitutive B cell receptor activation in multiple B cell cancers. The dysregulated PI3K/PTEN/AKT/mTOR axis exemplifies reliance on phosphoinositide conversion, membrane recruitment, and downstream signaling. Cholesterol and sphingolipids additionally support the integrity of lipid rafts for assembling oncogenic BCR signalosomes. Glycosphingolipid GM1 facilitates amplification of oncogenic BCR signaling while phosphatidylserine metabolism impacts the immunogenicity of apoptotic lymphoma cells. Beyond signaling, cholesterol sustains active proliferation through metabolites enhancing sterol/lipid biosynthesis and protein prenylation. Sphingolipids like S1P and ceramide reciprocally regulate survival versus death pathways. Fatty acids offer alternative fuels to augment bioenergetic and biosynthetic capacities. Hence multifaceted contributions of diverse lipids converge to promote aggressive B cell

malignancy phenotypes, which provides rationale to target the rewired lipid metabolism in treating B cell malignancies.

For instance, cholesterol biosynthesis inhibition by statins can reduce proliferation and induce apoptosis in CLL, ALL, and multiple myeloma cells. Combining statins with BCL2 inhibitors such as venetoclax or BTK inhibitors such as ibrutinib synergistically enhances cytotoxicity against CLL. Targeting the cholesterol uptake receptor SCARB1 with HDL nanoparticles also shows promise in depleting cholesterol. Sphingolipid pathway inhibitors such as SK1-I suppress anti-apoptotic S1P production and chemosensitize BCR-ABL1$^{+}$ ALL cells. Dual inhibition of SPHK1/2 reduces MYC expression and histone acetylation, overcoming ibrutinib resistance in ALL. Ceramide accumulation can be induced by inhibitors of glucosylceramide synthase (UGCG) and sphingomyelinase (SMS), reconstituting chemosensitivity in CLL and DLBCL. Orlistat, an FDA-approved FASN inhibitor, can achieve fatty acid synthesis inhibition. This drug can reduce cyclin D1 levels and induce apoptosis in MCL cells. CPT1 inhibitors such as ST1326 block mitochondrial fatty acid oxidation, compromising energetic metabolism in MYC-driven Burkitt lymphoma. The immunomodulator FTY720 antagonizes S1P signaling, mobilizing malignant cells from protective microenvironments. Overall, mounting evidence demonstrates the potential of therapeutic strategies targeting lipid metabolism leveraged by the pathogenic signaling driven by genetic aberrations to disrupt cancer development and resistance to anticancer drugs. Therefore, the combined treatment with small molecules targeting lipid metabolism with FDA-approved drugs for B cell malignancies such as imatinib, ibrutinib, dacinostat, CAL-101, T-5224, and chemotherapeutic drugs can produce synergistic effects, enhancing therapeutic efficacy and providing a broader array of strategies for personalized treatment (Fig 6).

B cells are pivotal in adaptive immunity through their roles in antigen presentation and antibody secretion. The development and differentiation of B cells rely on membrane, in particular lipid rafts where antigen-binding receptors, such as BCR and TRL, response to foreign antigen in support of a variety of lipid species including cholesterol, glycerophospholipids, and sphingolipids. Consequently, signals emanating from membrane proteins such as BCR, TLRs, and their co-receptors, such as cluster of differentiation (CD) molecules, are crucial for numerous B cell functions including antigen recognition, activation, exhaustion, antigen presentation, communication with other cells, migration, and sophisticated differentiation in response to variable pathogenic challenges within the context of adaptive immune response. The lipid composition and metabolism of the B cell membrane are crucial in these signaling pathways, which subsequently modulate intracellular lipid metabolism to either feed-back or -forward to the function of membrane proteins. In germinal center, somatic hypermutation and class switch recombination introduce intrinsic risk of collateral DNA damage, potentially causing pathological genetic alterations that lead to dysregulated BCR or its oncogenic mimicry, which is a characteristic feature of nearly all B cell malignancies. These oncogenic signaling pathways encompassing constitutively activated PI3K, MYC, and NF-κB signaling further crosstalk to signals from T-cells via various immune checkpoint molecules and CD molecules that are highly and specifically enriched in immune cells. These distinct features of B cells within the adaptive

immune system render them susceptible to changes in lipid metabolism, which can facilitate malignant transformation in the presence of oncogenic mutants.

