Review

Lipids and Longevity: Their Role in Aging and Neurodegenerative Decline

Justina Bora , Smita Lata , Sagar Mondal , Swati Priya , Dinusha Thazhathu Veettil , Sumira Malik * , Perinthottathil Sreejith *

Posted Date: 26 June 2025

doi: 10.20944/preprints202506.2175.v1

Keywords: aging; neurodegenerative decline; lipids

 doi:10.20944/preprints202506.2175.v1

Article

Lipids and Longevity: Their Role in Aging and Neurodegenerative Decline

Jutishna Bora [1], Smita lata [1], Sagar Mondal [1], Swati Priya [1], Dinusha T Veettil [2], Sumira Malik [1,*] and Sreejith Perinthottathil [2,*]

[1] Amity Institute of Biotechnology, Amity University Jharkhand, Ranchi, 834001, India

[2] Department of Biology, Eastern New Mexico University, 1500 S Ave K, Portales NM 88130

* Correspondence: author: smalik@amity.edu; sreejith.perinthottathil@enmu.edu

Abstract

Lipids are a diverse group of hydrophobic molecules including fats, oils, phospholipids, and steroids that are vital for numerous biological functions including energy storage, cellular structure, and signaling. Changes in lipid metabolism that occur as organisms age result in dysregulated lipid profiles that are increasingly linked to chronic conditions such as cardiovascular diseases, neurodegenerative disorders, and metabolic syndromes, thus highlighting the importance of lipids in health span and longevity. Research has shown that aging is characterized by certain changes in lipid composition. These shifts are not merely passive but actively contribute to cellular senescence and inflammation, mechanisms that are central to age-related decline. In particular, the accumulation of oxidized fatty acids has been shown to impair immune cell function, exacerbating inflammatory responses and furthering the trajectory of aging-related diseases. The controversies surrounding the role of dietary lipids in aging have emerged, particularly regarding the optimal types and ratios of fats that can promote healthier aging. Certain unsaturated fats are believed to confer protective effects, while others may contribute to health risks when consumed in excess. Furthermore, advancements in lipidomic technologies are enhancing our understanding of individual lipid profiles and their associations with health outcomes, paving the way for personalized dietary interventions aimed at mitigating the effects of aging. In this review, the exploration of lipids in the context of aging reveals a complex landscape where lipid metabolism intersects with cellular health, chronic inflammation, and disease susceptibility, presenting both opportunities for therapeutic intervention and ongoing challenges in nutritional science and gerontology.

Keywords: nanoimprint lithography (NIL); layout-to-SEM reconstruction; U-Net; conformal prediction; uncertainty quantification; optical proximity correction (OPC)

Introduction

Lipids are integral to various biological processes, influencing aging and longevity through multiple mechanisms. The relationship between lipid metabolism and aging has garnered considerable attention, particularly regarding how alterations in lipid composition can contribute to age-related physiological and pathological changes. Lipids function as crucial signaling molecules, modulating nuclear transcription and facilitating cellular communication. This signaling capacity allows lipids to play an active role in lifespan and health span regulation.

Aging can be closely associated with alterations in lipid metabolism, which can have significant effects on the overall health and progression of age-related diseases. Multiple studies show that aging is marked by dysregulated lipid metabolism, leading to changes in the lipid composition across various species, including humans. As individuals age, body adiposity typically increases, accompanied by shifts in lipid metabolite levels and the development of lipotoxicity. This increase in lipotoxicity contributes to various age-related diseases such as cardiovascular disease, cancer, type 2 diabetes, and Alzheimer's disease. The complexities of lipid metabolism make it difficult to

 doi:10.20944/preprints202506.2175.v1

understand its precise role in aging, but advancements in lipidomic technologies are shedding light on age-associated changes in lipid profiles. These changes are further influenced by factors such as diet and gender, highlighting the complex dynamics of lipid metabolism in aging. Multiple reviews have focused on how lipid metabolism contributes to aging, and in multiple cellular processes. Here in this review, we focus on how lipids play a role in multiple age-related diseases and pave way to timely interventions and identification of aging biomarkers to support healthy aging.

Lipid Composition Changes with Age

Lipid composition undergoes significant changes with age, influencing metabolic health, cellular function, and disease susceptibility. As individuals grow older, shifts in lipid metabolism contribute to various physiological alterations, including increased lipid peroxidation, disrupted lipid homeostasis, and impaired membrane integrity. These changes play a crucial role in aging-related disorders, such as cardiovascular diseases, neurodegenerative conditions, and metabolic dysfunctions.

One of the most notable changes in lipid composition with age is the accumulation of oxidized lipids. Lipid peroxidation, driven by oxidative stress, leads to the formation of reactive lipid species that damage cellular membranes and contribute to inflammation. This process is particularly detrimental in highly metabolic tissues such as the brain and heart, where oxidative damage accelerates age-related degeneration. For example, alterations in brain lipid composition have been linked to cognitive decline and neurodegenerative diseases like Alzheimer's disease (Mutlu, Duffy, & Wang, 2021; Wu, Liu, Yang, Ma, & Qin, 2023).

Aging also affects lipid homeostasis by altering cholesterol metabolism. Studies indicate that older adults experience an increase in total cholesterol and low-density lipoprotein (LDL) levels while high-density lipoprotein (HDL) levels decline, which contributes to a higher risk of atherosclerosis and cardiovascular diseases (Sharma & Diwan, 2023; Y. Wang, Hu, Chen, & Ma, 2025). These lipid imbalances not only impact vascular function but also promote systemic inflammation, further accelerating aging processes.

Membrane lipid composition is another critical aspect influenced by aging. The phospholipid content of cell membranes shifts with age, affecting membrane fluidity and cellular communication. Changes in phosphatidylcholine and sphingolipid levels, for instance, can alter signal transduction and impair cellular resilience against stressors. Additionally, lipid raft integrity declines with age, disrupting receptor localization and downstream signalling pathways essential for immune function and metabolic regulation.

Metabolic shifts associated with aging also contribute to lipid accumulation in non-adipose tissues. This phenomenon, known as ectopic lipid deposition, is frequently observed in the liver, muscle, and vascular system, leading to conditions such as fatty liver disease, insulin resistance, and increased cardiovascular risk (Adebo, Gieng, & Feng, 2025). As lipid storage becomes dysregulated, lipotoxicity further exacerbates cellular dysfunction and inflammation.

Role of Lipids in Age Related Diseases

a. Lipid Metabolism and Cardiovascular Health

The cardiovascular system of humans utilizes kilograms of ATP daily to maintain basal metabolism and promote regular contractions, which are crucial for sustaining systemic as well as pulmonary arterial compression. Ninety-five percent of the total energy generated by the heart is derived through oxidative metabolism inside the mitochondria, while anaerobic glycolysis accounts for five percent (Allard, Schonekess, Henning, English, & Lopaschuk, 1994). Changes in substrate accessibility as well as absorption, observed in diabetes along with other metabolic disorders, affect mitochondrial function along with cardiac metabolism of energy, including calcium dynamics alongside homeostasis, the generation for reactive oxygen species (ROS) (Wong, Dighe, Mezera, Monternier, & Brand, 2017), as well as the initiation of the pro-apoptotic cascade. Significantly,

 doi:10.20944/preprints202506.2175.v1

decreased fatty acid oxidation (FAO) might at times coincide with heightened glucose metabolism. In several cells, such as cardiomyocytes, the increased synthesis of malonyl CoA functions as an allosteric inhibitor of carnitine palmitoyl transferase, therefore restricting the transport of lipids within mitochondria (W. Wang et al., 2019).

The heart's muscular system can change its power source due to its significant flexibility in metabolism. The cardiac muscle diminishes its ability to generate energy effectively as well adapt to fluctuating metabolic situations, including coronary artery disease (Davila-Roman et al., 2002); (Neglia et al., 2007). The biology of cardiomyocytes, particularly mitochondrial function, is consequently impacted by this metabolic imbalance. Cardiomyopathies do alter mitochondrial dynamics, especially when it comes to the balance between fusion as well as fission. While improved mitochondrial fusion provides protection from pressure-induced heart failure (H. Yu, Guo, Mi, Wang, Li, & Gao, 2011), restricted integration of the inner mitochondrial membrane promotes apoptosis and the development of heart failure. Significant changes in oxidative pathways and metabolic models of cardiac tissue are both associated with mitochondrial dynamics. By reducing heart oxidative stress, elevated amounts of inner membrane binding protein may have an impact on ROS production. Cardiac substrate utilization may affect cardiac function irrespective of changes in ATP production. It also affects lipid homeostasis, which regulates fatty acid intake, storage, and oxidation (Schulze, Drosatos, & Goldberg, 2016).

A notable increase in anaerobic metabolism of glucose, which is associated with a greater glycolytic flux and the accumulation of lactate and pyruvate, is a characteristic of heart failure with reduced ejection fraction (HFrEF). Proton buildup in the cytosol is thus linked to heightened acidosis, which exacerbates cardiac contraction by blocking contractile proteins as well as intracellular Ca2+ transport (Diakos et al., 2016). This alteration in ionic balance reduces ATP synthesis and worsens heart failure, an energy-deficient illness. Insulin resistance is a major metabolic abnormality in HFpEF that is mostly associated with obesity (Da Dalt, Cabodevilla, Goldberg, & Norata, 2023).

There is a noticeable decrease in aerobic glycolysis in both HFrEF as well as HFpEF. Research on metabolism in HFpEF has been hindered by the lack of an appropriate animal model. In addition to FAO, 5–30% of the energy generated by a heart in good health comes from anaerobic glycolysis. Changes in glucose uptake and oxidation may occur in a damaged heart, much as changes in FAO. Research indicates that heightened glycolytic uptake in some heart failure models results in an augmented flux via the pentose phosphate pathway, which regulates both cardiac redox status and cellular proliferation (Da Dalt et al., 2023).

Lipoproteins are mostly composed of phospholipids, cholesterol, triglycerides, along with other types of lipids. The basic makeup of lipoproteins, comprising amphipathic components such as phospholipids as well as exterior protein molecules, alongside hydrophobic fatty acids like triglycerides along with cholesteryl ester within their core, facilitates interaction with receptors on cells and regulates enzymes critical to their metabolism. Chylomicrons, lipoproteins derived from dietary fats, facilitate the transport of fatty acids, especially fat-soluble vitamins, towards the colon more efficiently. The fatty acids are conveyed from liver cells to adjacent tissues, including the heart, skeletal muscle, including fat tissue, by very low-density lipoproteins (VLDL), that are additionally composed of low-density lipoproteins (LDL).

FAs, including fat-soluble vitamins, are transported across organs via a secondary lipid transport pathway. Insulin meticulously regulates blood fatty acid levels by inhibiting the activation of cytoplasmic lipases in adipocytes. Non-esterified fatty acids (NEFAs) bound to protein are released by fat cells during fasting and when insulin function is impaired, as shown in diabetic complications. Tocopherols (vitamin E) as well as retinoids (vitamin A) bind to particular proteins to facilitate their transport from the liver to other tissues around the body.

