Review

Signaling Pathways Shaping the Field of Lipidomics

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Review

Signaling Pathways Shaping the Field of Lipidomics

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Abstract

Lipidomics, the comprehensive study of cellular lipids and their roles in biological systems, has become a transformative tool across diverse fields of biology and medicine. Beyond its applications in studying metabolic disorders and cancer, lipidomics is gaining importance in areas such as developmental biology, ecology, and evolution, revealing critical insights into cellular processes and organismal adaptations. However, interpreting lipidomics data at the molecular level, particularly through the lens of signaling pathways, remains a challenge. Despite the central role of signaling pathways in regulating lipid metabolism and signaling, no comprehensive review has systematically compiled these pathways or explored their significance in lipidomics research. This review addresses this gap by providing a structured, catalogue-like overview of signaling pathways that regulate or are influenced by lipid signals. It includes pathways fundamental to lipid metabolism and related lipid-based biological processes, as well as emerging lipid-dependent mechanisms underlying energy balance, environmental adaptation, and developmental processes. Each pathway is briefly discussed in the context of its molecular roles in lipidomics and its potential impact on diverse research fields. By compiling this knowledge, the review serves as a guide for interpreting lipidomics data, identifying key pathways for targeted research, and bridging connections with other scientific disciplines. This structured approach promotes the integration of lipidomics into broader biological contexts, advancing our understanding of lipid-mediated processes and fostering innovation across multiple fields of study.

Keywords: lipidomics; signaling pathways; lipid metabolism; lipid mediated signals

1. Introduction

Lipidomics, the comprehensive study of cellular lipids and their roles in biological systems, has become a cornerstone of research in various fields of biology and biomedicine [1]. Beyond their structural functions in membranes, lipids act as dynamic regulators of energy homeostasis, signaling pathways, and protein function [2–4]. Lipidomics has been instrumental in revealing the complex roles of lipids in metabolic diseases [5], neurodegeneration [6], inflammation [7], cancer [8] and personalized medicine [9], while also shedding light on their relevance in ecology [10], toxicology [11], evolution [12] and developmental biology [13]. As lipidomics continues to integrate with other -omics approaches [14], it offers unparalleled insights into the molecular mechanisms underlying health and disease [15], positioning itself as a transformative tool for both fundamental and applied research.

Interpreting lipidomic data in the context of signaling pathways, however, remains a complex challenge. Lipid signaling pathways are central to lipid metabolism, cellular communication, and systemic regulation, making them indispensable for understanding the functional implications of lipidomic findings [16]. Despite significant progress, a comprehensive review that exclusively compiles all the known signaling pathways influencing lipidomics is lacking. Such a review would serve as a critical resource, offering researchers a systematic overview of these pathways, facilitating

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data interpretation, and highlighting pathways that warrant further investigation [14,17]. The purpose of this article is to fill that gap by providing a categorized overview of lipid signaling pathways, emphasizing their relevance to lipidomics, and identifying areas for future research [14]. Rather than going through the molecular details of each pathway, this review aims to provide a navigational framework to assist researchers in utilizing lipidomics for advances in biology and biomedicine.

The signaling pathways covered in this review are classified into three groups based on their level of study, functional significance, and emerging relevance. The central pathways in lipid signaling include well-established pathways like sphingolipid and phosphoinositide signaling, which regulate cellular membrane dynamics and intracellular communication, and metabolic regulators like the SREBP and PPAR pathways, which govern lipid synthesis and storage. These pathways form the foundation of lipid biology and are often implicated in metabolic diseases. The context-dependent lipid pathways focus on signaling mechanisms that are activated under specific physiological or pathological conditions, such as oxidative stress, energy imbalance, or inflammation. Lastly, the emerging pathways in lipidomics highlight cutting-edge areas such as ferroptosis-regulating lipids, the gut microbiota-lipid axis, and lipid-mediated epigenetic modifications, underscoring the expanding role of lipids in intercellular communication, brain function, and novel therapeutic development. These emerging pathways also emphasize the potential of lipidomics in identifying biomarkers for personalized medicine and exploring lipid adaptations to environmental influences.

This review adopts a structured approach to each signaling pathway, starting with a brief overview of its primary role in lipidomics, focusing on its contributions to lipid metabolism, signaling, or related processes. Key findings demonstrating the pathway's relevance are then highlighted, followed by emerging areas where it shows growing potential as a focus for future lipidomics research. This framework aims to bridge knowledge gaps, guide targeted studies, and enhance the integration of signaling pathways into lipidomics research.

2. Central Pathways in Lipid Signaling

2.1. Glycerophospholipid (GP) signaling pathway

GPs such as phosphatidylcholine (PC) and phosphatidylethanolamine (PE), are fundamental to membrane structure and intracellular signaling [18]. This pathway is notable for its role in generating bioactive lipids that modulate rapid responses to extracellular stimuli, such as during platelet activation [19]. In lipidomics, this pathway is crucial for understanding lipid homeostasis and the role of membrane dynamics in health and disease [20]. Studies have linked PC metabolism to obesity [21] and PE to mitochondrial function [22]. This pathway is particularly significant in metabolic syndrome, liver diseases, and cell biology [20]. Apart from their basic well-characterized roles, recent findings reveal novel roles for GP across biological contexts. In neurodevelopment, they regulate synaptic formation and neuronal differentiation, influencing cognitive health and neurological disorders [23]. In eukaryotes, GPs serve as signaling molecules during abiotic stress enhancing adaptive responses such as hypoxia in yeast [24] and salinity changes in plant [25]. Moreover, pathogens manipulate host GP metabolism to promote infection and immune evasion, emphasizing their role in host-pathogen interactions [26]. These discoveries open new directions for lipidomics research in health, disease, and environmental resilience.

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Table 1. The extent of lipid-related studies in the central pathways in lipid signaling. From top to bottom, the pathways are sorted based on the most to least studied in the field of lipidomics, and from left to right, the fields of study are sorted based on the extent of lipidomics or lipid-related research. H = Highly studied, M = Moderately studied, P = Poorly studied.

Pathways	Lipidomics Studies	Lipid signaling / metabolism	Metabolic Disorders	Cancer biology	Immune System	Reproduction /Endocrinology	Neurobiology	Toxicology	Developmental Biology	Ecology /Evolution
Sphingolipid	H	H	H	H	H	H	M	M	M	P
Phosphoinositide	H	H	H	H	M	H	M	M	M	P
Eicosanoid	H	H	H	H	H	M	M	M	M	M
Glycerophospholipid	H	H	M	M	M	M	M	M	M	P
Endocannabinoid	H	M	M	M	H	M	H	M	M	P
LPA	H	H	H	H	M	H	M	M	M	P
SREBP	H	H	H	H	M	H	M	M	M	P
PPAR	H	H	H	H	M	H	H	M	M	P
LXR	H	H	H	M	M	H	M	P	M	P
GPCR	H	H	M	H	H	M	M	M	P	P
PLC	H	H	H	H	H	M	M	M	M	P
COX	H	H	H	H	M	M	M	H	M	P
Prostaglandin & leukotriene	H	H	M	H	H	M	M	M	M	P
Ceramide	H	M	H	H	M	M	H	M	P	P
Hedgehog	M	M	M	M	M	M	M	M	H	M
FXR	M	H	H	M	M	M	M	P	M	P
TLR	M	M	M	M	H	M	M	M	M	P

Table 2. The extent of lipid-related studies in the context-dependent lipid pathways. From top to bottom, the pathways are sorted based on the most to least studied in the field of lipidomics, and from left to right, the fields of study are sorted based on the extent of lipidomics or lipid-related research. H = Highly studied, M = Moderately studied, P = Poorly studied.