Overall, malignant B cells display enhanced uptake, synthesis, and accumulation of bioactive lipids that activate oncogenic signaling, meet energetic demands, and impart resistance to chemotherapy. Targeting these bioactive lipids via inhibition of lipid uptake transporters, synthesis enzymes, bioactive lipid signaling, and cholesterol efflux represents potential therapeutic strategies. Further research should delineate the contextual contribution of specific lipids in each subtype of B cell malignancy. Multifaceted approaches that match lipid dependencies to genetic drivers like MYC or NF-κB to guide tailored therapeutic strategies have the potential for improved clinical outcomes. Comprehensively targeting the extrinsic and intrinsic lipid alterations in B cell malignancies is a promising therapeutic opportunity that merits further investigation. Integrative multi-omics approaches can provide deeper insight into lipid rewiring associated with aggressive disease behavior, disease recurrence, and chemotherapy resistance. In summary, leveraging lipid dysregulation is key to developing potent, combinatorial therapies that interrupt the supply of critical lipids supporting the progression of B cell lymphomas, which harbor outstanding promise for advancing clinical management against heterogeneous B cell lymphoma subtypes.

## Acknowledgment

This work was supported by the National Research Foundation of Korea (NRF) grant (RS-2024-00339966 to J.L.) and by the Ministry of Health and Welfare (RS-2022-00060247 to J.L) of the government of the Republic of Korea. A.M. is funded by the R01HL171054-01 from NHLBI and R01DK134329-01A1 from NIDDK.

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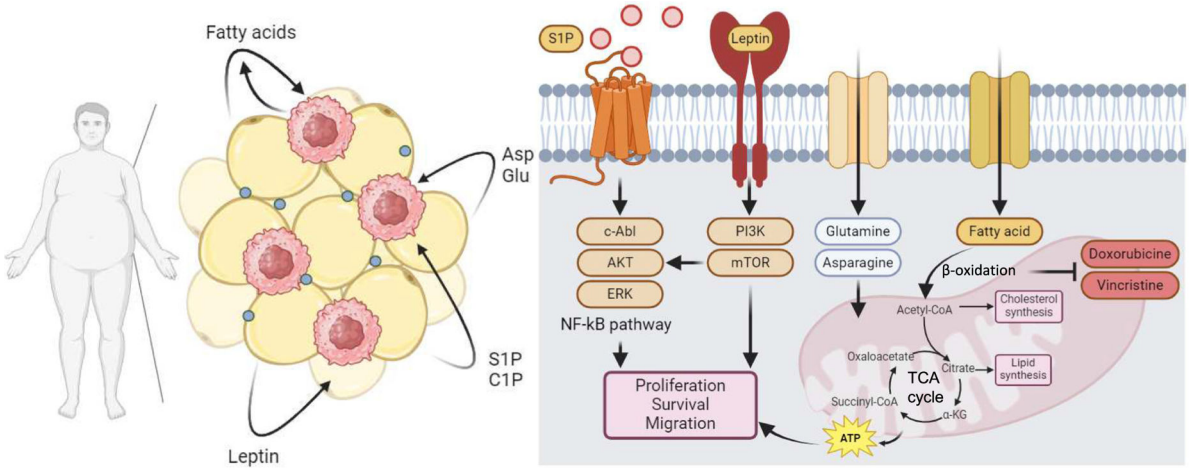


**Fig. 1.**

The secretome released from adipocytes plays a crucial role in enhancing the growth and resistance to drugs in malignant B cells. Components of the adipocyte secretome, including sphingosine-1-phosphate (S1P), ceramide-1-phosphate (C1P), leptin, amino acids, and fatty acids, directly stimulate the proliferation, survival, migration, and resistance to chemotherapy of malignant B cells. The binding of extracellular S1P to S1PR triggers the activation of c-Abl, ERK, AKT, and NF-ºB, thereby contributing to the progression of B cell malignancy. This effect is further potentiated by leptin receptor-mediated PI3K signaling upon binding with leptin. Glutamate and asparagine provide compensatory sources for cellular metabolism in B-ALL cells with treatment by chemotherapeutic reagents such as ASNase targeting amino acid metabolism. Fatty acids supplied by adipocytes are utilized as an alternative energy source through β-oxidation, thereby promoting resistance to chemotherapy drugs such as daunorubicin and vincristine.