The oxidation process of FAs generates roughly ten times the amount of ATP per molecule than glucose. Thus, it is not unexpected since energy-demanding structures such as the kidneys and cardiovascular system mostly depend on circulating lipids for sustenance. The cardiac muscle acquires FAs from three sources: non-esterified fatty acids (NEFAs), chylomicrons, and very low-

 doi:10.20944/preprints202506.2175.v1

density lipoproteins (VLDL). The importance of esterified FA intake, namely lipoprotein-derived FAs, providing a primary energy source for cardiac activity was established by studies on arterial-venous changes in the human heart carried out in the 1960s (Ballard, Danforth, Naegle, & Bing, 1960). Lipids from chylomicrons along with VLDL are lipolyzed and assimilated by the heart. The absorption and almost total utilization of FAs were confirmed by a recent and comprehensive study of metabolites in the cardiovascular systems of fasting patients undergoing cardiac catheterization. Some HF individuals have decreased absorption of fatty acids and increased use of lactate and ketones (Murashige et al., 2020). This research unexpectedly revealed little glucose consumption in the hearts of both normal subjects and patients with heart failure, and did not see increased glucose absorption in heart failure after the injection of 2-deoxyglucose.

The heart is a primary location for the absorption of non-esterified fatty acids (NEFAs). All tissues, irrespective of morphology or circulatory supply, will take in NEFAs owing to its non-specific translocation through cellular membranes. A receptor-mediated mechanism must be implied by the increased absorption rates in cardiac as well as brown adipose tissues. Translocation through the endothelium layer, movement from endothelial towards sub-endothelial tissues, and eventual lipid absorption into cardiomyocytes are a few steps involved in the heart's absorption of NEFA. The fatty acid transporter CD36 facilitates these activities in vivo (Glatz & Luiken, 2018; Son et al., 2018). The genetic loss of CD36 diminishes intra-myocellular accumulation of lipid droplets, whereas CD36 overexpression enhances lipid absorption and oxidation in the heart. Although studies did not demonstrate impaired cardiac NEFA absorption in cardiomyocyte-specific CD36 deletion mice during acute experimental conditions (Son et al., 2018), others have shown a decrease in fatty acid oxidation in ex vivo functional cardiac specimens using cardiomyocyte-specific inducible CD36 deletion animals. Consequently, it is probable that CD36 in cardiomyocytes and endothelial cells facilitates either parallel or distinct phases of a singular NEFA absorption mechanism. "CD36 being a downstream target of peroxisome proliferator-activated receptors (or PPARs)"; substantial upregulation of either PPARα (Finck & Kelly, 2002)or PPARγ (Son et al., 2007) amplifies CD36 expression, possibly leading to lipotoxicity due to heightened uptake of NEFA. The ablation of CD36 safeguarded PPARα transgenic mice against heart failure (Umbarawan et al., 2018).

The lack of lipoprotein lipase (LpL) reduces the heart's intake of the two substances, chylomicron and VLDL triglycerides, which is in line with studies on substrate extraction in the cardiac muscle. The cardiac cells synthesize the bulk of lipoprotein lipase (LpL), which also operates on the luminal layer of capillary endothelial cells, where it is tethered to glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1 (Basu & Goldberg, 2020). The dimensions as well as apoprotein composition of triglyceride-rich lipids, together with their associated amino acids, angiopoietin-like proteins (Angptls) 3, 4, and 8, collectively affect LpL functioning. The mechanism by which LpL exits the cardiomyocyte to initiate delivery from it to endothelial cell layer remains ambiguous. One explanation is that the release of LpL from cardiomyocytes as well as matrix heparan sulphate proteoglycans requires heparinase activity, which is influenced by blood flow along with hyperglycemia (C. S. Lee et al., 2022)

The reduction of LpL as well as reduced lipid absorption is, in non-stressed settings, compensated by an increased glucose uptake. In conditions of increased energy demand under tension, LpL knockout hearts exhibit increased heart failure in the presence of transaortic coarctation along with hypertension. The transgenic production of GLUT1 in cardiomyocytes improves the absorption of glucose as well as fixes a number of defects seen in cardiac LpL knockout animals (Khan et al., 2013). A similar phenotype is produced by the sustained overexpression of the specific LpL blocker angiopoietin-like protein 4 (Angptl4). These data indicate that heart LpL deletion results in cardiac dysfunction owing to inadequate substrate for ATP synthesis. Those lacking LpL have no signs of cardiac failure, maybe owing to the elevated requirement for energy of the mouse heart, that beats about eight to ten times more frequently than the human heart (Shang & Rodrigues, 2021), therefore indicating a deficiency within substrate delivery .

 doi:10.20944/preprints202506.2175.v1

The pivotal role of lipid utilization in cardiac function is shown by obesity, a disease linked to increased fatty acid oxidation. Fast insulin resistance is induced in the heart by high-fat diets; however, the phenotype is quite moderate due to the ablation of insulin signalling. Mice with GLUT1 mutations unique to the heart show a 50% reduction in glucose uptake and utilization. These animals' vulnerability to heart failure is not increased by elevated FAO. When fed a normal diet, GLUT1 transgenic mice exhibit normal cardiac function; nevertheless, when fed a high-fat diet, they develop heart failure. Therefore, compounds that promote the breakdown of both glucose and fatty acids are not harmless. According to this theory, diabetic cardiomyopathy is caused by increased fatty acid and glucose uptake in the heart. As a result, it is precise to predict that the sodium-glucose co-transporter inhibitors, as opposed to insulin sensitizers, would lessen heart failure in diabetic patients.

b. Lipids in Neurodegenerative Diseases

The proper growth along with the operation of the central nervous system (CNS) depends on lipids. The two most prevalent lipid classes in the central nervous system are sphingolipids as well as cholesterol, which are mostly present in myelin fiber (Giussani, Prinetti, & Tringali, 2020). The basic building blocks of membranes are lipids, whose composition, level of unsaturation, along with fatty acyl tail length may influence vesicle fusion and secretion, lipid raft microdomains, and membrane fluidity. Sphingosine, a ceramide metabolite, is bioactive and regulates several cellular activities, including signalling, apoptosis, mitochondrial activity, immunological response, and metabolism (G. Wang & Bieberich, 2018)

Neurodegenerative diseases are increasingly linked to lipids. Alzheimer's disease (AD), Parkinson's disease (PD), along with other neurological conditions have been related to an increasing proportion of genes relevant to lipid metabolism that have been identified by Mendelian genetics, genome-wide association studies (GWAS), and transcriptome investigations. The main genetic risk factor for AD is the apolipoprotein epsilon4 allele, which is essential for the brain's uptake of cholesterol. Recent studies using GWAS for AD have identified many risk genes linked to lipid metabolism (Chew, Solomon, & Fonteh, 2020). Lipid metabolism has been connected to a growing number of PD-related risk loci and responsible genes, such as PLA2G6/PARK14, SCARB2, SMPD1, SREBF1, as well as DGKQ, that have been recently studied (Alecu & Bennett, 2019). Since mutations in GBA are the most important genetic risk factor for Parkinson's disease, as was previously mentioned, GBA is a crucial gene in ceramide metabolism.

FAs, glycerolipids, glycerophospholipids, sphingolipids, along with cholesterol are among the lipids whose contents have changed in lipidomic analysis of tissues from AD patients and animal models (Chew, Solomon, & Fonteh, 2020). Autopsy tissue from AD patients' brains revealed deficiencies in phospholipids, particularly the proportion of ethanolamine plasmalogen to phosphatidylethanolamine. Since the balance of these two interconnected and individually controlled lipids can influence cellular death vs viability, ceramide has attracted a lot of interest due to the ceramide-sphingosine-1-phosphate (S-1-P) rheostat (Taniguchi & Okazaki, 2020). Ceramide possesses pro-inflammatory, pro-apoptotic, as well as autophagic characteristics, while S-1-P exhibits a pro-survival effect via G-protein coupled receptor signalling. By promoting the aggregation of Aβ via associations with lipid rafts—which are rich in cholesterol and sphingolipids—and ceramide-enriched exosomal membranes, ceramide contributes to the aetiology of AD (Czubowicz, Jesko, Wencel, Lukiw, & Strosznajder, 2019). Ceramide levels have been shown to be higher in a number of investigations that have looked at tissue from AD patients and animal models of the illness. Compared to age-matched controls, brain cells from AD patients with mild, moderate, to severe symptoms showed higher levels of total ceramide (Han, M Holtzman D Fau - McKeel, McKeel Dw Jr Fau - Kelley, Kelley J Fau - Morris, & Morris, 2002). Immunohistochemical study of the frontal cortex revealed increased ceramide levels in astrocytes, and ceramide concentrations were higher in the cerebrospinal fluid (CSF) in AD patients compared to ALS patients and controls. Elevated initial levels of both long-chain ceramides C22:0 as well as C24:0 were shown to be suggestive of cognitive

 doi:10.20944/preprints202506.2175.v1

decline and hippocampus shrinkage in plasma from a small group of people with AD, moderate cognitive impairment, and control subjects (Mielke et al., 2010). Increased initial concentrations of long-chain ceramides are associated with an increased risk of AD, according to a study of sera from a longitudinal experiment that included 99 women in their 80s (Mielke et al., 2012). According to Savica et al. (Savica et al., 2016), patients with AD and DLB had higher serum ceramide concentrations. It has been shown that animal models of AD have higher levels of ceramides in their brain tissue.

PD is also associated with significant changes in lipid metabolism. Even spontaneous PD patients without GBA mutations were found to have reduced GCase activity in postmortem tissue, despite the fact that it is not unexpected that GBA carriers with PD may have lipid metabolic disorders (Murphy et al., 2014). Furthermore, there was an inverse relationship between the degree of GBA enzyme activity decline and α-syn expression; however, this study did not assess big molecular weight α-syn oligomers (Murphy et al., 2014). Further research has shown that GCase enzyme activity is reduced in PD patients with sporadic PD who do not have GBA mutations, but to a lesser extent than in GBA carriers with PD. The idea of GBA enzymatic dysfunction is not a prerequisite for ceramide accumulation is supported by the fact that sporadic PD patients exhibit changed levels of glucosylceramide and ceramide, the two components of substrate and product generated by GCase enzyme activity. Extracellular vesicles extracted from Parkinson's disease (PD) patients' brain tissue showed greater levels of membrane ceramides, which improved their binding affinity for α-synuclein and led to increased α-synuclein accumulation, aggregation, and propagation (Kurzawa-Akanbi et al., 2021). These studies suggest that reduced GCase activity and the resulting alterations in the breakdown of lipids play a key role in the pathogenic process of Parkinson's disease. Finally, reducing the GCase substrate in a mouse model of GBA PD by inhibiting glucosylceramide synthase reduced insoluble α-syn oligomerisation and ubiquitinated protein accumulation, providing strong evidence that addressing impaired the metabolism of lipids in PD can lessen the underlying pathology.