Pathways	Lipidomics Studies	Lipid signaling / metabolism	Metabolic Disorders	Cancer biology	Immune System	Reproduction /Endocrinology	Neurobiology	Toxicology	Developmental Biology	Ecology /Evolution
AMPK	H	H	H	M	M	H	M	M	P	P
mTOR	H	H	H	H	M	H	M	M	M	P
MAPK	H	H	H	H	M	M	M	M	M	P
Autophagy	H	H	M	M	M	M	H	M	M	P
ROS	H	H	M	M	H	M	H	H	M	M
Adiponectin	H	H	H	M	M	H	M	M	M	P
RXR	H	H	H	H	M	H	M	M	M	M
NF-κB	M	H	H	H	H	M	H	M	M	M
TNF-α	M	M	H	M	H	M	M	M	P	P
Wnt	M	M	M	H	M	M	M	P	H	M
Notch	M	M	M	H	M	M	P	P	H	M
NADPH	M	M	M	M	H	P	M	H	P	P
HIF	M	M	M	H	M	M	M	M	M	M
Lipoxin & resolvins	M	M	M	M	H	M	M	M	M	M
PAF	M	M	M	P	H	M	P	M	P	P
RAS	M	H	H	M	M	H	M	M	P	P
AhR	M	M	M	P	M	H	H	H	M	M

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Table 3. The extent of lipid-related studies in the emerging pathways/areas in lipidomics. From top to bottom, the pathways are sorted based on the most to least studied in the field of lipidomics, and from left to right, the fields of study are sorted based on the extent of lipidomics or lipid-related research. H = Highly studied, M = Moderately studied, P = Poorly studied.

Pathways	Lipidomics Studies	Lipid signaling / metabolism	Metabolic Disorders	Immune System	Cancer biology	Neurobiology	Reproduction /Endocrinology	Toxicology	Developmental Biology	Ecology /Evolution
Ferroptosis	H	H	H	M	H	H	M	M	P	P
Exosomal lipids	H	M	M	H	M	M	M	M	M	M
Gut microbiota	H	H	H	H	M	M	M	M	M	H
UPR	H	H	H	M	M	M	M	M	M	P
N-3	H	H	H	M	M	H	H	M	M	P
Oxysterols	M	M	M	M	H	M	M	M	M	P
Cardiolipin	M	H	H	M	M	M	M	M	M	P
Perilipin	M	M	M	M	M	M	M	M	P	P
Ether lipids	M	M	M	M	M	M	M	M	M	P
Posttranscriptional mechanisms	M	M	P	M	M	M	M	M	M	P
FABPs	M	M	M	M	M	M	M	M	M	P
Epigenetics	M	M	M	M	M	M	M	P	M	P
Hippo	M	M	M	P	H	M	P	H	P	P
Brassinosteroid	P	P	P	P	P	P	P	P	H	H
Cold shock lipids	P	P	P	P	P	P	P	P	P	H

2.2. Sphingolipid signaling pathway

The sphingolipid signaling pathway involves bioactive molecules like ceramide, sphingosine, and sphingosine-1-phosphate (S1P), which regulate key cellular processes including apoptosis, proliferation, and inflammation [27]. This pathway uniquely integrates spatial and temporal dynamics of sphingolipid metabolites to fine-tune cellular processes such as autophagy and endocytosis, making it central to membrane trafficking studies [2]. In lipidomics, this pathway is pivotal for understanding how sphingolipid metabolism influences cell signaling and membrane integrity. Major discoveries include the identification of S1P as a critical regulator of immune cell trafficking, and ceramide's role in inducing apoptosis, linking this pathway to cancer, neurodegeneration, immune regulation, and cardiovascular disorders [28–30]. Recent studies have uncovered surprising roles for the sphingolipid signaling pathway in diverse biological contexts, expanding its potential research applications. First, sphingolipids have been linked to evolutionary adaptation in extreme environments, with variations in sphingolipid profiles contributing to stress tolerance in organisms exposed to high salinity or extreme temperatures [31,32]. Second, sphingolipid signaling is implicated in symbiotic interactions in ecology, where sphingolipid molecules mediate communication between plants and their mycorrhizal fungi, enhancing nutrient exchange and resilience against pathogens [33]. Third, in developmental biology, S1P has emerged as a critical player in embryonic axis formation, influencing vascular development and tissue patterning during early embryogenesis [34]. These emerging roles highlight the need for targeted lipidomics research to explore these unexpected dimensions of sphingolipid biology.

2.3. Phosphoinositide signaling pathway

The phosphoinositide signaling pathway includes phosphatidylinositol and its phosphorylated derivatives, which serve as signaling molecules regulating cytoskeletal dynamics, vesicle trafficking, and cell growth [35]. The pathway is distinct in its ability to generate compartment-specific signaling pools of phosphoinositides, which regulate organelle identity and intracellular vesicle trafficking [36]. This pathway is essential in lipidomics for studying intracellular signaling and membrane lipid modifications. Key discoveries include the role of phosphatidylinositol-4,5-bisphosphate (PIP2) in

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membrane dynamics [37] and PIP3 in activating the AKT pathway, linking this pathway to cell survival and cancer [38]. It is highly relevant in cancer biology, diabetes research, and neurobiology. Recent studies have unveiled novel roles for the phosphoinositide signaling pathway in other biological fields. For instance, phosphoinositides have been implicated in plant stress responses, where they modulate processes regulating plant adaptation to environmental stress [39]. This pathway also influences microbial pathogenesis, as certain pathogens exploit host phosphoinositide metabolism to facilitate their entry and survival within host cells, highlighting its importance in host-pathogen interactions [40,41]. Moreover, phosphoinositide signaling contributes to stem cell pluripotency and differentiation, affecting lineage specification and maintenance of stem cell states [42]. These emerging roles present new avenues for lipidomics research to explore the diverse functions of phosphoinositide signaling across different biological systems.

2.4. Lysophosphatidic acid (LPA) signaling pathway

LPA, a bioactive phospholipid, signals through GPCRs to regulate cell proliferation, motility, and survival. LPA signaling is distinctive due to its ability to act as both a local and systemic signaling molecule, influencing diverse physiological processes from wound healing to reproduction [43]. Lipidomics has linked LPA signaling to cancer metastasis and fibrosis. Major discoveries include LPA's role in ovarian cancer progression and tissue repair [44,45]. This pathway is central to cancer biology, fibrosis, and regenerative medicine. Emerging roles of LPA signaling include modulation of immune responses via macrophage activation and cytokine production [46], contribution to neurodevelopment by regulating neural progenitor proliferation and differentiation [47], and regulation of angiogenesis and vascular maturation in cardiovascular development [48]. These discoveries expand lipidomics research into immunology, developmental biology, and vascular biology.

2.5. Ceramide-activated protein kinase pathway

The ceramide-activated protein kinase pathway is initiated by ceramides (Cer), which function as bioactive sphingolipids regulating cellular stress responses, apoptosis, and inflammation [49]. Ceramides act as second messengers in stress-related signaling cascades, bridging metabolic dysfunction and apoptotic pathways [50,51]. Lipidomics studies have elucidated Cer 's role in mitochondrial dysfunction, linking it to insulin resistance in metabolic disorders [52]. Notably, Cer mediates tumor necrosis factor-alpha (TNF-α)-induced apoptosis, underscoring its relevance to metabolic syndrome and cancer [53]. Emerging research has further implicated Cer in neurodegeneration, where its accumulation contributes to neuronal apoptosis and amyloid-beta production in Alzheimer's disease [54]. Moreover, Cer plays a role in aging by promoting cellular senescence and age-related tissue decline [55]. Moreover, Cer modulates immune responses by influencing T-cell activation and macrophage polarization, highlighting its role in immune regulation [56]. These insights underscore the pathway's critical roles in diabetes, cancer, stress-related diseases, and newly recognized fields such as neurodegeneration and aging.

2.6. Cholesterol-dependent hedgehog signaling

The hedgehog signaling pathway is modulated by cholesterol-modified Hedgehog proteins, regulating development and tissue repair [57]. This pathway uniquely requires covalent cholesterol attachment for Hedgehog protein activity, linking lipid metabolism directly to developmental signaling [58]. Lipidomics has shown how cholesterol influences Hedgehog pathway activity, particularly in cancer and congenital disorders [59]. A major discovery is the identification of cholesterol binding sites that regulate Hedgehog activation [60]. This pathway is critical in developmental biology, cancer, and regenerative medicine. Emerging roles of the Hedgehog pathway include regulation of glucose and lipid metabolism, linking it to obesity and diabetes [61,62], maintenance of stem cell self-renewal, impacting regeneration and aging [63], and modulation of

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immune cell differentiation, relevant to autoimmune diseases [64,65]. These discoveries expand lipidomics research into metabolic, regenerative, and immune-related fields.