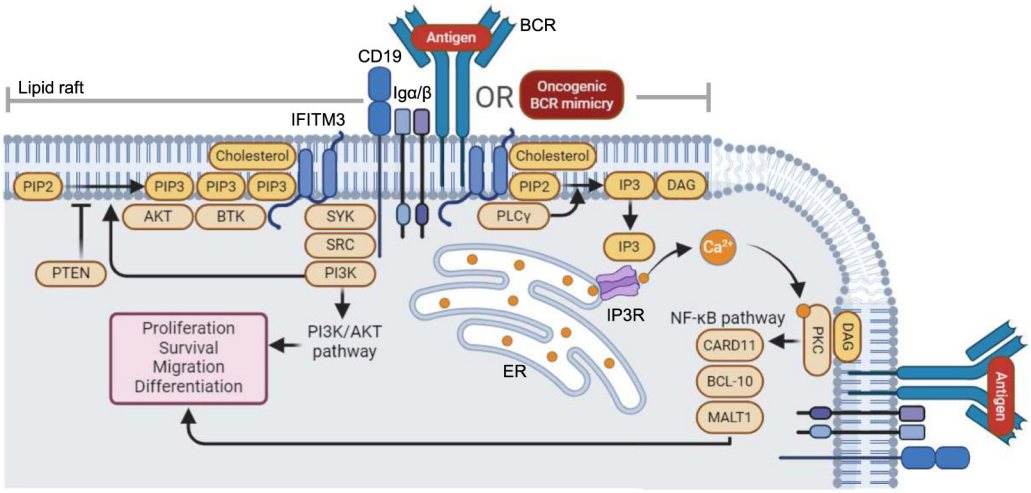


**Fig. 2.**

Phospholipids and their binding proteins mediate normal or malignant B cell activation. The B cell receptor (BCR) stimulated with antigen activates BCR signaling pathway by recruiting SYK and PI3K to CD19, a co-receptor of BCR. The lipid raft-localized PI3K transiently synthesizes phosphatidylinositol-3,4,5-trisphosphate (PIP3) at the expense of phosphatidylinositol-4,5-bisphosphate (PIP2) that is stabilized and concentrated by IFITM3 near the BCR signalosome. Consequently, IFITM3 promotes the PIP3-mediated recruitment of downstream effector molecules such as BTK and AKT, thereby enhancing PI3K/AKT signaling. On the other hand, lipid raft-anchored PLCγ hydrolyzes PIP2 into DAG and inositol-1,4,5-trisphosphate (IP3). DAG facilitates the translocation of PKC from the cytoplasm to the lipid raft. Concurrently, the IP3-mediated influx of $Ca^{2+}$ enables $Ca^{2+}$ binding to the regulatory domain of PKC, subsequently releasing the catalytic activity of PKC. PKC-mediated activation of NF-ºB signaling is crucial for the proliferation and survival of normal or malignant B cells. Oncogenic lesions in B cell malignancy frequently mimic the active BCR signaling pathway.