Ceramides have a variety of bioactive activities, however it's unclear whether they have neurotoxic or neuroprotective qualities. It is hypothesized that decreased ceramide may also contribute to the pathophysiology of GBA-related Parkinson's disease (PD), as GBA mutations cause glucosylceramide to accumulate and perhaps lower ceramide levels. In support of this theory, GCase-deficient HEK293 cells treated with exogenous C18-Ceramide or the acid-dependent ceramidase Carmofur showed decreased levels of α-syn and restored autophagy secretion (M. J. Kim, Jeon, Burbulla, & Krainc, 2018). In iPSC-derived dopaminergic neurons heterozygous for a GBA mutation, similar outcomes were seen, with Carmofur treatment resulting in lower amounts of oxidized α-synuclein species and ubiquitinated proteins (M. J. Kim et al., 2018).

Improved ceramide as well as glucosylceramide breakdown leads to further downstream lipid alterations with unclear pathogenic consequences at this time. Glucosyl sphingosine levels were significantly higher in the double-mutant transgenic mouse model heterozygous for GBA and expressing wild-type human α-syn through its endogenous promoter, while glucosylceramide, ceramide, along with sphingosine concentrations were similar to those of wild-type GBA controls that were not expressing human α-syn (Ikuno et al., 2019). This is most likely caused by lysosomal acid ceramidase deacylating glucosylceramide, which results in the buildup of glucosyl sphingosine, which is also seen in Gaucher's disease. When glutamyl sphingosine exits the lysosome, non-lysosomal GBA2 hydrolyses it into ceramide, sphingosine, and sphingosine-1-phosphate (Abed Rabbo, Khodour, Kaguni, & Stiban, 2021), causing complex and poorly understood alterations in downstream lipids.

Due to their concentration in late endosome-lysosomes, phospholipid bis(monoacylglycerol)phosphate (BMP) molecules are important lipids in neurodegeneration. Cultured neurons along with an induced knockout mouse model exhibit increased exosome secretion when Vps34, a lipid kinase required for the synthesis of phosphatidylinositol-3-phosphate (PI3P), which is reduced in the AD brain and is an important regulator of endosomal trafficking, is inhibited

 doi:10.20944/preprints202506.2175.v1

(Miranda et al., 2018). Lysosomal stress increased the generation of exosomes, and C-terminal APP fragments were identified as exosomal cargo during this time. Along with ceramides as well as sphingomyelin, the resulting exosomes showed a notable concentration of BMPs (Miranda et al., 2018). Interestingly, several urine BMPs were shown to be associated with bearers of the LRRK2 G2019S mutant who had cognitive decline and Parkinson's disease (Alcalay et al., 2020). BMPs may be a biomarker for lipid alterations associated with neurodegeneration involving endo-lysosomal failure, since LRRK2, the main genetic component in Parkinson's disease, is also related to endo-lysosomal function (Erb & Moore, 2020).

Changes in the breakdown of lipids may potentially contribute to neurodegenerative illness by directly affecting aggregation-prone proteins. This claim about α-syn is supported by substantial evidence. In the presence of polyunsaturated FAs, α-syn oligomerizes into insoluble clusters; saturated fatty acids do not cause this process, while oligomerization is influenced by the length of the fatty acyl chain. When α-syn interacted with the lipid bilayer in an in vitro system utilizing microscopic uni-lamellar vesicles, it took on an amyloid-like form (Galvagnion et al., 2015). Studies show that in Alzheimer's disease, exposure to specifically engineered phospholipid vesicles accelerates Aβ fibrillization and increases binding because of the vesicles' prominent membrane curve (~30 nm diameter; (Sugiura, Ikeda, & Nakano, 2015). However, it is unknown if the level of Aβ aggregation seen in this in vitro study is comparable to that observed in exosomes or synaptic vesicles (SVs) in vivo.

c. Inflammation and Lipids

Lipid metabolism is crucial in regulating inflammation in both acute and chronic illnesses. Dietary and endogenous lipids exhibit both pro-inflammatory and anti-inflammatory characteristics, even though lipoprotein profiles along with composition influence atherogenic and immunomodulatory mechanisms. Therapeutic tactics and dietary treatments aimed at lipid metabolism are potential methods to reduce inflammation and enhance immune response in people with obesity, cardiovascular disease, chronic metabolic along with inflammatory illnesses, autoimmunity, and pathogen defense (Andersen, 2018, 2022; Andersen, Murphy, & Fernandez, 2016).

Diverse lipid species exhibit immunomodulatory and pro-/anti-inflammatory characteristics, including fatty acids including their metabolites, sterols, complex lipids (such as glycerophospholipids as well as sphingolipids), and lipoproteins. Kumar et al. examined the distinct impacts of polyunsaturated fatty acids and their metabolites on immunological function and health consequences in humans. The recent developments of how fatty acids influence the inflammatory activity of various immune cell subsets (e.g., T cells, neutrophils, macrophages) by modulating membrane fluidity, acting as precursors for bioactive oxylipin derivatives, and additionally activating membrane-associated pattern recognition receptors (PRRs), including those in the toll-like receptor (TLR) family, as well as functioning as agonists for members of the peroxisome proliferator-activated receptor (PPAR) family of nuclear receptors—all of which play a role in regulating cellular inflammatory responses. The recent clinical trials examined the beneficial impact of n-3 polyunsaturated fatty acids as well as Mediterranean-style eating habits on various health outcomes, including coronary heart disease, obesity, preservation of muscle strength in ageing, chronic kidney disease, allergies, and depression. Kumar et al. examined current advancements in analytical mass spectrometry techniques and statistical methodologies for lipidomics research, highlighting the need for more standardization and comparative analysis as the field evolves (Kumar et al., 2019) (Table 1).

Table 1. Effects of Various Lipids and Their Metabolites on Immune Cells.

Lipid	Source	Immune Cell	Function	Reference
FA 18:0, 18:2, 18:3, 20:4	Endogenous	Macrophages, including hepatocytes	Acts as a ligand for PPAR-α and PPAR-γ receptors, regulating immune responses	(Kliewer et al., 1997)

 doi:10.20944/preprints202506.2175.v1

FA 18:2 n-6	Dietary intake	Dendritic cells	Reduces LN infiltration and T-cell activation; decreases IL-12 and increases IL-10	(Draper et al., 2014)
FA 18:3 n-3	Supplement	Alveolar macrophages	Enhances phagocytosis and increases TNF-α production	(Turek, Schoenlein, Clark, & Van Alstine, 1994)
FA 18:3 n-3	Oral	T-cells	Suppresses T-cell proliferation	(Rossetti, Seiler, DeLuca, Laposata, & Zurier, 1997)
FA 20:4	PLA2-II mediated release of arachidonic acid (no metabolism)	Neutrophils	Increases mac-1 (CD-11b/CD18) expression, supporting immune response	(Takasaki, Kawauchi, Yasunaga, & Masuho, 1996)
FA 20:5	Synthetic	Mast cells	Reduces mast cell activation	(X. Wang, Ma, Kang, & Kulka, 2015)
FA 20:4, FA 20:5, FA 22:6	Endogenous, supplement	Neutrophils	Promotes adhesion to endothelial cells (CD11a and CD11b)	(Bates, Ferrante, Harvey, & Poulos, 1993)
FA 22:6 n-3	Synthetic	Dendritic cells	Increases IL-12 levels while reducing IL-6 and IL-10	(Zapata-Gonzalez et al., 2008)
Leukotriene B4	Endogenous, supplement	Neutrophils	Facilitates adhesion to endothelial cells (CD11a and CD11b)	(Bates et al., 1993)
PGE2	Endogenous	Lymphocytes	Suppresses TH1 response by inhibiting IL-12 production	(Van der Pouw Kraan, Boeije, Smeenk, Wijdenes, & Aarden, 1995)
Palmitic acid (C16:0)	Supplement	NLRP3 inflammasome	Increases production of IL-1β and IL-18	(Sui, Luo, Xu, & Hua, 2016)
Oleic acid (C18:1)	Supplement and dietary sources	NLRP3 inflammasome	Reduces IL-1β, TNF-α, and IL-6 levels	(Wen et al., 2011)

Using ex vivo peripheral blood mononuclear cells (PBMCs) from patients with metabolic syndrome, Sureda et al. (Sureda et al., 2020) described the unique effects of free non-esterified saturated (palmitic acid), monounsaturated (oleic acid), n-3 polyunsaturated (α-linolenic and docosahexaenoic acid (DHA)), and n-6 polyunsaturated (γ-linolenic alongside arachidonic acid (AA)) fatty acids on inflammatory gene expression and H2O2 production. With the conditions of metabolic and fat tissue dysfunction marked by increase in blood concentrations in unrestricted non-esterified fatty acids, this translational research approach mimics the physiological environment of diverse immune cell populations within the cardiovascular system. By reducing the mRNA expressions of interleukin 6 (IL-6), nuclear factor κ B (NFκB), as well as tumor necrosis factor α (TNFα) in lipopolysaccharide (LPS)-stimulated peripheral blood mononuclear cells (PBMCs), Sureda et al. (Sureda et al., 2020) showed that DHA had the strongest anti-inflammatory effect. Conversely, oleic acid decreased the expression of cyclooxygenase 2 (COX2) while increasing the expression of TLR2 in both LPS-stimulated and non-stimulated PBMCs. Remarkably, both the anti-inflammatory α-linolenic acid and the traditionally pro-inflammatory arachidonic acid (AA) exhibited pro-oxidative along with anti-inflammatory properties, as evidenced by increased H2O2 production and decreased inflammatory gene expression in lipopolysaccharide-stimulated peripheral blood mononuclear cells (PBMCs). These findings highlight the complexity and diversity of evaluating the inflammatory

 doi:10.20944/preprints202506.2175.v1

characteristics of fatty acids in varied cell types and complex disease states, such metabolic syndrome, which are marked by varying degrees of associated risk factors. To determine if these findings are consistent with inflammation-induced functional and protein-level changes in immune cells and whether similar ex vivo immunological reactions to fatty acids are seen in individuals without metabolic syndrome, further investigation is required.

Both Hellström et al. (Hellstrom et al., 2020) and Yakah et al. (Yakah et al., 2021), investigated the relationship between fatty acid profiles as well as markers of inflammation in both infants along with preterm animal models, offering proof that emphasizes the importance of preserving AA:DHA ratios to improve health in infancy.

Yakah et al. (Yakah et al., 2021) investigated the effects of several lipid drops on inflammatory immune responses to Escherichia coli-derived LPS in preterm pigs, which at 32 weeks gestation and later show similar developmental stages and clinical traits to human newborns. Since lipid emulsions rich in soybean oil or n-3 polyunsaturated fatty acids are frequently given to preterm newborns yet associated with different health outcomes, this study has important therapeutic implications. Importantly, whereas elevated levels of AA in the cell membrane are associated with detrimental health outcomes in chronic inflammatory diseases, they may provide vital protection against infections in premature infants. While n-3 polyunsaturated FA-rich lipid drops reduced immunostimulatory sphingomyelin metabolites and IL-1β concentrations in response to LPS, 100% soybean oil administration resulted in increased plasma AA:DHA ratios as well as levels of AA-derived prostaglandins as well thromboxanes. This suggests that fish-oil-based lipid emulsions may weaken pathogen defenses in preterm infants.