2.7. Sterol regulatory element-binding protein (SREBP) pathway

The SREBP pathway regulates lipid biosynthesis and homeostasis by controlling genes involved in cholesterol and fatty acid metabolism [66,67]. SREBPs are distinct in their activation by ER-to-Golgi transport, a regulatory mechanism that ties lipid synthesis to sterol sensing [68]. Lipidomics has highlighted its role in diseases like NAFLD and insulin resistance [69]. A key discovery is the activation of SREBP in metabolic diseases, linking it to lipid-related pathologies [67]. This pathway is crucial in metabolic syndrome, diabetes, and liver diseases. Recent studies reveal additional roles for the SREBP pathway in modulating immune responses, including macrophage activation and cytokine production, linking it to inflammation [70]. SREBP activity has also been implicated in cancer progression by supporting tumor growth through lipid metabolism, making it a promising target in oncology [71]. These findings expand lipidomics research into immunology and cancer biology.

2.8. Nuclear liver X receptor (LXR) pathway

LXR regulates cholesterol homeostasis and lipid metabolism. The LXR pathway is unique in its ability to regulate reverse cholesterol transport by activating genes involved in cholesterol efflux, such as ABCA1, which are critical for maintaining lipid homeostasis [72]. Lipidomics has elucidated its role in reverse cholesterol transport and lipid clearance [73]. Discoveries include the potential of LXR agonists to reduce atherosclerosis [74]. This pathway is essential in cardiovascular research and metabolic syndrome [75]. Recent studies reveal new roles for the LXR pathway in diverse biological contexts. In neurodegenerative diseases, LXR activation has been shown to regulate cholesterol metabolism and inflammatory responses, suggesting therapeutic potential in conditions like Alzheimer's disease [76]. Moreover, LXRs have emerged as critical modulators in chronic inflammatory lung diseases by suppressing pro-inflammatory pathways and enhancing resolution of inflammation [77]. These findings expand the relevance of the LXR pathway in lipidomics research, linking it to neurobiology and respiratory health.

2.9. Farnesoid X receptor (FXR) and bile acid signaling

FXR, activated by bile acids, regulates lipid metabolism and liver health [78,79]. FXR is distinct in its role as a bile acid sensor that coordinates lipid, bile acid, and glucose metabolism by modulating the expression of genes like *SHP* and *CYP7A1* [80]. Lipidomics has shown FXR's role in reducing hepatic steatosis and bile acid metabolism [81,82]. Discoveries include FXR as a therapeutic target in NAFLD [83]. This pathway is crucial in liver disease and metabolic studies [80]. Recent studies have identified novel roles for FXR in broader biological contexts. In intestinal health, FXR activation has been shown to influence gut microbiota composition and improve intestinal barrier function, thereby impacting systemic metabolic health [84]. Moreover, FXR is implicated in cancer biology, particularly in liver and gastrointestinal cancers, where it modulates tumor growth and progression [80]. These emerging roles expand the relevance of FXR in lipidomics, linking it to microbiome research and oncology.

2.10. Toll-like receptor (TLR)-lipid interactions in immune signaling

Toll-like receptors (TLRs) detect lipid antigens and trigger immune responses by recognizing lipid-based microbial molecules, such as lipopolysaccharides (LPS), directly linking innate immune responses to lipid signaling [85]. Lipidomics has revealed TLR activation by oxidized low-density lipoprotein (oxLDL), which plays a crucial role in the pathogenesis of atherosclerosis and cardiovascular diseases [86,87]. This pathway is central to immunology and cardiovascular research due to its involvement in inflammatory responses and lipid-driven pathologies. Recent studies have

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identified novel roles for TLR-mediated lipid signaling in metabolic and neurological contexts. In metabolic disorders, TLR4 activation by saturated fatty acids contributes to insulin resistance, linking lipid metabolism to systemic inflammation and obesity [88]. Furthermore, TLRs recognize lipid components from damaged neurons, implicating these receptors in neuroinflammatory processes associated with neural infection and neurodegenerative diseases [89]. These emerging roles expand the scope of lipidomics research into metabolic and neurodegenerative diseases.

2.11. Eicosanoid signaling pathway

The eicosanoid signaling pathway, derived from arachidonic acid, produces bioactive lipids such as prostaglandins, leukotrienes, and thromboxanes that mediate inflammation, immunity, and vascular function [90]. Eicosanoids are unique as they function as highly localized signaling mediators with autocrine and paracrine effects, allowing precise modulation of inflammation and immune responses [91,92]. In lipidomics, this pathway has been studied for its role in generating lipid mediators that regulate disease processes. Key discoveries include the identification of cyclooxygenase (COX) enzymes and their inhibition by NSAIDs, which target prostaglandin production [93]. This pathway is a primary target in interpretation of lipidomics studies involving inflammation, cardiovascular research, and cancer biology [91,94,95]. Recent studies have unveiled novel roles for the eicosanoid signaling pathway in various biological fields. For example, eicosanoids have been implicated in plant and insect defense mechanisms, where they act as signaling molecules in response to pathogen attacks, regulating immune-like responses [96,97]. This pathway influences microbial communication, as certain bacteria produce eicosanoid-like molecules to modulate host immune responses, facilitating pathogen survival or immune evasion [98]. Furthermore, eicosanoid signaling contributes to invertebrate development, particularly in regulating molting and reproductive processes in arthropods, which highlights its evolutionary significance [99]. Finally, emerging evidence suggests eicosanoids play a role in environmental adaptation, such as in fish responding to hypoxic stress [100,101].

2.12. Endocannabinoid signaling pathway

Endocannabinoids, such as anandamide and 2-arachidonoylglycerol (2-AG), are lipid-derived mediators that regulate mood, appetite, and immune responses through activation of cannabinoid receptors. Uniquely, this pathway employs a retrograde signaling mechanism wherein endocannabinoids are synthesized and released from postsynaptic neurons to modulate neurotransmitter release from presynaptic terminals [102]. Lipidomics studies have elucidated the roles of endocannabinoids in energy homeostasis and neuroprotection [103,104]. A pivotal discovery is the involvement of CB1 receptor signaling in obesity and metabolic disorders, where its blockade has been shown to attenuate obesity by affecting multiple areas, including leptin signaling and reducing inflammation [105]. Consequently, this pathway holds significant relevance in neuroscience, obesity, and pain management. Recent studies reveal additional roles for the endocannabinoid system in reproduction, regulating gametogenesis, fertilization, and early embryonic development [106,107]. It also modulates the HPA axis, influencing stress hormone secretion and adaptation to stress [108], and supports synaptic plasticity, impacting learning and memory processes [109]. These findings expand the scope of lipidomics research into new physiological and developmental contexts.

2.13. Peroxisome proliferator-activated receptor (PPAR) pathway

PPARs are nuclear receptors that regulate lipid metabolism, inflammation, and energy balance [110]. PPARs are uniquely ligand-activated nuclear receptors that integrate lipid-derived signals with transcriptional control of metabolic genes. Lipidomics has advanced the understanding of how PPAR agonists reduce lipid accumulation and improve insulin sensitivity [111]. Discoveries include PPARγ agonists' therapeutic effects in type 2 diabetes and atherosclerosis [112,113]. This pathway is

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significant in metabolic diseases, cardiovascular research, and inflammation. Recent studies reveal additional roles for PPARs in diverse contexts. In cancer biology, PPARs have been implicated in tumorigenesis, where they influence cancer cell proliferation, apoptosis, and metabolism, suggesting their potential as therapeutic targets [114]. Furthermore, PPAR activation has shown promise in neurodegenerative diseases, particularly in modulating neuroinflammation and oxidative stress in conditions like Alzheimer's disease [115]. These findings expand the scope of lipidomics research into oncology and neurodegenerative disorders.

2.14. G-protein-coupled receptor (GPCR)-mediated lipid signaling

GPCRs mediate lipid signaling in processes like inflammation and neurotransmission [116,117]. GPCRs are uniquely versatile in their ability to mediate lipid signaling across diverse physiological contexts, including energy homeostasis, through ligands such as LPA and sphingosine-1-phosphate (S1P) [118]. Lipidomics has identified GPCR-mediated lysophospholipid signaling in cancer. This pathway is vital in cancer, obesity, and neuroscience [119]. Recent studies highlight additional roles for GPCR-mediated lipid signaling in neurodegenerative diseases, where LPA and S1P modulate neuroinflammation and neuronal survival in conditions like Alzheimer’s disease [120]. GPCRs also regulate adipose tissue function and energy balance, emphasizing their significance in obesity and diabetes management [121]. These roles broaden the scope of lipidomics research in neurobiology and metabolic health.