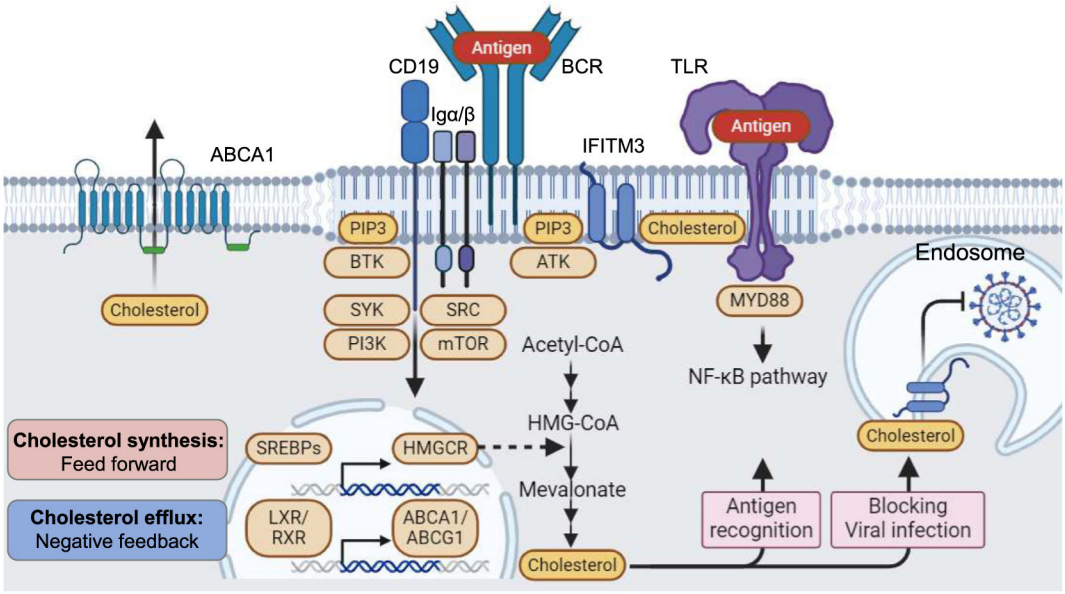


**Fig. 3.**

Cholesterol metabolism is necessary to defend against foreign antigens. Upon viral infection, including influenza or SARS-CoV, IFITM3 expression is upregulated through IFN receptor-mediated activation of the JAK/STAT pathway. Subsequently, the accumulated IFITM3 proteins within endosomal membranes induce negative membrane curvature by inserting the amphipathic helix structure into the endosomal membrane. The amphipathic helix of IFITM3 directly interacts with cholesterol, increasing membrane rigidity. Consequently, the accumulation of cholesterol at the endosomal membrane restricts the release of viral particles into the cytosol, thus blocking viral infection. In B cells, activated BCR signaling induces the localization of IFITM3 at the lipid raft in the plasma membrane, where IFITM3 amplifies BCR-PI3K-AKT signaling upon encountering antigens. In response to the recognition of conserved patterns displayed in bacteria or viruses, activation of TLRs harboring cholesterol-binding motifs depends on the accumulation of cholesterol at the lipid raft. mTOR signaling downstream of active BCR promotes the nuclear accumulation of SREBP2. SREBP2 upregulates the levels of molecules involved in cholesterol synthesis, such as HMGCR, which, in turn, feed cholesterol forward to contributes to B cell activation against foreign antigens. Conversely, high cholesterol conditions block SREBP2 activation, and instead induces oxysterol-mediated activation of LXRs promoting the elimination of excess cholesterol *via* upregulation of cholesterol transporters such as ABCA1.

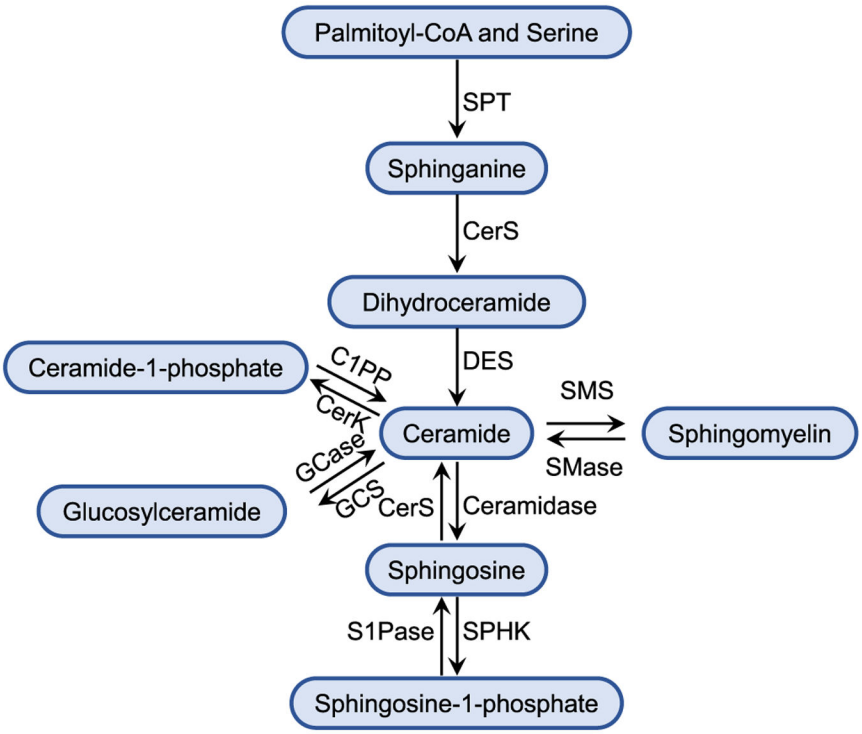


**Fig. 4.**

Schematic representation of sphingolipid metabolism. The pleotropic properties of sphingolipids play a pivotal role in hematopoiesis, migration of lymphocytes, immune response, and the signaling pathway for progression of B cell malignancies. SPT, serine palmitoyl transferase; CerS, dihydroceramide synthase; DES, dihydroceramide desaturase; SPHK, Sphingosine kinase; CerK, ceramide kinase; C1PP, ceramide-1-phosphate phosphatase; GCase, gluco-cylceramidase; GCS, glucosylceramide synthase; SMS, sphingomyelinase synthase; SMase, sphingomyelinase.