The association between blood DHA as well as AA levels and systemic inflammatory markers was examined by Hellström et al. (Hellstrom et al., 2020) in 90 preterm infants (less than 28 weeks gestation), with as well as without early systemic inflammation, which is defined by elevated levels of C-reactive protein (>20 mg/L) and IL-6 (>1000 pg/mL) within 72 hours of birth, regardless of whether the infants' blood cultures tested positive for bacteria or fungi, which would indicate sepsis. While there were no differences in AA levels, extremely preterm neonates with early systemic inflammation had lower DHA concentrations in cord blood on postnatal day 1 than those without. Similarly, although cord blood IL-6 levels showed a negative relationship with DHA and AA levels, there was no discernible difference in DHA and AA levels between infants regardless of fetal inflammatory response condition or histological chorioamnionitis, which are defined by umbilical cord inflammation with or without neutrophil infiltration into fetal stem vessels, as well as maternal neutrophil penetration through the amnion, chorionic plate, or subchorionic space. While the injection of lipid emulsions rich in certain fatty acids may vary in their ability to modulate inflammatory responses, research suggests that blood concentrations of DHA and AA may influence some clinical results in preterm neonates. Furthermore, these studies suggest possible differences across taxa (humans vs pigs) as well as the classification of preterm birth based on gestational age (preterm versus very preterm, for example).

In a different preliminary study, Laparra Llopis et al. (Laparra Llopis, Brown, & Saiz, 2020) demonstrated the possible impact of non-lipid bioactive food ingredients on lipid-immune pathways and the correlation between hepatic fatty acid composition as well as immune inflammation in a mouse model for hepatocellular carcinoma (HCC) fed a high-fat diet. The investigation team found that the PI components of these bioactive foods reduced mortality and inhibited HCC tumor advancement, which was correlated with a decrease in hepatic triglyceride accumulation. This was in accordance with previous studies that identified the immunomodulatory as well as macrophage-polarizing characteristics of glucosides compared to Chenopodium quinoa ("quinoa") as well as glycoproteins from Salvia hispanica ("chia seeds") exhibiting serine-type protease inhibitor (PI) activity. Better liver health was associated with the PI generated from Chenopodium quinoa, which also improved hepatic PUFA enrichment and reduced plasma hepcidin. Dietary PIs further increased the levels of immune markers F4/80 and CD74, leading to better hepatic cytokine as well as chemokine profiles. These findings imply a more robust immune response to combat HFD-induced

 doi:10.20944/preprints202506.2175.v1

immunosuppression and the progression of HCC. Additionally, PI helped to mitigate negative changes in intestinal immune markers, but it did not fully restore the altered microbiome profiles associated with high-fat diets and HCC. In addition to providing evidence that dietary and non-lipid food components may be used as therapeutic tools to target endogenous lipid metabolism and enhance immune results in chronic disease contexts, these findings are consistent with other research that highlights the importance of the lipid-immune relationship in cancer pathophysiology (G. Yu, Yang, Peng, & Lv, 2021).

Among the different kinds of lipids or derivatives, lipoproteins may also affect inflammation along with immune cell function. Because of their capacity to carry biologically active lipids, anti-inflammatory as well as antioxidant proteins, and regulate immune cell activation by promoting cellular cholesterol efflux and rearranging receptors for pattern recognition and associated coreceptors inside membrane lipid rafts, high-density lipoproteins (HDL) are known for their various immunomodulatory as well as anti-inflammatory properties. In their first research publication, Huang et al. (J. Huang et al., 2020) underlined the importance of HDL lipid peroxidation in preserving its anti-inflammatory along with cholesterol-accepting qualities. Researchers found that the pro-oxidative enzyme myeloperoxidase (MPO) may be inhibited by paraoxonase 1 (PON1), an HDL-associated antioxidant enzyme that neutralizes oxidized phosphatidylcholine moieties and prevents lipid hydroperoxides from building up in lipoproteins. As a result of this inhibition, less malondialdehyde (MDA) is produced, which may covalently crosslink HDL-associated apolipoprotein A1 (apoA1) and hinder HDL's advantageous anti-inflammatory and cholesterol-effluxing capabilities. The study's findings suggested that PON1 and HDL function may work together to influence the progression of CVD in patients with familial hypercholesterolemia (FH), an autosomal dominant condition marked by significantly elevated levels of low-density lipoprotein cholesterol (LDL-C) and early onset cardiovascular disease (CVD). These individuals also showed decreased PON1 activity, increased MDA-apoA1 crosslinking, and impaired cholesterol efflux capacity. They also found that the negative effects of MPO on HDL function were mitigated by the reactive dicarbonyl scavengers pentyl-pyridoxamine (PPM) and 2-hydroxybenzylamine (2-HOBA). According to the results, PON1 and HDL antioxidant pathways may be targeted in order to improve the outcomes of immunomodulatory and cardiovascular diseases.

Lipids and Inflammation

Lipids play a crucial role in inflammation both as structural components of cell membranes and as bioactive signaling molecules. Among them eicosanoids are a class of lipid-derived mediators synthesized from arachidonic acid and other polyunsaturated fatty acid (PUFAs).They are central to the regulation of inflammation, with pro - inflammatory and anti-inflammatory effects.

Eicosanoids and Inflammation

Eicosanoids have diverse effects on inflammation depending on their type and context:

Different types of Eicosanoids are Prostaglandins, Thromboxanes, Leukotrienes, Lipoxins which regulate inflammation in different conditions. **Prostaglandins (PGs)** are lipid compounds derived from arachidonic acid that play a crucial role in the inflammatory response. Prostaglandins are synthesized via the cyclooxygenase (COX) pathway, which includes COX-1 and COX-2 enzymes. COX-1 is constitutively expressed and involved in homeostatic functions, whereas COX-2 is induced during inflammation and leads to the production of pro-inflammatory prostaglandins such as PGE_2 and PGI_2 (J. Liu, 2025). PGE_2 is the most studied prostaglandin in inflammation. It promotes vasodilation, enhances leukocyte infiltration, and modulates cytokine production. In rheumatoid arthritis, increased levels of PGE_2 correlate with disease severity, making it a potential biomarker and therapeutic target (J. Liu, 2025). Despite their role in inflammation, some prostaglandins contribute to resolution and tissue repair. Lipid mediators derived from PGs, such as lipoxins and resolvins, help dampen excessive immune responses and promote healing (Fukuishi, 2025). This dual nature

 doi:10.20944/preprints202506.2175.v1

makes prostaglandins an interesting target for drug development, as selective modulation could lead to better therapeutic outcomes. **Thromboxanes (TXs)** is a bioactive lipid derived from arachidonic acid via the cyclooxygenase (COX) pathway. It plays a vital role in **hemostasis, vasoconstriction, platelet aggregation, and immune cell recruitment.** Thromboxane A_2 (TXA_2) is synthesized from prostaglandin H_2 (PGH_2) through the action of thromboxane synthase. TXA_2 acts via the thromboxane-prostanoid (TP) receptor, which is present on platelets, endothelial cells, smooth muscle cells, and immune cells. This activation leads to different responses like: Platelet aggregation which can cause enhanced thrombosis and inflammation, Vasoconstriction which reduces blood flow and increasing local inflammatory responses, Leukocyte recruitment which stimulate neutrophil and monocyte adhesion, cytokine release which promote TNF-α, IL-1β, and IL-6 production, amplifying inflammation (Paredes, Hernandez-Cortes, Falahat, Rancan, Arias-Diaz, & Vara, 2024). **Leukotrienes,** particularly leukotriene B4 (LTB4) , which is a potent chemoattractant for neutrophils and cysteinyl leukotrienes (CysLTs: LTC4,LTD4 and LTE4), which are primarily involved in bronchoconstriction and increased vascular permeability (Ghorbanzadeh, Azizolahi, Behmanesh, Forouhar, Foroughinia, & Nabizadeh, 2025). They contribute to neutrophil recruitment, increased vascular permeability, and bronchoconstriction, making them central players in allergic reactions and airway inflammation (Rahmawati et al., 2024). Moreover, leukotriene receptor antagonists, such as montelukast, have been widely used to manage asthma and allergic rhinitis due to their ability to block the pro-inflammatory effects of CysLTs (Conway, White, Borish, Shaker, & Lee, 2024).

3.2 Lipoxins (LXs) are specialized pro-resolving lipid mediators derived from arachidonic acid that play a pivotal role in orchestrating the resolution phase of inflammation (Brennan, Kantharidis, Cooper, & Godson, 2021). Unlike pro-inflammatory eicosanoids, lipoxins act as endogenous "braking signals" to dampen excessive immune responses and restore tissue homeostasis (Chiang & Serhan, 2020). Lipoxins, primarily lipoxin A_4 (LXA_4) and lipoxin B_4 (LXB_4), exert their anti-inflammatory effects through the formyl peptide receptor 2 (FPR2/ALX) (Serhan & Levy, 2018). Activation of this receptor reduces neutrophil recruitment, stimulates macrophage efferocytosis, and inhibits pro-inflammatory cytokine production (Levy, Clish, Schmidt, Gronert, & Serhan, 2001). Additionally, lipoxins modulate endothelial cell function, preventing excessive vascular permeability and tissue damage (Pils, Terlecki-Zaniewicz, Schosserer, Grillari, & Lammermann, 2021). Several studies highlight the therapeutic potential of lipoxins in inflammatory diseases such as asthma, arthritis, and cardiovascular conditions (Chandrasekharan & Sharma-Walia, 2015; Serna, Mosquera Escudero, & García-Perdomo, 2023). For example, in asthma, lipoxins reduce leukocyte infiltration and mucus hypersecretion, mitigating airway inflammation (Serna, Mosquera Escudero, & García-Perdomo, 2023)In cardiovascular diseases, lipoxins help resolve vascular inflammation and prevent atherosclerotic plaque progression (Serhan, Chiang, & Dalli, 2015).

Lipoxins promote the resolution of inflammation through multiple mechanisms:

1. Inhibition of Neutrophil Recruitment and Activation: Lipoxins counteract the pro-inflammatory actions of leukotrienes by suppressing neutrophil migration, adhesion, and activation (Basil & Levy, 2016). LXA4 binds to its receptor FPR2/ALX (formyl peptide receptor 2/lipoxin A4 receptor), inhibiting neutrophil chemotaxis and reducing oxidative burst activity (Serhan & Levy, 2018).

2. Promotion of Macrophage-Mediated Clearance: A crucial step in resolving inflammation is the clearance of apoptotic cells (efferocytosis). Lipoxins enhance macrophage phagocytosis of apoptotic neutrophils, thereby preventing secondary necrosis and the propagation of inflammation (Schwab, Chiang, Arita, & Serhan, 2007).