2.15. Cyclooxygenase (COX) pathway in lipid-derived mediators

Cyclooxygenase (COX) enzymes convert arachidonic acid into prostaglandins, mediating inflammation and pain [122]. The COX pathway is distinct in its role as a primary source of prostaglandins and is a major target of nonsteroidal anti-inflammatory drugs (NSAIDs), which inhibit COX activity to alleviate inflammatory symptoms [123]. Lipidomics has clarified prostaglandin roles in inflammatory diseases, enhancing our understanding of their biosynthesis and function [124]. Discoveries include NSAIDs targeting COX as a therapeutic strategy, underscoring the pathway's centrality in inflammation and drug development. Recent studies have uncovered additional functions of the COX pathway. In cancer biology, COX-2-derived prostaglandins have been implicated in tumor progression and immune evasion, suggesting that COX inhibition could enhance anti-tumor immunity [125]. In neurobiology, COX-2 activity has been linked to neuroinflammatory conditions, neuronal homeostasis in memory and anxiety, indicating potential therapeutic avenues for neurodegenerative diseases [126]. These emerging roles present new targets for lipidomics research to explore the diverse functions of COX-mediated signaling across different biological systems.

2.16. Prostaglandin and leukotriene signaling pathways

Lipid mediator pathways generate bioactive lipids, such as leukotrienes and prostaglandins, which play pivotal roles in inflammation and immunity [127]. Leukotrienes are particularly distinguished by their role in bronchoconstriction and asthma, mediating airway constriction and contributing to asthma pathophysiology [128]. Lipidomics has linked leukotrienes to asthma [129] and prostaglandins to pain regulation [130], enhancing our understanding of their roles in inflammatory diseases. While, these pathways are crucial in immunology and respiratory research, recent studies have uncovered additional functions of lipid mediator pathways. In cancer biology, leukotrienes have been implicated in tumor progression and metastasis, suggesting that targeting leukotriene pathways could offer new therapeutic strategies [131]. In neurobiology, prostaglandins and leukotrienes have been associated with neuroinflammatory conditions, indicating potential therapeutic avenues for neurodegenerative diseases [132,133]. These emerging roles present new targets for lipidomics research to explore the diverse functions of lipid mediator pathways across different biological systems.

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2.17. Phospholipase C (PLC) pathway in signal transduction

The phospholipase C (PLC) pathway hydrolyzes phosphatidylinositol 4,5-bisphosphate (PIP_2) to produce two key second messengers: inositol 1,4,5-trisphosphate (IP_3) and diacylglycerol (DAG). This dual generation is unique, as IP_3 mobilizes calcium from intracellular stores, while DAG activates protein kinase C (PKC), collectively regulating intracellular calcium signaling and various cellular functions [134]. Lipidomics studies have linked aberrant PLC activity to cancer progression and neurodegenerative diseases, highlighting its role in pathological conditions [135]. Furthermore, PLC is crucial for T-cell activation, as it mediates signals essential for T-cell development and function [136]. Therefore, the PLC pathway is critical in immunology and neuroscience. Recent research highlights new roles for the PLC pathway in developmental biology, where it is essential for vasculogenesis and hematopoiesis during embryogenesis [137,138]. Also, evolutionary studies suggest variations in PLC components among species reflect adaptive mechanisms in signal transduction pathways [139]. These findings expand the relevance of PLC signaling in lipidomics research.

3. Context-Dependent Lipid Pathways

3.1. Wnt/β-catenin pathway and lipid metabolism

The Wnt/β-catenin pathway is a signaling cascade involved in cell proliferation, differentiation, and development. This pathway is special due to its lipid modification of Wnt proteins via palmitoleoylation, which is essential for their secretion and activity [140]. In lipidomics, this pathway is of particular interest due to its role in lipid metabolism and adipogenesis [141]. Studies have shown that Wnt signaling inhibits adipocyte differentiation by suppressing PPARγ activity, thus regulating lipid storage [142]. Key discoveries include the identification of Wnt3a as a modulator of lipid droplet formation [143] and β-catenin's role in regulating lipid synthesis enzymes [144]. This pathway is particularly relevant in obesity, cancer, and metabolic syndrome, where altered lipid metabolism plays a significant role in disease progression [145]. Recent research highlights additional roles of the Wnt/β-catenin pathway. In developmental biology, its lipid dependent function can be important during embryonic patterning and organogenesis [146,147]. Evolutionary studies reveal its conserved lipid-dependent role across species, emphasizing its importance in developmental processes [148,149]. In stem cell biology, it regulates pluripotency and self-renewal, impacting tissue regeneration [150,151]. These findings broaden the pathway's relevance for lipidomics research.

3.2. AMP-activated protein kinase (AMPK) and lipid homeostasis

The AMPK pathway is a central regulator of cellular energy homeostasis, activated under conditions of low energy [152]. It controls lipid metabolism by inhibiting lipid synthesis pathways and promoting fatty acid oxidation [153]. AMPK is unique for its ability to sense cellular energy states through AMP/ATP ratios and directly phosphorylate enzymes involved in lipid oxidation [154]. In lipidomics, AMPK has been instrumental in understanding the regulation of lipid accumulation and its role in metabolic disorders [155–157]. Key discoveries include the role of AMPK in suppressing hepatic lipogenesis through SREBP downregulation and its ability to enhance mitochondrial lipid oxidation [154]. This pathway is particularly significant in metabolic syndrome, obesity, and diabetes, where lipid dysregulation is a hallmark. Recent research has expanded the understanding of the AMPK pathway beyond metabolic regulation. AMPK has been shown to influence reproduction, fertility and embryonic development by modulating energy availability during rapid cellular differentiation [158–160]. In evolutionary biology, AMPK's conservation across diverse species suggests its critical role in energy management under environmental pressures [161], aiding species adaptation to nutrient-scarce habitats [162]. In immunology, AMPK has been implicated in macrophage polarization, where it favors anti-inflammatory M2 phenotypes, linking energy regulation to immune responses [163]. In ecological studies, AMPK activation has been observed in

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organisms under climate-induced stress, such as extreme temperature fluctuations, enhancing their survival by optimizing metabolic pathways [164,165]. These findings highlight AMPK as a versatile target for lipidomics research in diverse biological systems.

3.3. mTOR pathway and lipid synthesis

The mTOR (mechanistic target of rapamycin) pathway is a nutrient-sensing signaling cascade that regulates cell growth, proliferation, and metabolism. The mTOR pathway is distinct in its dual-complex nature (mTORC1 and mTORC2), allowing it to simultaneously regulate lipid metabolism and cytoskeletal organization [166]. In lipidomics, mTOR is crucial for understanding how nutrient availability influences lipid metabolism, particularly in lipid synthesis and storage [167][168]. Key findings include mTOR's role in promoting de novo lipogenesis through the activation of SREBP1 and its regulation of lipid droplet biogenesis [169,170]. The pathway is relevant in cancer biology, obesity, and aging research, where lipid alterations mediated by mTOR play critical roles in disease progression [170,171]. Recent findings have expanded the understanding of the mTOR pathway beyond its traditional roles. mTOR has been shown to coordinate energy availability with organ size during embryogenesis, linking nutrient sensing to developmental timing [172]. In plant biology, mTOR signaling has emerged as a key player in regulating lipid synthesis during seed germination, demonstrating its conserved role across kingdoms [173]. In neurobiology, dysregulated mTOR activity has been linked to synaptic plasticity and cognitive deficits, with implications for neurodegenerative diseases [174]. Additionally, ecological studies suggest that mTOR influences metabolic flexibility in organisms under environmental stress, enabling survival in nutrient-scarce conditions [175,176]. These emerging roles highlight the versatility of the mTOR pathway, presenting new opportunities for lipidomics research across various biological systems.