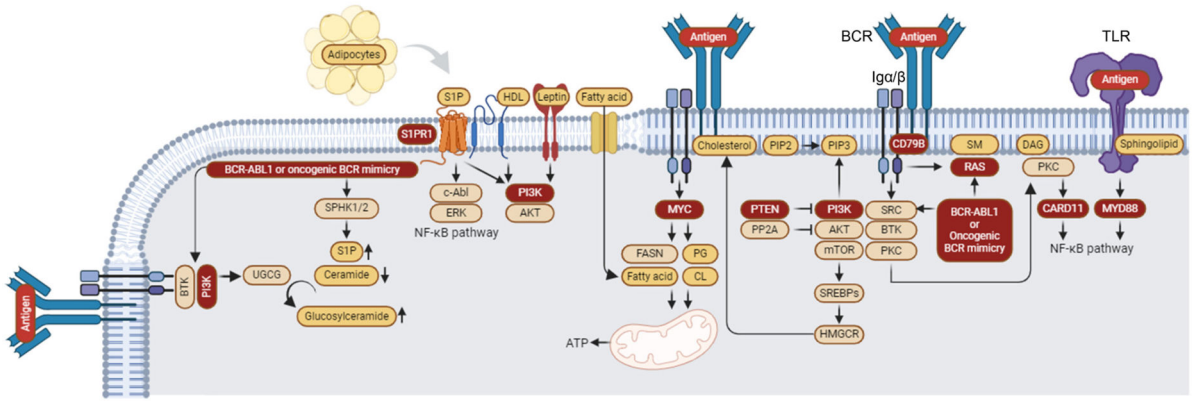


**Fig. 5.**

The schematic diagram summarizes the regulation of lipid metabolism in normal or malignant B cells. In response to foreign antigens, BCR signaling triggers a pro-inflammatory immune response *via* activation of the NF-κB signaling pathway and promotes intensive proliferation supported by various lipid species such as fatty acids, PG, CL, sphingolipids, phospholipids, and cholesterol. In B cell malignancy, constitutive BCR signaling, achieved by mutations in genes such as BCR-ABL1 in early B cell leukemia or PI3K, MYC, PTEN, CD79B, CARD11, MYD88, and RAS in mature B cell lymphoma, contributes to uncontrolled cell proliferation, survival, and drug resistance.

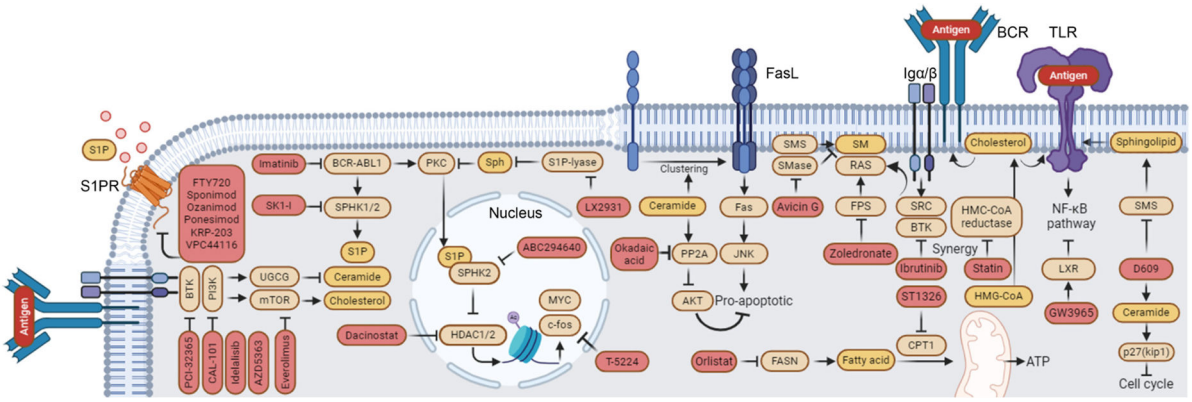


**Fig. 6.**

The schematic diagram summarizes the potential therapeutic targets of different lipid species and related pathways to treat inflammatory disease or B cell malignancy. Multiple studies have demonstrated promising immunomodulatory or therapeutic effects of small molecules targeting different layers of lipid metabolism in B cells. Combined treatment with FDA-approved small molecules and drugs for B cell malignancies such as imatinib, ibrutinib, dacinostat, CAL-101, and T-5224 can produce synergistic effects, enhancing therapeutic efficacy and offering a broader array of strategies for personalized treatment. All the figures were generated using biorender.com.