3. Regulation of Pro-Inflammatory Cytokines: Lipoxins inhibit the release of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 while promoting the production of anti-inflammatory cytokines such as IL-10 (Hodges et al., 2017). This shift creates a favorable environment for inflammation resolution.

4. Restoration of Tissue Homeostasis: Lipoxins facilitate tissue regeneration by modulating fibroblast activity and promoting wound healing (Ortiz-Munoz, Mallavia, Bins, Headley, Krummel,

 doi:10.20944/preprints202506.2175.v1

& Looney, 2014). They also reduce vascular permeability, thereby preventing excessive fluid accumulation in inflamed tissues.

3.3. Sphingolipids and inflammatory Responses

Sphingolipids are a class of bioactive lipids that play crucial roles in cellular processes, including inflammation, apoptosis, and immune responses. These lipids include ceramide, sphingosine, and sphingosine-1-phosphate (S1P), which regulate inflammatory signaling pathways (Hannun & Obeid, 2018). Ceramide, a central molecule in sphingolipid metabolism, is known to induce inflammatory responses by activating signaling cascades such as nuclear factor-kappa B (NF-κB) and mitogen-activated protein kinases (MAPKs) (Maceyka, Harikumar, Milstien, & Spiegel, 2012). These pathways promote the production of pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1 beta (IL-1β), which are key mediators in inflammatory diseases such as atherosclerosis and rheumatoid arthritis (Chaurasia & Summers, 2021). S1P, another crucial sphingolipid metabolite, exhibits dual roles in inflammation. It can act as a pro-inflammatory molecule by binding to its G-protein-coupled receptors (S1PR1-5) and modulating immune cell trafficking and vascular integrity (Gaire & Choi, 2021). In contrast, S1P also has anti-inflammatory effects by promoting the resolution of inflammation and tissue repair mechanisms (Spiegel & Milstien, 2003). Dysregulation of sphingolipid metabolism (Xie et al., 2025) has been implicated in various chronic inflammatory disorders, including inflammatory bowel disease (IBD), asthma, and neuroinflammatory diseases like multiple sclerosis (Green, Maceyka, Cowart, & Spiegel, 2021). Targeting sphingolipid signaling has emerged as a potential therapeutic strategy, with sphingosine kinase inhibitors and S1P receptor modulators being explored for treating inflammatory diseases (Brinkmann et al., 2010).

In conclusion, sphingolipids play a pivotal role in inflammatory responses through complex signaling pathways that regulate immune cell function and cytokine production. Understanding their mechanisms provides insights into developing novel therapeutic interventions for inflammatory disorders.

3.4. Lipid Signaling Pathways in Neurodegeneration

Lipid signaling plays a crucial role in the regulation of neuronal function and survival. Various lipid molecules, including sphingolipids, phospholipids, and cholesterol derivatives, are key modulators of cellular signaling pathways that control inflammation, oxidative stress, and cell death. In neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS), alterations in lipid metabolism and signaling contribute to disease progression. This article explores the major lipid signaling pathways implicated in neurodegeneration, highlighting recent research and potential therapeutic strategies.

A. Role of Sphingolipid signaling in neurodegeneration

Sphingolipids, particularly ceramides and sphingosine-1-phosphate (S1P), regulate cell fate by mediating apoptosis, autophagy, and inflammation. Ceramide accumulation has been observed in neurodegenerative diseases and is linked to neuronal apoptosis and synaptic dysfunction (Alaamery et al., 2021; Green et al., 2021). S1P, on the other hand, plays a neuroprotective role by activating pro-survival pathways, including the PI3K/Akt pathway. The PI3K/Akt pathway is critical for neuronal survival, as it prevents apoptosis and oxidative stress. S1P binds to its receptors (S1PR1–5), triggering a cascade that includes activation of PI3K, which in turn phosphorylates and activates Akt. This activation promotes cell survival by inhibiting pro-apoptotic factors like Bad and caspase-9, while stimulating survival proteins such as Bcl-2. It was observed that S1P protects against oxidative stress-induced neuronal death by activating the PI3K/Akt pathway in neurodegenerative models. Their findings suggest that targeting S1P metabolism could be a therapeutic strategy for AD and PD ((Czubowicz et al., 2019)). S1P counteracts neuroinflammation and apoptosis in AD by activating PI3K/Akt and ERK pathways, reducing neurotoxic effects. Disruptions in S1P receptor 1 (S1PR1) signaling impair PI3K/Akt activation in AD mouse models, leading to neuronal loss and cognitive

 doi:10.20944/preprints202506.2175.v1

deficits. S1P signaling through PI3K/Akt enhances neuronal resilience against oxidative stress, reducing dopaminergic neuron loss in PD models (W. Wang, Zhao, & Zhu, 2023).

1. Phospholipase and lipid metabolism

Phospholipase A2 (PLA2) regulates lipid homeostasis and inflammation. Overactivation of PLA2 leads to excessive production of arachidonic acid and eicosanoids, exacerbating neuroinflammation in diseases like multiple sclerosis (MS) and AD (Monaghan, 2025). This process disrupts neuronal membranes and promotes neurotoxicity.

2. Lipid Peroxidation and Ferroptosis

Lipid peroxidation, a form of oxidative damage to lipids, contributes to neurodegeneration. The ferroptosis pathway, characterized by iron-dependent lipid peroxidation, is implicated in conditions such as PD and ALS (Lin et al., 2022; Russo et al., 2025). The Nrf2 signaling pathway has been identified as a key regulator of lipid metabolism, offering a potential therapeutic target.

3. Cholesterol and Alzheimer's Disease

Cholesterol metabolism is vital for synaptic function, but its dysregulation is a hallmark of neurodegenerative diseases. Impaired cholesterol transport due to mutations in apolipoprotein E (ApoE) leads to amyloid-beta plaque formation in AD (Mesmin, 2025). The modulation of lipid rafts and their interaction with amyloid precursor protein (APP) influences disease progression.

4. Wnt Signaling and Lipid interaction

The Wnt signaling pathway is involved in neuronal survival and plasticity. Studies have shown that lipids influence Wnt signaling by modulating its receptors and downstream targets (Jia, Bian, & Chang, 2025). Disruptions in this pathway have been linked to neurodevelopmental and neurodegenerative disorders.

3.5. Lipid Accumulation and Neuroinflammation

Lipid metabolism plays a critical role in maintaining brain homeostasis, and its dysregulation can lead to neuroinflammation, a key pathological feature of various neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), and multiple sclerosis (MS). Lipid accumulation in the central nervous system (CNS) can trigger immune responses, leading to chronic inflammation that exacerbates neuronal damage**.** The brain is highly enriched in lipids, including phospholipids, sphingolipids, and cholesterol, which are essential for synaptic function, neuronal survival, and myelin sheath integrity (Estes Raja Elizabeth, 2021), However, disturbances in lipid metabolism, such as excessive accumulation of cholesterol and sphingolipids, have been linked to neuroinflammation and neurodegeneration (Zhao, Zhang, Sanders, & Duan, 2023).

Mechanisms of Lipid-Induced Neuroinflammation

Lipid accumulation in the CNS contributes to neuroinflammation through several mechanisms:

1. **Microglial Activation:** Excessive lipids can activate microglia, the primary immune cells of the CNS, leading to the release of pro-inflammatory cytokines such as interleukin-1β (IL-1β), tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6) (Shao, Wang, Wu, Wu, & Zhang, 2022).
2. **Oxidative Stress:** Lipid peroxidation products, such as malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE), contribute to oxidative damage, exacerbating neuroinflammation (Nixon, 2013; Stern & Johnson, 2008).
3. **Dysregulated Lipophagy:** Impairment of lipophagy, a lipid clearance mechanism mediated by autophagy, results in lipid droplet accumulation in microglia and astrocytes, leading to persistent inflammation (Haidar, Loix, Bogie, & Hendriks, 2021)

Dietary Lipids and Aging

Effects of Dietary Interventions

Dietary lipid interventions have a profound impact on human health, influencing metabolic processes, cardiovascular function, and overall disease risk. Lipids, including saturated fats,

 doi:10.20944/preprints202506.2175.v1

unsaturated fats, and essential fatty acids, play crucial roles in cellular function, inflammation, and energy metabolism. The quality and quantity of dietary lipids consumed can significantly affect lipid profiles, inflammatory markers, and chronic disease progression.

One of the most well-documented effects of dietary lipid interventions is their role in cardiovascular health. Replacing saturated fats with unsaturated fats, particularly omega-3 fatty acids, has been shown to reduce low-density lipoprotein (LDL) cholesterol levels, lower inflammation, and decrease the risk of atherosclerosis and coronary artery disease (Dawczynski et al., 2025). Omega-3 fatty acids, found in fatty fish and flaxseeds, are particularly effective in improving endothelial function and reducing triglyceride levels, making them essential components of heart-healthy diets.

Additionally, lipid interventions play a crucial role in metabolic health. High-fat, low-carbohydrate diets, such as the ketogenic diet, have gained attention for their ability to improve insulin sensitivity and promote weight loss in individuals with type 2 diabetes (Kolivas, Fraser, Schweitzer, Brukner, & Moschonis, 2025). By shifting energy metabolism from glucose to fatty acids and ketones, these diets can enhance metabolic flexibility and reduce reliance on insulin. However, long-term adherence and potential cardiovascular risks associated with high saturated fat intake remain areas of ongoing research.

Lipid intake also influences inflammatory pathways. Diets rich in monounsaturated and polyunsaturated fats, such as the Mediterranean diet, have been shown to reduce systemic inflammation, partly through modulation of lipid rafts in immune cells (Lai, Gervis, Parnell, Lichtenstein, & Ordovas, 2025). In contrast, excessive intake of trans fats and omega-6 fatty acids, commonly found in processed foods, has been linked to chronic inflammation and an increased risk of metabolic syndrome.

Beyond metabolic and cardiovascular health, dietary lipid interventions impact cognitive function and neurodegenerative diseases. Omega-3 fatty acids, particularly docosahexaenoic acid (DHA), are essential for maintaining neuronal integrity and synaptic plasticity. Studies have demonstrated that diets enriched with omega-3s can reduce the risk of Alzheimer's disease and age-related cognitive decline by lowering neuroinflammation and oxidative stress (Liang, Zhao, Jin, & Hou, 2025). Conversely, diets high in saturated fats may promote neurodegeneration by increasing oxidative damage and impairing blood-brain barrier function.

Furthermore, lipid interventions play a role in gut health. Recent studies suggest that dietary fats influence the gut microbiome, which in turn affects systemic inflammation and metabolic health. High-fat diets rich in healthy fats, such as olive oil, have been associated with a more diverse gut microbiota, while excessive saturated fat intake may promote dysbiosis and contribute to inflammatory diseases (Busanello, Menezes, Koller, Volz Andreia, & de Almeida, 2025).