3.4. Autophagy-linked lipid signaling pathways

Autophagy is a cellular recycling process that degrades and recycles cellular components, including lipids, under stress conditions. This pathway is unique for its involvement in lipophagy, a selective autophagic process targeting lipid droplets for degradation, which maintains lipid homeostasis [177]. Lipidomics has revealed the role of autophagy in regulating lipid droplet turnover and maintaining lipid homeostasis [178]. Key findings include the identification of lipophagy, where lipid droplets are degraded through autophagy, and its role in metabolic adaptation during starvation [179,180]. This pathway is particularly relevant in neurodegenerative diseases [181], where lipid accumulation is linked to autophagy dysfunction, and in metabolic disorders involving lipid storage diseases [182]. Recent studies have highlighted novel roles for autophagy in diverse biological contexts. In developmental biology, autophagy has been shown to influence the differentiation of adipocytes and the remodeling of lipid stores [183], emphasizing its role in energy allocation during organismal growth [184]. In neurodegeneration, the pathway has emerged as a critical regulator of neuronal health by preventing toxic lipid accumulation linked to disease progression [185]. Autophagy has also been implicated in the maintenance of metabolic balance by regulating lipid trafficking between organelles during cellular stress [186]. Furthermore, ecological studies suggest that autophagy contributes to organismal adaptation by mediating lipid responses to environmental changes, such as nutrient scarcity or fluctuating temperatures [187–189]. These findings underscore the versatility of autophagy in lipid regulation, presenting opportunities for future lipidomics research across various systems.

3.5. Tumor necrosis factor alpha (TNF-α) lipid signaling axis

The tumor necrosis factor-alpha (TNF-α) pathway is a critical inflammatory signaling cascade activated during immune responses and stress conditions. Notably, TNF-α influences lipid metabolism by promoting lipogenesis, inducing lipolysis, inhibiting lipid-metabolism-related enzyme activity, regulating cholesterol metabolism, and modulating adipokines [190]. In lipidomics,

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TNF-α is recognized for its regulatory effects on lipid metabolism, including the induction of lipolysis and alterations in lipid biosynthesis [191]. Significant findings highlight TNF-α's role in promoting insulin resistance through ceramide accumulation [192]. Furthermore, TNF-α contributes to hepatic steatosis via dysregulated lipid metabolism [193]. This pathway is key player in research areas such as cancer, obesity, and metabolic syndrome, where inflammatory lipid alterations are prevalent [194]. Recent studies have uncovered novel roles for the TNF-α pathway beyond its established functions. For instance, TNF-α has been implicated in the regulation of embryonic development and organogenesis [195]. In evolutionary biology, variations in TNF-α signaling components have been linked to species-specific immune responses, suggesting an evolutionary adaptation mechanism [196,197]. Ecological research indicates that environmental stressors can modulate TNF-α activity, affecting organismal resilience and adaptation. Finally, in neurobiology, TNF-α has been associated with neuronal plasticity and cognitive functions, highlighting its broader significance beyond immune regulation [198].

3.6. Adiponectin-receptor-mediated lipid signaling

Adiponectin, a hormone secreted by adipose tissue, regulates lipid metabolism through its receptors, (AdipoR1 and AdipoR2) [199] These receptors activate lipid oxidation and inhibit lipid synthesis via pathways like AMPK and PPAR-α. Adiponectin signaling is unique for its dual receptor-mediated activation of AMPK and PPARα pathways, which enhance lipid oxidation and reduce hepatic lipid accumulation [200]. Lipidomics has shown that adiponectin signaling influences lipid profiles, particularly in metabolic disorders [201]. Examples of related key findings include adiponectin's role in reducing hepatic lipid accumulation and improving insulin sensitivity [202], sex-specific lipid related metabolism [203] and lipid-specific opsonin function [204]. Recent findings have uncovered novel roles for adiponectin signaling beyond its conventional functions. In neurobiology, adiponectin has been found to influence brain function, including modulation of neurogenesis and neuroprotection [205]. In immunology, adiponectin plays a role in modulating immune responses, impacting inflammation and autoimmune conditions. Adiponectin signaling has been found to play key roles in linking obesity to various cancer types [206], sex-specificity in cancers [207] as well as regulation of skeletal muscle and skin homeostasis beyond its metabolic [208,209]. Finally, in reproductive biology, adiponectin influences fertility and reproductive system function [210], indicating its broader physiological significance.

3.7. Renin-angiotensin system (RAS) and lipid metabolism

The renin-angiotensin system (RAS) is integral to regulating blood pressure and fluid balance. Beyond these functions, RAS significantly influences lipid metabolism, affecting both lipid storage and oxidation processes [211]. A distinctive feature of RAS is its capacity to connect blood pressure regulation with lipid metabolism, primarily through angiotensin II's role in promoting oxidative stress and inflammation within adipose tissue [212–214]. Lipidomics studies have highlighted angiotensin II's contribution to oxidative stress and lipid dysregulation, factors that are instrumental in the development of cardiovascular diseases [215]. Angiotensin II has been shown to regulate adipocyte growth and differentiation, lipid metabolism, and the expression and release of adipokines and RAS components, thereby promoting oxidative stress [216]. Key discoveries include angiotensin II's role in inducing adipose tissue inflammation and its impact on lipid homeostasis, particularly in the context of metabolic disorders [216]. Research indicates that angiotensin II modulates adipocyte lipid metabolism, increases inflammatory gene expression, and decreases adiponectin expression, all of which contribute to metabolic dysregulation [217]. Recent studies have unveiled novel roles for the RAS beyond its traditional functions. RAS components have been implicated in development and organogenesis, e.g., kidney, vascular system and embryonic emergence of hematopoietic stem cells, as well as reproductive biology and aging [218–222]. Evolutionary biology research indicates that variations in RAS genes may have contributed to species-specific [223,224]. Ecological studies have found that environmental factors can influence RAS activity, affecting organismal responses to stress

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and habitat changes [225,226]. Moreover, in neurobiology, RAS has been associated with cognitive function and neuroprotection, highlighting its broader physiological significance beyond cardiovascular regulation [227].

3.8. Retinoid X receptor (RXR) in lipid homeostasis

Retinoid X Receptor (RXR) is a nuclear receptor that forms heterodimers with various nuclear receptors, including peroxisome proliferator-activated receptors (PPARs), to regulate lipid metabolism, such as fatty acid oxidation and lipid storage [228]. RXR's unique ability to partner with multiple nuclear receptors enables it to influence diverse lipid metabolic pathways, including bile acid metabolism [229]. Lipidomics studies have highlighted RXR's role in maintaining lipid homeostasis, particularly through its interactions with PPARγ. Significant discoveries include the identification of RXR agonists as potential therapies for metabolic disorders by modulating lipid [230–232]. Recent research has uncovered novel roles for RXR beyond its established functions. For instance, RXR has been implicated in neuronal and bone differentiation and development [233,234]. Moreover, RXR signaling has been linked to tumor progression and cancer cell metabolism, indicating potential therapeutic targets [235]. Finally, in reproductive biology, RXR influences fertility and reproductive system function through regulation of gametogenesis, highlighting its broader physiological significance [236].

3.9. Hypoxia-inducible factor (HIF) and lipid metabolism

The HIF pathway is activated under low oxygen conditions, regulating cellular adaptation to hypoxia. The HIF pathway is unique for its ability to reprogram lipid metabolism under hypoxic conditions, promoting lipid storage and anaerobic energy generation [237,238]. In lipidomics, HIF has been implicated in reshaping lipid metabolism to meet energy demands during hypoxia, such as increasing lipid uptake and storage [239]. Key discoveries include HIF's regulation of lipid droplet formation in cancer cells [240] and its role in promoting fatty acid oxidation during oxygen deprivation [237]. This pathway is highly relevant in cancer biology and cardiovascular research, where hypoxia is a defining feature [238,241]. Recent studies have highlighted new roles for the HIF pathway in other fields. In developmental biology, HIF has been found to influence the formation of blood vessels and tissue patterning [242], cellular adaptation to hypoxia during embryonic development [243]. In evolutionary contexts, variations in HIF-regulated genes have been linked to adaptations in species that thrive in hypoxic environments, such as high-altitude animals [244]. Ecological studies suggest that environmental hypoxia can modulate HIF signaling, impacting ecosystem dynamics, species resilience and life expectancy [245–247]. Furthermore, in neurobiology, HIF is emerging as a regulator of neural function under stress conditions [248]. These findings suggest significant potential for HIF-centered lipidomics research to uncover novel biological insights across diverse fields.