Interestingly, dietary interventions and lifestyle modifications have been shown to mitigate some of these age-related lipid changes. For instance, diets rich in omega-3 fatty acids and antioxidants can help preserve membrane integrity and reduce lipid peroxidation, thereby improving metabolic and cognitive health in aging individuals (P. Liu, Chen, Jiang, & Diaz-Cidoncha Garcia, 2025). Additionally, caloric restriction and intermittent fasting have been associated with improved lipid metabolism, reducing the accumulation of harmful lipid species and promoting longevity. Lipid composition undergoes significant alterations with age, influencing health and disease progression. Understanding these changes provides valuable insights into aging-related conditions and highlights potential therapeutic strategies to promote healthy aging.

Personalized Dietary Approaches

Personalized dietary lipid approaches focus on tailoring fat intake to an individual's genetic profile, metabolic needs, and health conditions. Advances in nutrigenomics and lipidomics have allowed researchers to identify how different lipid types affect people based on genetic variations, lifestyle, and microbiome composition. These approaches offer a promising way to optimize health, manage metabolic disorders, and reduce disease risk.

 doi:10.20944/preprints202506.2175.v1

One of the primary motivations behind personalized lipid interventions is the variation in lipid metabolism among individuals. Genetic differences influence how efficiently a person processes and utilizes dietary fats. For example, polymorphisms in the *Apolipoprotein E (APOE)* gene affect lipid transport and metabolism, altering the risk of cardiovascular diseases and Alzheimer's disease (Krishnamurthy et al., 2024; C. C. Liu, Liu, Kanekiyo, Xu, & Bu, 2013). Individuals with the *APOE4* variant may benefit from reducing saturated fat intake and increasing omega-3 fatty acids to improve lipid profiles and cognitive function.

Beyond genetics, gut microbiota plays a crucial role in lipid metabolism and inflammation. The gut microbiome composition affects how dietary lipids are digested and absorbed, influencing cholesterol metabolism and the production of bioactive lipid molecules (Brown, Clardy, & Xavier, 2023). Recent research suggests that specific probiotic and prebiotic interventions can modify lipid absorption and reduce inflammation, making microbiome-targeted dietary adjustments a promising strategy in personalized nutrition.

Personalized lipid approaches are also essential in managing metabolic disorders such as obesity and diabetes. Low-carbohydrate, high-fat diets, such as the ketogenic diet, have been effective in improving insulin sensitivity and promoting weight loss, but their success varies among individuals. Some people respond better to higher monounsaturated or polyunsaturated fat intake, while others benefit from reduced overall fat consumption (DiNicolantonio & O'Keefe, 2022). Understanding individual lipid responses can help optimize dietary recommendations for metabolic health.

Cardiovascular health is another area where personalized dietary lipid strategies are beneficial. Traditional dietary guidelines recommend reducing saturated fat intake to lower LDL cholesterol and cardiovascular risk. However, emerging evidence suggests that individual responses to dietary fats are highly variable, with some people experiencing no adverse effects from moderate saturated fat intake (Berisha, Hattab, Comi, Giglione, Migliaccio, & Magni, 2025). Omega-3 fatty acids from fish oil or plant sources are commonly recommended for cardiovascular protection, but their effectiveness depends on an individual's genetic and metabolic background.

Personalized lipid approaches also extend to cognitive health. Omega-3 fatty acids, particularly docosahexaenoic acid (DHA), are essential for brain function, and deficiencies have been linked to neurodegenerative diseases. However, the extent of benefit from DHA supplementation depends on genetic factors, age, and baseline lipid status (Cuffaro, Lamminpaa, Niccolai, & Amedei, 2024). This highlights the need for tailored dietary strategies to support brain health throughout life. Personalized dietary lipid approaches offer a more effective way to optimize health by considering genetic, metabolic, and microbiome variations. As research advances, integrating precision nutrition into dietary guidelines will help improve disease prevention and treatment outcomes.

Energy Regulation and Lipid Metabolism

Lipid metabolism plays a fundamental role in energy regulation, influencing processes such as energy storage, mobilization, and expenditure. Lipids serve as the body's primary energy reservoir, with triglycerides stored in adipose tissue acting as a long-term fuel source. When energy demand increases, lipid breakdown (lipolysis) releases free fatty acids into circulation, providing an efficient means of sustaining cellular metabolism.

A key regulator of lipid metabolism is the balance between lipogenesis (fat synthesis) and lipolysis (fat breakdown). Insulin, secreted in response to high glucose levels, promotes lipogenesis by stimulating fatty acid and triglyceride synthesis in adipose tissue and the liver (Zhang, Lan, Ma, Ji, & Li, 2025). Conversely, during fasting or energy scarcity, lipolysis is activated, driven by hormones such as glucagon, catecholamines, and cortisol, which trigger the hydrolysis of triglycerides into glycerol and free fatty acids for oxidation (Y. Wang et al., 2025). The process of β-oxidation occurs in the mitochondria, where fatty acids undergo sequential degradation to generate ATP, the primary cellular energy currency.

Mitochondria play a central role in lipid metabolism by converting fatty acids into energy through oxidative phosphorylation. Dysregulation of mitochondrial function has been implicated in

 doi:10.20944/preprints202506.2175.v1

metabolic disorders such as obesity, diabetes, and cardiovascular disease (J. H. Lee et al., 2025). Emerging research highlights the impact of mitochondrial efficiency in determining energy expenditure, with variations in mitochondrial function influencing an individual's propensity for weight gain or metabolic flexibility (Das, Sauceda, & Webster, 2021; Hartsoe, Holguin, & Chu, 2024).

Lipid metabolism is also intricately linked to thermogenesis and energy homeostasis. Brown adipose tissue (BAT) and beige fat are specialized fat depots that burn lipids to generate heat, a process known as non-shivering thermogenesis. This process is mediated by uncoupling protein 1 (UCP1), which disrupts the mitochondrial proton gradient, allowing energy dissipation as heat instead of ATP synthesis (Duan, Ren, Jiang, Ding, Wang, & Wang, 2025). Activating thermogenic pathways has been proposed as a strategy for combating obesity and improving metabolic health.

Another critical aspect of lipid metabolism is its role in signalling pathways that regulate energy homeostasis. Lipid-derived molecules such as ceramides, diacylglycerols, and lysophosphatidic acids act as bioactive mediators that influence insulin signalling, inflammation, and metabolic adaptation (Shen, Zhang, Jiang, Li, Chen, & Jiang, 2025). Disruptions in lipid signalling contribute to insulin resistance and metabolic syndrome, underscoring the importance of maintaining lipid balance for overall health.

Dietary lipid composition also plays a significant role in regulating energy metabolism. Diets rich in omega-3 fatty acids, for example, have been shown to enhance fatty acid oxidation and reduce inflammation, whereas excessive consumption of saturated fats may lead to lipid accumulation and metabolic dysfunction (DiNicolantonio & O'Keefe, 2022). The gut microbiome further modulates lipid metabolism, with certain bacterial species influencing fat absorption and energy extraction from food. Lipid metabolism is central to energy regulation, affecting processes such as fat storage, oxidation, thermogenesis, and metabolic signalling. Understanding the mechanisms governing lipid metabolism offers insights into metabolic health and provides avenues for therapeutic interventions targeting obesity, diabetes, and other metabolic disorders.

Table 2.

Aspect	Key Findings	Mechanisms Involved	Reference
Lipid Metabolism & Aging	Lipid accumulation contributes to metabolic disorders in aging populations. Increased dietary inflammatory index (DII) scores correlate with metabolic dysfunction, especially in individuals under 60.	Dysregulation of lipid metabolism, increased fat storage, and inflammation accelerate metabolic aging.	(Zeb et al., 2025)
High-Fat Diets & Longevity	Diets rich in saturated fats accelerate aging by increasing oxidative stress and inflammation. Older adults show reduced metabolic flexibility, making it harder to metabolize high-fat diets efficiently.	Increased oxidative stress, mitochondrial dysfunction, and systemic inflammation.	(Leitao et al., 2022)
Omega-3 Fatty Acids & Cognitive Aging	Omega-3 polyunsaturated fatty acids (PUFAs) protect against neurodegeneration, cardiovascular diseases, and metabolic decline.	Anti-inflammatory effects, improved synaptic function, neuroprotection, and reduced lipid peroxidation.	(Haapala, 2025)

 doi:10.20944/preprints202506.2175.v1

Gut Microbiota & Lipids	Lipid composition influences gut microbiota, impacting immune function and inflammation regulation, which affect aging.	Fatty acids modulate gut bacteria diversity, improve gut barrier integrity, and regulate inflammation.	(Bezirtzoglou, Plaza-Diaz, Song, Xie, & Stavropoulou, 2025)
Cholesterol & Cognitive Decline	High cholesterol levels are linked to increased risk of Alzheimer's disease and cognitive decline. Managing cholesterol levels through diet can reduce these risks.	Affects β-amyloid plaque formation, neuronal inflammation, and synaptic plasticity.	(Kroglund, Ciesielski, Østnes, Patten, Borgå, & Jaspers, 2025)
Aging & Obesity	Aging alters metabolic response to dietary fats, increasing the risk of obesity-related diseases. Unlike diet-induced obesity, aging-related obesity is more resistant to weight loss interventions.	Hormonal changes, reduced metabolic rate, and impaired lipid oxidation.	(Z. Liu et al., 2025)
Mitochondrial Function & Aging	Lipid mediators regulate mitochondrial health, affecting cellular aging. Impaired lipid metabolism in mitochondria contributes to aging-related diseases.	Dysregulated lipid transport in mitochondria leads to oxidative stress and apoptosis.	(Gonzales, Seubert, & Paes, 2025)
Centenarian Diets & Longevity	Traditional diets high in plant-based lipids (olive oil, nuts, seeds) are associated with lower oxidative stress and better lipid profiles.	Plant-based lipids provide anti-inflammatory effects and support cardiovascular health.	(Zhang et al., 2025)
Flexitarian Diet & Aging	Moderate animal product intake combined with a plant-based diet improves lipid profiles and cardiovascular health, supporting healthier aging.	Balances essential fatty acid intake, reduces saturated fat consumption, and enhances metabolic health	(Bruns-Numrich, 2025)

Lipids in Cellular Signalling

Mechanisms of Lipid Signalling

Lipids play a crucial role in cellular signalling, acting as key regulators of various physiological processes, including cell growth, differentiation, apoptosis, and immune responses. Lipid signalling is primarily mediated by bioactive lipid molecules such as phosphoinositide's, sphingolipids, and eicosanoids, which participate in complex signalling cascades that regulate cellular functions. The mechanisms of lipid signalling involve lipid modifications, lipid-protein interactions, and the activation of signalling pathways that lead to specific cellular responses.

One of the most well-studied lipids signalling pathways involves phosphoinositide's, which are phosphorylated derivatives of phosphatidylinositol. These lipids serve as substrates for kinases such

 doi:10.20944/preprints202506.2175.v1

as phosphoinositide 3-kinase (PI3K), which phosphorylates phosphatidylinositol 4,5-bisphosphate (PIP_2) to generate phosphatidylinositol 3,4,5-trisphosphate (PIP_3) (Vanhaesebroeck, Guillermet-Guibert, Graupera, & Bilanges, 2010). PIP_3 acts as a secondary messenger that recruits and activates signalling proteins, including Akt, a key kinase involved in cell survival and metabolism. The hydrolysis of PIP_2 by phospholipase C (PLC) generates two important secondary messengers: inositol 1,4,5-trisphosphate (IP_3), which promotes calcium release from the endoplasmic reticulum, and diacylglycerol (DAG), which activates protein kinase C (PKC), further modulating cellular responses (Berridge & Irvine, 1989).

Sphingolipid metabolism also plays a significant role in lipid-mediated signalling. Sphingolipids such as ceramide, sphingosine, and sphingosine-1-phosphate (S1P) act as critical regulators of cell fate. Ceramide, often generated in response to cellular stress, induces apoptosis by activating stress-related kinases such as c-Jun N-terminal kinase (JNK) and p38 mitogen-activated protein kinase (MAPK) (Hannun & Obeid, 2018). In contrast, S1P promotes cell survival, proliferation, and immune cell trafficking through its interaction with S1P receptors, which are G-protein-coupled receptors (GPCRs) (Maceyka et al., 2012). The balance between ceramide and S1P levels is crucial for determining cell fate, highlighting the importance of lipid signalling in maintaining cellular homeostasis.

Another critical class of lipid signalling molecules is eicosanoids, which are derived from arachidonic acid metabolism. These bioactive lipids include prostaglandins, leukotrienes, and thromboxane's, which are synthesized by cyclooxygenases (COX) and lipoxygenases (LOX). Eicosanoids play essential roles in inflammation, immune responses, and vascular homeostasis (Funk, 2001). Prostaglandins, for instance, mediate pain and inflammation by activating specific GPCRs, leading to downstream signalling events that regulate gene expression and cellular responses.

Lipid rafts, specialized membrane microdomains rich in cholesterol and sphingolipids, also serve as signalling platforms that facilitate interactions between membrane proteins and intracellular signalling molecules. These lipid rafts modulate the activation of receptors such as receptor tyrosine kinases (RTKs) and GPCRs, which initiate downstream signalling pathways that control cell proliferation and immune responses (Simons & Toomre, 2000). Lipid signalling is a fundamental aspect of cellular regulation, involving multiple pathways and molecules that coordinate cellular responses. The interplay between different lipid species and their signalling mechanisms is crucial for maintaining cellular function and homeostasis, and dysregulation in lipid signalling pathways is associated with various diseases, including cancer, neurodegenerative disorders, and metabolic diseases.

Role of Specific Lipids

Increases in Membrane Cholesterol Impact on Receptor Signalling

Structural studies have identified cholesterol as a key regulator of G-protein coupled receptor (GPCR) signalling (Byrne et al., 2016). The cysteine-rich domain of Smoothened (Smo), which binds extracellular cholesterol, is essential for proper Hedgehog (Hh) signalling. This site functions as an allosteric agonist, and mutations or antagonists that block it inhibit Hh pathway activation (P. Huang et al., 2016). Additionally, sterol-induced conformational shifts are sufficient to activate Smo, though the precise origin of these sterols and their regulatory mechanisms remain unclear. Notably, increased cellular cholesterol levels have been associated with enhanced Hh signalling (Luchetti et al., 2016).

Membrane lipid composition is highly dynamic and tightly regulated. Liver X receptor (LXR) activation by elevated oxysterol levels stimulates ATP-binding cassette transporter (ABCA1) expression, promoting cholesterol efflux (Luchetti et al., 2016). If this process is impaired, cholesterol accumulation can become cytotoxic and has been linked to Toll-like receptor (TLR) activation (Joseph, Castrillo, Laffitte, Mangelsdorf, & Tontonoz, 2003). While LXR signalling is known to suppress TLR-driven inflammatory gene expression, the direct interaction between these pathways remains

 doi:10.20944/preprints202506.2175.v1

debated. Recent research in macrophages has demonstrated that LXR/ABCA1-mediated reduction of cholesterol in lipid rafts disrupts TLR4 recruitment of key adaptor proteins, such as MyD88 and TRAF6, ultimately preventing inflammatory signalling (Ito et al., 2015).

Given the profound impact of membrane composition on cellular function and disease, lipid-targeted therapies are emerging as a promising field. However, due to the complexity and dynamic nature of lipid-protein interactions, a deeper understanding of how lipids influence receptor activity is essential for the development of effective treatments.

Extent of Phospholipid Saturation and Cell Signalling

Phospholipid saturation plays a crucial role in cell signalling by influencing membrane stiffness and elasticity, enabling adaptation to varying temperatures (McIsaac, Stadnyk, & Lin, 2012). Polyunsaturated fatty acids (PUFAs) have been shown to interfere with lipopolysaccharide (LPS)-induced activation of Toll-like receptor 4 (TLR4), which subsequently promotes nuclear factor kappa B (NF-κB) signalling. Recent findings by Schoeniger et al. revealed that instead of acting at the gene expression level, PUFA enrichment alters TLR4 signalling by disrupting plasma membrane (PM) microdomains (Schoeniger, Fuhrmann, & Schumann, 2016). Lipid rafts, which serve as essential platforms for TLR4 activation by facilitating protein-ligand interactions, are particularly affected by these modifications. This study highlights how subtle changes in membrane composition can significantly influence inflammation and cellular responses (Schumann, Leichtle A Fau - Thiery, Thiery J Fau - Fuhrmann, & Fuhrmann, 2015).

Dietary intake also modulates phospholipid saturation in cell membranes. In fruit flies, Randall et al. demonstrated that dietary manipulation reduced polyunsaturated phospholipid content sevenfold, leading to a two- to threefold decline in photoreceptor responses. This reduction impacted G-protein coupled receptor (GPCR) signalling in Drosophila photoreceptors, which relies on membrane mechanical forces induced by phospholipase C (PLC)-mediated phosphoinositide (PIP) hydrolysis (Randall et al., 2015).

Additionally, diet influences Notch1 signalling in endothelial cells, affecting inflammation and atherosclerosis (Briot et al., 2015). A study showed that high cholesterol feeding in mice for three days significantly reduced Notch1 protein levels in the aortic endothelium without altering transcript levels. Although the underlying mechanism remains unclear, this reduction in Notch1 signalling led to increased inflammatory cell adhesion and robust atherosclerotic plaque formation, mirroring effects observed in Notch1-deficient mice. These findings underscore the critical role of lipid composition in regulating cellular signalling and disease progression.

Plasma Membrane Proteins Contribute to the Formation of Lipid Microdomains

Integral membrane proteins and those linked to the cytoskeleton can restrict the lateral diffusion of plasma membrane (PM) lipids, thereby retaining specific lipids within the inner leaflet. For instance, cortical actin assemblies, or asters, which bind and immobilize phosphatidylserine (PS) in the inner leaflet, have also been implicated in clustering glycophosphatidylinositol (GPI)-anchored proteins in the outer leaflet, significantly influencing cell signalling (Fritzsche et al., 2017). Proteins anchored via lipid modifications, including GPI, palmitoyl, myristoyl, or cholesterol moieties, naturally segregate into ordered lipid raft domains (M. Tomishige, Sako, & Kusumi, 1998). Additionally, cholesterol-mediated interactions between PS immobilized by asters in the inner leaflet and lipid anchors in the outer leaflet are believed to facilitate raft formation (N. Tomishige, Takahashi, Pollet, Richert, Mély, & Kobayashi, 2024).

Similarly, caveolae—vesicular invaginations of the membrane—are stabilized by scaffolding proteins such as caveolin, which interacts with cholesterol (Laude & Prior, 2004). These domains not only regulate cell signalling and endocytosis but also contribute to cholesterol transport and homeostasis, highlighting their crucial role in membrane organization and function.

 doi:10.20944/preprints202506.2175.v1

Interplay Between Lipids and Proteins in Vesicular Formation, Trafficking and Signalling

Cell signalling depends on the precise regulation of receptor delivery and removal from the cell surface, a process tightly controlled by protein-lipid interactions during exocytosis and endocytosis (Tabeling et al., 2015). Recent research has highlighted how both lipids and proteins influence vesicular trafficking and intracellular transport, which in turn modulates signalling pathways. Glycerophospholipids, for instance, play a key role in regulating vesicle movement, while glycosylphosphatidylinositol (GPI) anchors and sphingolipids affect SNARE-mediated membrane fusion by altering lipid sorting in the endoplasmic reticulum (Ogiso, Taniguchi, & Okazaki, 2015).

Vesicle formation is another critical aspect of lipid-protein interactions in signalling (Milovanovic et al., 2015). Membrane curvature, essential for vesicle budding, is driven by hydrophobic mismatch caused by protein crowding, as well as scaffolding interactions with coat proteins (Busch, Houser, Hayden, Sherman, Lafer, & Stachowiak, 2015). When membrane proteins with large extramembrane domains diffuse within the bilayer, they create molecular crowding, reducing available membrane surface area and influencing lipid organization. These lipid-protein interactions play a fundamental role in shaping vesicular transport and its impact on cellular communication.

Impact on Aging and Health

Lipids play a fundamental role in aging and health, influencing metabolic processes, cellular signalling, and disease susceptibility. As individuals age, lipid metabolism undergoes significant changes, contributing to both beneficial and detrimental health outcomes. Alterations in lipid composition impact cellular function, inflammation, and neurodegenerative diseases, making them critical targets for aging-related research and interventions.

Aging is associated with shifts in lipid metabolism that influence systemic health. One major change is an increase in circulating lipid levels, which can lead to metabolic disorders such as obesity, insulin resistance, and cardiovascular disease (Naik et al., 2025). Lipid peroxidation, driven by oxidative stress, accelerates aging by damaging cellular membranes and promoting inflammation, which is a key factor in age-related diseases such as atherosclerosis and neurodegeneration (P. Wang, Li, Kong, Zheng, & Miao, 2025). Furthermore, cholesterol homeostasis is disrupted with age, leading to an accumulation of lipid droplets in tissues, a phenomenon that has been linked to increased inflammation and reduced cellular resilience (Ahmad & Fusciello).

Lipids also play a crucial role in cognitive aging and neurodegenerative diseases such as Alzheimer's disease. Disruptions in lipid metabolism affect synaptic plasticity, myelin integrity, and neuronal survival. Studies have shown that high serum lipid levels correlate with cognitive decline, with lipid peroxidation contributing to neuronal damage and impaired brain function (Boccardi et al., 2025). Antioxidants and lipid-modulating therapies are being explored as potential strategies to counteract oxidative stress and improve lipid balance in the aging brain (Naik et al., 2025).

Mitochondrial function, which declines with age, is heavily influenced by lipid metabolism. Mitochondria rely on lipid-derived energy sources, and any disruption in lipid availability or processing can contribute to reduced energy production and increased oxidative damage. Pahal et al. (Pahal, Mainali, Balasubramaniam, Shmookler Reis, & Ayyadevara, 2025) emphasize that lipid imbalances can impair mitochondrial respiration, leading to accelerated aging and increased vulnerability to metabolic diseases.