3.10. Aryl hydrocarbon pathway in lipotoxicity

The Aryl Hydrocarbon Receptor (AhR) is a transcription factor activated by binding to a variety of ligands, including environmental pollutants, dietary components, and endogenous metabolites. Once activated, AhR translocates to the nucleus, where it influences the expression of genes involved in detoxification, inflammation, and metabolic regulation. In the realm of lipid biology, AhR plays a crucial role by modulating pathways that govern lipid storage and breakdown, particularly through its effects on fatty acid oxidation and homeostasis [249–251]. Research has demonstrated that AhR activation can inhibit adipogenesis and regulate lipid-mediated inflammatory processes, such as those involved in metabolic disorders. Notable discoveries include the role of AhR in managing lipid accumulation in fatty liver disease [252] and its interaction with lipid-derived inflammatory mediators in immune cells [253]. This pathway holds significant promise in linking lipidomics and toxicology [254], where its response to xenobiotic lipophilic molecules is critical, and in metabolic

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and immune system studies [250,255], where its influence on lipid signaling pathways provides valuable insights for future lipidomics investigations. Beyond its conventional roles, the AhR pathway has increasingly been recognized over the past decade for its involvement in diverse fields, including developmental biology, neural function, tissue repair, environmental sensing and adaptation, and evolutionary divergence [256–261]. These findings suggest that the AhR pathway could serve as a pivotal link between lipid-related mechanisms and these fields in future lipidomics research.

3.11. Notch signaling and lipid crosstalk

The Notch signaling pathway is a cell-cell communication system that regulates cell fate, proliferation, and apoptosis [262]. Notch signaling is unique in that its receptor cleavage is lipid raft-dependent, tying lipid microdomains to cell fate decisions [263]. In lipidomics, Notch signaling has been linked to lipid metabolism through its regulation of fatty acid oxidation and lipid biosynthesis pathways [264,265]. Discoveries include Notch1-mediated regulation of lipolysis in adipocytes and its role in macrophage lipid metabolism during inflammation [266]. This pathway is particularly important in cancer biology, immune regulation, and cardiovascular diseases, where Notch signaling impacts lipid homeostasis [267]. Furthermore, in developmental biology, it is critical for embryonic patterning and organogenesis [268,269]. Evolutionary studies reveal its conservation across species, emphasizing its role in fundamental processes [270]. In stem cell biology, Notch regulates pluripotency and self-renewal, impacting tissue repair [271]. Moreover, it mediates organismal adaptation to environmental stressors, broadening its relevance to ecological research [272,273]. These findings expand the importance of lipidomics research in diverse biological systems.

3.12. Mitogen-activated protein kinase (MAPK) pathway and lipid modulation

The MAPK pathway is a signaling cascade that transmits extracellular signals to regulate cell growth, stress responses, and apoptosis. The MAPK pathway is distinctive in its dual regulation by lipid signals such as Cer and in its ability to influence cellular proliferation and differentiation [274]. In lipidomics, the MAPK pathway is key to understanding how lipid mediators influence signaling and vice versa. For instance, studies have shown that lipid-derived signals including Cer can activate MAPK pathways to induce apoptosis, while MAPK activity regulates lipid synthesis enzymes [274–277]. Notable discoveries include the role of the MAPK pathway in lipid-induced inflammation and metabolic stress [278]. This pathway is central in research on metabolic disorders, neurodegeneration, and [274,279]. Recent studies have uncovered additional functions of the MAPK pathway. In developmental biology, MAPK signaling is crucial for embryonic development and differentiation, influencing processes such as cell fate determination and tissue patterning [280–282]. Evolutionary studies indicate that the conservation of lipid-MAPK signaling components across species in cellular processes regulating aging and longevity [283]. In cancer biology, MAPK signaling regulates has emerged as an important player in glycosphingolipid-associated tumorigenesis [284]. Moreover, in ecology, lipid-dependent MAPK signaling has been implicated in the response of organisms to environmental stressors, affecting adaptation and survival mechanisms [285,286]. These emerging roles present new targets for lipidomics research to explore the diverse functions of MAPK-mediated signaling across different biological systems.

3.13. NADPH oxidase-lipid interplay in oxidative stress

NADPH oxidase is an enzyme complex that generates reactive oxygen species (ROS) as part of cellular signaling and defense. This pathway is distinctive for producing ROS as signaling molecules, which drive lipid peroxidation [287]. In lipidomics, the interplay between NADPH oxidase and lipids is significant because ROS production triggers lipid peroxidation, generating bioactive lipid mediators [288]. Notably, NADPH oxidase-induced ROS promote atherosclerosis through the oxidation of low-density lipoprotein (LDL) [289], and lipid peroxidation products act as secondary

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messengers in inflammation [290]. This pathway is particularly important in cardiovascular diseases [289], neurodegeneration [291], and toxicology [292], where oxidative lipid damage plays a critical role. Emerging research over the past decades has uncovered roles of the NADPH oxidase pathway in other fields as well. For instance, NADPH oxidase-derived ROS have been found to regulate hematopoietic stem cell differentiation [293]. In ecology, studies suggest that NADPH oxidase influences organismal responses to environmental stress, affecting ecosystem dynamics [294]. Evolutionary biology research indicates that variations in NADPH oxidase genes contribute to species-specific adaptations to oxidative stress [295]. Moreover, in immunology, NADPH oxidase-generated ROS have been shown to modulate immune cell signaling, impacting inflammatory responses [296]. These findings open new avenues for lipidomics research to explore the diverse roles of NADPH oxidase across different biological systems.

3.14. Platelet-activating factor (PAF) signaling pathway

The platelet-activating factor (PAF) pathway centers on bioactive GP that mediate critical biological processes such as inflammation, thrombosis, and immune responses [297]. This pathway is uniquely characterized by PAF's potency as an inflammatory mediator, functioning at nanomolar concentrations to initiate platelet aggregation and modulate immune cell activity. In lipidomics, PAF has been extensively studied for its ability to mediate lipid signaling (e.g. in inflammatory and allergic responses) [298]. Notable discoveries include PAF's role in amplifying inflammation through receptor-mediated signaling and its involvement in lipid remodeling during immune activation [299]. This pathway has been identified as a key regulator in lipid-dependent mechanisms in immunology, inflammation, and cardiovascular diseases [299–301]. Recent studies have revealed novel and unexpected functions of the PAF pathway across various biological fields. For instance, PAF signaling has been shown to regulate early stages of embryogenesis, including cellular differentiation and tissue organization, highlighting its role in shaping developmental processes [302,303]. In evolutionary research, PAF's conservation across diverse species, from microorganisms to higher organisms, underscores its pivotal role in fundamental biological processes like adaptation of immune responses [304]. Ecological studies suggest that PAF signaling is involved in organismal responses to environmental stressors, such as oxidative stress and extreme temperatures, providing a survival advantage in challenging ecosystems [305,306]. These findings broaden the understanding of the PAF pathway and open new directions for lipidomics research in unexplored biological contexts.

3.15. Nuclear factor-kappa B (NF-κB) pathway

The NF-κB pathway is a master regulator of inflammation, activated in response to stimuli such as cytokines, pathogens, and oxidative stress. This pathway is uniquely activated by lipid oxidation products such as oxidized LDL, which directly modulates its inflammatory response [307]. In lipidomics, NF-κB plays a significant role in lipid-mediated inflammatory responses, particularly through its interaction with lipid peroxidation products and oxidized LDL [191]. Major discoveries include NF-κB activation by lipid oxidation products, contributing to atherosclerosis [307], and its regulation by lipid-derived inflammatory mediators like prostaglandins [308]. Emerging research has revealed unexpected roles for the NF-κB pathway in various biological contexts. In developmental biology, NF-κB has been shown to influence critical processes like embryogenesis and tissue patterning [309]. Evolutionary studies suggest that changes in NF-κB signaling pathways have contributed to the adaptive diversification of immune responses across species [310], and conserved mitochondrial functions [311]. Furthermore, in neurobiology, NF-κB has emerged as a regulator of synaptic function and learning, underscoring its importance in brain health beyond its traditional role in inflammation [312].

3.16. Lipoxin and resolvins in inflammation prevention

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Lipoxins and resolvins are lipid mediators derived from arachidonic acid and other n-3 fatty acids, respectively, that play key roles in resolving inflammation [313,314]. Lipoxins and resolvins are unique for their specialized pro-resolving functions, actively dampening inflammation and promoting tissue repair, unlike other lipid mediators [314]. Lipidomics has been instrumental in characterizing these molecules and their anti-inflammatory effects [315]. Key findings include the identification of lipoxins as modulators of neutrophil apoptosis and resolvins' role in promoting tissue repair [315]. These pathways are crucial in immunology and inflammatory research, with applications in diseases such as arthritis and asthma [316].

Recent studies have uncovered novel roles for lipoxins and resolvins beyond their established functions. In neurobiology, they have been shown to modulate synaptic plasticity, homeostasis and repair [317,318]. In cardiovascular research, these mediators have been found to reduce atherosclerotic plaque formation and promote heart tissue repair following ischemic injury [316]. Ecological studies indicate that dietary intake of n-3 fatty acids, leading to increased production of resolvins, can influence inflammatory responses in wildlife, affecting their adaptation to environmental stressors [319]. Furthermore, in cancer biology, lipoxins have been observed to inhibit tumor growth and metastasis by modulating the tumor microenvironment and immune responses [320].

3.17. Reactive oxygen species (ROS)-linked lipid signaling

Reactive oxygen species (ROS) are byproducts of oxidative metabolism that significantly influence lipid signaling by generating lipid peroxidation products [321]. Two notable example are 4- hydroxy-2-nonenal (4-HNE) and malondialdehyde (MDA), which function as secondary messengers in oxidative stress responses [322]. In lipidomics, understanding ROS-linked signaling is crucial for comprehending oxidative stress and its impact on lipid homeostasis [323]. Major discoveries have identified lipid peroxidation products like 4-HNE as signaling molecules that regulate inflammation and apoptosis [290]. This pathway is particularly relevant in toxicology, cardiovascular diseases, and neurodegeneration, where oxidative lipid damage is a common feature [324–326]. Recent studies have revealed novel roles for ROS-induced lipid peroxidation in diverse biological contexts. In developmental and cell biology, for instance, ROS-driven lipid peroxidation plays key roles in guiding cell differentiation and shaping organ development from plants to animals [327–329]. In evolutionary biology, differences in ROS regulation and lipid peroxidation pathways have been connected to species-specific adaptations to oxidative stress and pathogens as well as efficiency in energy production, highlighting their role in evolutionary resilience [330–332]. Ecological research has shown that environmental pressures, such as temperature and pollutants, can alter ROS production, leading to lipid peroxidation that impacts organismal stress responses and survival strategies. Furthermore, in immunology, lipid peroxidation products have emerged as regulators of immune function, influencing inflammation and adaptive immune responses, thereby expanding the functional scope of ROS beyond oxidative damage [333].

4. Emerging Pathways/Areas in Lipidomics

4.1. Ferroptosis-regulating lipid signaling

Ferroptosis is an iron-dependent form of regulated cell death characterized by lipid peroxidation and ROS generation. Ferroptosis is distinct for its reliance on lipid peroxidation of polyunsaturated phospholipids, setting it apart as an iron-dependent lipid-driven cell death mechanism [334]. Lipidomics has uncovered the role of phospholipids containing polyunsaturated fatty acids (PUFAs) as substrates for peroxidation in ferroptosis [335]. Discoveries include the identification of acyl-CoA synthetase long-chain family member 4 (ACSL4) as a regulator of ferroptosis via lipid metabolism. This pathway can be considered as a key target for future lipidomics research of iron-lipid dependent cancer therapy [336], neurological diseases [337], detoxification [338], and ischemia-reperfusion injury [339], where ferroptosis contributes to disease pathology.

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4.2. Exosomal lipid signaling in cell communication

Exosomes are small extracellular vesicles that facilitate cell-to-cell communication by delivering bioactive molecules, including lipids, proteins, and nucleic acids [340]. What sets exosomal lipid signaling apart is its ability to transfer distinct lipid profiles that can influence the metabolism and signaling pathways of recipient cells [340,341]. Lipidomics has been instrumental in uncovering the specific lipid composition of exosomes and their role in mediating intercellular lipid exchange [342,343]. Significant findings include the involvement of exosomal lipids in promoting cancer metastasis and shaping immune responses [344,345]. This pathway holds particular importance in the study of neuron-glia communication and central nervous system diseases [346,347], where exosome-driven signaling mechanisms are increasingly recognized as contributors to disease progression and therapeutic targets.

4.3. Gut microbiota-lipid signaling axis

The gut microbiota influences host lipid metabolism by producing bioactive metabolites such as short-chain fatty acids and secondary bile acids [348,349]. This pathway is special in that microbial lipids such as short-chain fatty acids influence host lipid metabolism and systemic inflammation [350]. Lipidomics has highlighted the role of these microbial metabolites in regulating lipid absorption, storage, and immune responses [351]. Discoveries include the impact of gut microbial-derived lipids on obesity, atherosclerosis and the role of bile acid signaling in metabolic homeostasis [352,353]. This pathway can be a target of future lipidomics studies in metabolic syndrome, cardiovascular diseases, and gastrointestinal disorders.

4.4. Oxysterol-driven pathways in aging and degenerative diseases

Oxysterols are oxidized cholesterol derivatives involved in lipid metabolism and signaling [354]. Oxysterols are distinctive for their dual roles as metabolic intermediates [355] and nuclear receptor ligands, particularly for LXRs [356]. Lipidomics has revealed their roles in aging and neurodegenerative diseases, particularly in regulating cholesterol homeostasis and inflammatory responses [357,358]. Key discoveries include oxysterols' role in Alzheimer's disease pathogenesis and their regulation of liver X receptor (LXR) activity [359]. This pathway can be a target of future lipidomics studies in aging research, neurodegeneration, and atherosclerosis.

4.5. Cardiolipin signaling in mitochondrial function

Cardiolipin, a specialized phospholipid found in the inner mitochondrial membrane, plays a crucial role in maintaining mitochondrial structure and facilitating energy production [360,361]. Its distinct function lies in regulating mitochondrial bioenergetics and apoptosis by interacting with cytochrome C, a key mediator of programmed cell death [362]. Lipidomics has shed light on cardiolipin's involvement in processes such as mitophagy, apoptosis, and mitochondrial dysfunction. Notable discoveries include the contribution of cardiolipin peroxidation to the pathology of Parkinson's disease [363] and cancer [364], by influencing mitochondrial dynamics and stability. This pathway can be a target of lipidomics studies particularly in future neurological diseases [365], metabolic disorders [366], and the aging process [367], where mitochondrial health is a critical factor.

4.6. Brassinosteroid and phospholipid crosstalk in plant lipidomics

Brassinosteroids are plant hormones that regulate growth and stress responses, interacting with phospholipids in membrane signaling [368]. Brassinosteroids uniquely interact with phospholipids to regulate membrane fluidity and stress responses in plants, enabling rapid adaptation to environmental challenges such as drought and salinity [369]. Moreover, they modulate phosphatidic acid (PA) production, which acts as a secondary messenger in plant signaling [370]. Lipidomics has uncovered how brassinosteroids influence lipid metabolism and signaling under stress conditions [371]. Discoveries include their role in modulating phospholipid composition during drought and

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pathogen attack [372,373]. This pathway is highly relevant for lipidomics studies in plant biology and agricultural research.

4.7. Perilipin-mediated lipid droplet signaling

Perilipins are a family of proteins that play a critical role in managing lipid droplet stability and regulating lipolysis [374]. Their distinct function lies in controlling the balance between lipid storage and breakdown by forming a protective barrier around lipid droplets, preventing premature lipolysis during nutrient abundance, and facilitating lipid release when energy demands increase [375]. This dynamic regulation helps maintain energy homeostasis and protects cells from lipotoxic effects [376]. Lipidomics has provided insights into perilipins' contributions to lipid mobilization, storage, and overall energy regulation [377]. Key findings include their role in stabilizing lipid droplets and their involvement in metabolic disorders, e.g., those linked to obesity and cancer, where disrupted perilipin function is linked to impaired lipid handling [378]. This pathway is highly relevant in studies of metabolic syndrome, energy balance, and obesity-related health issues.

4.8. Unfolded protein response (UPR) and lipid signaling

The unfolded protein response (UPR) is a vital cellular mechanism activated to mitigate stress in the endoplasmic reticulum (ER) and restore its functional balance, with lipid metabolism playing an integral role [379]. Unlike other pathways, the UPR specifically adjusts lipid biosynthesis to maintain ER membrane integrity and support its protein-folding capacity during stress [380–383]. Furthermore, it facilitates the reorganization of phospholipid composition in response to prolonged ER dysfunction. Lipidomics has provided valuable insights into how the UPR dynamically regulates lipid synthesis and remodeling to adapt to cellular demands [384]. Notable findings include its regulation of phospholipid production and its connection to diseases driven by chronic ER stress. This pathway is particularly significant in conditions such as lipid-mediated neurodegenerative disorders [385], diabetes [386], and cancer [387], where ER stress and lipid imbalances are key contributing factors.

4.9. Lipid-associated cold shock and thermoregulation pathways

Under cold stress, cells adjust their lipid composition to preserve membrane fluidity and ensure proper cellular function. The cold shock response is distinct in its ability to alter membrane lipids, notably increasing unsaturated fatty acids, which prevent membranes from becoming rigid at low temperatures [388]. This lipid remodeling is essential for organisms' survival in cold environments, such as arctic species and frost-tolerant plants [389]. Lipidomics has revealed the pivotal role of unsaturated fatty acids and other lipid molecules in enabling thermoregulation. Key findings include the remodeling of lipid profiles in brown adipose tissue during cold exposure, which supports heat generation through thermogenesis [390]. The cold associated signals are particularly significant in future lipidomics studies of metabolism and environmental adaptation.

4.10. Emerging roles of ether lipids in cellular stress response

Ether lipids, including plasmalogens, are a class of lipids known for their role in preserving cellular integrity and providing defense against oxidative damage [391]. Their unique ability to scavenge free radicals makes them essential in protecting cells from oxidative stress. Lipidomics studies have uncovered their significant contributions to antioxidant mechanisms and cellular communication [392]. Notable findings include the reduction of plasmalogens in chronic inflammatory diseases [393], neurological diseases (e.g. Alzheimer’s disease) [394], obesity [395], digestive system cancers [396], aging [397], and their involvement in mitigating oxidative damage in various stress conditions [398]. The ether-lipids holds particular relevance in future lipidomics research in these areas linking lipid signals to cellular stress responses.

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4.11. FABPs in intracellular lipid transport

Fatty acid-binding proteins (FABPs) are specialized proteins that facilitate the transport of fatty acids within cells while also modulating lipid-related signaling pathways [399]. Their unique function lies in their ability to act as carriers of lipid molecules, such as fatty acids and eicosanoids, to nuclear receptors like PPARs, thereby directly influencing gene regulation [400]. Lipidomics has been instrumental in uncovering FABPs' roles in lipid uptake, metabolic processes, and inflammatory responses [401,402]. Key findings include their contribution to obesity, cardiovascular and inflammatory diseases through the regulation of lipid signaling [402,403]. The FABPs have particular relevance in future lipidomics research in these areas linking lipid transports to various cellular dysfunctions.

4.12. N-3-derived signaling in neuroprotection and cardioprotection

N-3 fatty acids, including EPA and DHA, are essential lipids known for producing bioactive mediators with anti-inflammatory and protective properties [404]. Their distinctive role involves the synthesis of resolvins and protectins, which are specialized mediators that facilitate the resolution of inflammation and support tissue healing in the brain and heart [405–407]. N-3 fatty acids also modulate ion channel activity in heart cells, helping to reduce the risk of arrhythmias [408]. Lipidomics has revealed their critical roles in mitigating inflammation and offering protection against neurodegenerative conditions, aging and cardiovascular disorders [409]. Notable discoveries include the identification of resolvins and protectins as key molecules in neuroprotection and inflammation resolution [410]. The n-3 related signals are highly significant in the lipidomics of protective properties of lipids in various fields of inflammatory and metabolic disorders.

4.13. Hippo signaling pathway in lipid biosynthesis and energy homeostasis

The Hippo signaling pathway plays a central role in regulating cell growth, programmed cell death, and organ size by modulating the activity of transcriptional regulators YAP (Yes-associated protein) and TAZ. In lipid biology, this pathway has gained attention for its involvement in lipid metabolism, particularly in the formation of lipid droplets, fatty acid synthesis, regulation of ferroptosis and adipogenesis [411–413]. Research has demonstrated that YAP and TAZ influence the expression of genes critical for lipid biosynthesis, with dysregulation of this pathway contributing to abnormal lipid accumulation in conditions like cancer and metabolic disorders [414]. For example, YAP activation has been linked to the enhancement of lipid droplet formation in cancer cells, enabling their rapid growth. The Hippo pathway is significant across multiple fields, including cancer research, where altered lipid metabolism fuels tumor progression [415], and developmental biology and tissue regeneration, where it governs organ development and energy regulation [416]. These roles highlight its potential as a valuable focus for lipidomics studies aiming to explore its broader impact on cellular lipid dynamics and organ development.

4.14. Lipidomics in epigenetic modulation and chromatin remodeling

Lipids, including fatty acids and phosphatidylserine, play a critical role in modulating chromatin architecture and gene activity through epigenetic processes [417–419]. Unique among these functions is the role of lipid-derived metabolites like acetyl-CoA, which acts as a key substrate for histone acetylation, directly connecting metabolic pathways to the regulation of gene expression [420]. Lipidomics has provided significant insights into how lipid metabolites influence histone modification patterns and DNA methylation states [421]. Notable findings include the impact of acetyl-CoA on histone acetylation and its role in lipid-dependent transcriptional regulation. This area of research is particularly relevant in fields where lipid-mediated epigenetic mechanisms contribute to disease progression and cellular adaptation [422–424]. A dedicated review focusing on lipidomics and epigenetics could shed light on this rapidly evolving field and its implications for understanding disease and metabolism [424].

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4.15. The emerging role of post-transcriptional mechanisms in lipidomics

Post-transcriptional regulation, involving processes such as microRNAs (miRNAs), alternative splicing, and m6A RNA methylation, is essential for modulating gene expression after transcription. In the realm of lipid biology, these regulatory mechanisms are gaining more attention due their diverse roles in maintaining lipid metabolism and balance [425–428]. Notable examples of discoveries linking these mechanisms to lipidomics are regulation of cholesterol homeostasis and lipid-mediated neural dysfunction by alternative splicing [429,430], regulation of lipid-mediated apoptosis and cellular de-differentiation by miRNAs [431,432], and regulation of lipid-dependent insulin sensitivity and liver development by m6A RNA modifications [433,434]. Beyond their established roles in biomedical research, these post-transcriptional mechanisms are gaining prominence in fields like environmental biology, ecology, and evolution [435,436]. These areas present exciting opportunities to uncover novel connections between lipidomics and broader biological processes, paving the way for future interdisciplinary discoveries.

5. Conclusions

Lipidomics has emerged as a powerful discipline for unraveling the complexity of lipid-mediated biological processes, yet its full potential can only be realized through a deeper integration with signaling pathway analysis. This review highlights the diverse and interconnected signaling networks that regulate or are modulated by lipid signals, providing a structured reference for researchers navigating this complex landscape. By systematically compiling well-established and emerging lipid-related pathways, this work not only aids in data interpretation but also reveals critical knowledge gaps where future lipidomics research can expand. A key takeaway from this review is the broad influence of lipid signaling across various biological systems, extending beyond traditional metabolic and disease contexts into areas such as developmental biology, environmental adaptation, and evolutionary dynamics. Many of the pathways discussed here are deeply interconnected with cellular energy balance, immune regulation, and stress responses, emphasizing on the need for a more integrated, systems-level approach in lipidomics studies. Furthermore, the rapid advancements in high-resolution mass spectrometry and multi-omics approaches offer unprecedented opportunities to dissect lipid-mediated signaling with greater specificity and depth. Moving forward, a major challenge remains in translating lipidomic discoveries into actionable insights, particularly in precision medicine, biomarker discovery, and therapeutic interventions. Understanding how lipid-driven signaling is altered across different physiological and pathological states will be crucial for bridging fundamental lipid biology with clinical and translational research. By encouraging interdisciplinary collaborations and utilizing cutting-edge analytical technologies, the field of lipidomics can continue to evolve, providing novel perspectives on cellular communication, metabolic regulation, and organismal adaptation in both health and disease.

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