The relationship between lipids and aging extends to immune regulation. Chronic low-grade inflammation, also known as inflammaging, is driven in part by lipid metabolism dysfunction. Elevated levels of free fatty acids and cholesterol contribute to immune dysregulation, promoting a pro-inflammatory state that exacerbates age-related conditions (Mohammed et al., 2025). Interestingly, interventions targeting lipid metabolism, such as dietary modifications and

 doi:10.20944/preprints202506.2175.v1

pharmacological approaches, have been shown to reduce inflammation and improve metabolic health in aging individuals.

Lipid-lowering therapies, including statins, are widely used to mitigate cardiovascular risk, but emerging research suggests they may also influence aging processes beyond cardiovascular health. Some studies indicate that lipid-lowering drugs can modulate inflammatory pathways and oxidative stress, potentially extending lifespan and improving overall health outcomes (D. H. Kim et al., 2025). However, the effects of long-term lipid modulation on aging are still being investigated. Lipid metabolism is intricately linked to aging and overall health. Dysregulation of lipid homeostasis contributes to metabolic disorders, cognitive decline, mitochondrial dysfunction, and immune system aging. Understanding the role of lipids in aging provides valuable insights for developing targeted interventions to promote healthy aging and reduce the burden of age-related diseases.

Table 3.

Lipid Type	Signalling Role	Pathway Involved	Mechanism	Reference
Phosphatidylinositol (PI) Lipids	Key regulators of intracellular signalling	PI3K-AKT Pathway	PIP2 and PIP3 activate kinases involved in cell growth, survival, and metabolism	(Neff & Radka, 2025)
Sphingolipids	Regulate cell survival, apoptosis, and inflammation	Sphingomyelinase Pathway	Ceramide accumulation induces apoptosis and stress response	(Wei, Wong, & Boland, 2023)
Sterols (Cholesterol, Oxysterols)	Modulate membrane fluidity and receptor function	Hedgehog & Wnt Signalling	Cholesterol acts as a co-factor for Hedgehog proteins, affecting developmental processes	(Jiang et al., 2025)
Eicosanoids (Prostaglandins, Leukotrienes, Lipoxins)	Mediate inflammation and immune responses	NF-κB and MAPK Pathways	Prostaglandins (PGE2) activate EP receptors, modulating cytokine release	(Hao et al., 2025; Tang et al., 2025)
Lysophospholipids (LPA, S1P)	Control cell proliferation, migration, and immune cell trafficking	GPCR Signaling (LPA, S1P Receptors)	LPA and S1P activate G-protein-coupled receptors, influencing cytoskeletal remodelling and immune function	(Hao et al., 2025)
Endocannabinoids (Anandamide, 2-AG)	Neuromodulation, pain perception, and synaptic plasticity	CB1/CB2 Receptor Signaling	Activation of cannabinoid receptors modulates neurotransmitter release and anti-inflammatory pathways	(Kasatkina, Rittchen, & Sturm, 2021)
Oxidized Phospholipids	Impact inflammation and redox homeostasis	ROS & Nrf2 Pathways	Interact with pattern recognition receptors,	(Srivastava et al., 2025)

 doi:10.20944/preprints202506.2175.v1

			modulating oxidative stress responses	
Exosomal Lipids	Mediate intercellular communication	EV-mediated Signaling	Lipid components in exosomes transport bioactive molecules between cells, influencing tumor progression and immune response	(Odehnalová et al., 2025)
Ferroptosis-Associated Lipids	Regulate iron-dependent cell death	p38 MAPK & ERK Signaling	Lipid peroxidation products drive ferroptosis, affecting cancer and neurodegenerative diseases	(Chen et al., 2025)
Lipid Nanoparticles (LNPs)	Enhance drug delivery and immune modulation	mRNA Therapeutics	LNPs encapsulate RNA and modulate cellular uptake via lipid composition	(Papp et al., 2025)

Therapeutic Implications

Therapeutic Strategies Targeting Thromboxane

Since thromboxane plays a central role in inflammation, several therapeutic approaches have been explored. Aspirin (COX-1 Inhibitor) blocks thromboxane synthesis, reducing inflammation and cardiovascular risk (Fabbrini & Vago, 2024). Thromboxane Receptor (TP) Antagonists is like the drug Terutroban block TXA_2 receptors, showing promise in vascular and autoimmune diseases (Adão, Perez-Vizcaino, Redwan, & Brás-Silva, 2024). TXA_2 Synthase Inhibitors prevent TXA_2 formation, reducing platelet activation and leukocyte infiltration (Reilly, Doran, Smith, & FitzGerald, 1986).

Therapeutic Strategies Targeting Leukotrienes

Due to their strong inflammatory role, leukotrienes are targets for anti-inflammatory drugs, including. 5-Lipoxygenase (5-LOX) Inhibitors this drugs block leukotriene synthesis at the enzyme level, reducing inflammation (Parvez, Bhavani, Gupta, Werz, & Aparoy, 2025). Leukotriene Receptor Antagonists (LTRAs) are drugs like montelukast and zafirlukast selectively block leukotriene receptors, providing relief from asthma and allergic inflammation (Matera, Cazzola, Rogliani, & Patella, 2025).

Therapeutic Potential of S1P(Sphingosine-1-phosphate)-Based Modulators

Given its neuroprotective effects, S1P modulation has been proposed as a potential therapeutic strategy. Drugs like fingolimod, an S1P receptor modulator, have shown promise in experimental models of neurodegeneration. fingolimod enhances PI3K/Akt signaling, preventing neuronal loss in neurodegenerative models.

Targeting Lipid Signaling Pathways Offer Potential Therapeutic Strategies for Neurogenerative Disease

Lipid metabolism modulators Drugs that alter ceramide and sphingolipid levels can prevent apoptosis in neurodegenerative conditions. Antioxidants agents that inhibit lipid peroxidation, such as Nrf2 activators, reduce oxidative stress in PD and ALS. Cholesterol-lowering drugs like Statins

 doi:10.20944/preprints202506.2175.v1

and ApoE modulators may slow AD progression. PLA2 inhibitors substances that reduce PLA2 activity could decrease neuroinflammation and membrane damage.

References

1. Abed Rabbo, M., Khodour, Y., Kaguni, L. S., & Stiban, J. (2021). Sphingolipid lysosomal storage diseases: from bench to bedside. *Lipids Health Dis, 20*(1), 44. doi:10.1186/s12944-021-01466-0
2. Adão, R., Perez-Vizcaino, F., Redwan, B., & Brás-Silva, C. (2024). Therapeutics in pulmonary arterial hypertension. In (Vol. 11, pp. 1463305): Frontiers Media SA.
3. Adebo, O. A., Gieng, J., & Feng, X. (2025). Editorial: Enhancing nutrient profile, safety, and sustainability with fermentation technology. *Front Nutr, 12*, 1571781. doi:10.3389/fnut.2025.1571781
4. Ahmad, A., & Fusciello, M. Molecular bases of adipose tissue aging. doi:https://doi.org/10.32948/ajsep.2025.02.08
5. Alaamery, M., Albesher, N., Aljawini, N., Alsuwailm, M., Massadeh, S., Wheeler, M. A., Quintana, F. J. (2021). Role of sphingolipid metabolism in neurodegeneration. *J Neurochem, 158*(1), 25-35. doi:10.1111/jnc.15044
6. Alcalay, R. N., Hsieh, F., Tengstrand, E., Padmanabhan, S., Baptista, M., Kehoe, C., Merchant, K. (2020). Higher urine bis (monoacylglycerol) phosphate levels in LRRK2 G2019S mutation carriers: implications for therapeutic development. *Movement disorders, 35*(1), 134-141. doi:https://doi.org/10.1002/mds.27818
7. Alecu, I., & Bennett, S. A. L. (2019). Dysregulated Lipid Metabolism and Its Role in alpha-Synucleinopathy in Parkinson's Disease. *Front Neurosci, 13*, 328. doi:10.3389/fnins.2019.00328
8. Allard, M. F., Schonekess, B. O., Henning, S. L., English, D. R., & Lopaschuk, G. D. (1994). Contribution of oxidative metabolism and glycolysis to ATP production in hypertrophied hearts. *Am J Physiol, 267*(2 Pt 2), H742-750. doi:10.1152/ajpheart.1994.267.2.H742
9. Andersen, C. J. (2018). Impact of Dietary Cholesterol on the Pathophysiology of Infectious and Autoimmune Disease. *Nutrients, 10*(6). doi:10.3390/nu10060764
10. Andersen, C. J. (2022). Lipid Metabolism in Inflammation and Immune Function. *Nutrients, 14*(7). doi:10.3390/nu14071414
11. Andersen, C. J., Murphy, K. E., & Fernandez, M. L. (2016). Impact of Obesity and Metabolic Syndrome on Immunity. *Adv Nutr, 7*(1), 66-75. doi:10.3945/an.115.010207
12. Ballard, F. B., Danforth, W. H., Naegle, S., & Bing, R. J. (1960). Myocardial metabolism of fatty acids. *J Clin Invest, 39*(5), 717-723. doi:10.1172/JCI104088
13. Basil, M. C., & Levy, B. D. (2016). Specialized pro-resolving mediators: endogenous regulators of infection and inflammation. *Nat Rev Immunol, 16*(1), 51-67. doi:10.1038/nri.2015.4
14. Basu, D., & Goldberg, I. J. (2020). Regulation of lipoprotein lipase-mediated lipolysis of triglycerides. *Current opinion in lipidology, 31*(3), 154-160. doi:10.1097/MOL.0000000000000676
15. Bates, E. J., Ferrante, A., Harvey, D. P., & Poulos, A. (1993). Polyunsaturated fatty acids increase neutrophil adherence and integrin receptor expression. *J Leukoc Biol, 53*(4), 420-426. doi:10.1002/jlb.53.4.420
16. Berisha, H., Hattab, R., Comi, L., Giglione, C., Migliaccio, S., & Magni, P. (2025). Nutrition and Lifestyle Interventions in Managing Dyslipidemia and Cardiometabolic Risk. *Nutrients, 17*(5). doi:10.3390/nu17050776
17. Berridge, M. J., & Irvine, R. F. (1989). Inositol phosphates and cell signalling. *Nature, 341*(6239), 197-205. doi:10.1038/341197a0
18. Bezirtzoglou, E., Plaza-Diaz, J., Song, J., Xie, G., & Stavropoulou, E. (2025). Rodent model organisms: therapeutic treatments and drugs interaction with the gut microbiome. In (Vol. 16, pp. 1581166): Frontiers Media SA.
19. Boccardi, V., Mancinetti, F., Guazzarini, A. G., Murasecco, I., Melis, F., Bastiani, P., Mecocci, P. (2025). Sex-specific associations between serum lipid levels and cognitive performance in older adults: results from a cross-sectional real-world study. *Aging Clinical and Experimental Research, 37*(1), 62. doi:10.1007/s40520-025-02976-y

 doi:10.20944/preprints202506.2175.v1

20. Brennan, E., Kantharidis, P., Cooper, M. E., & Godson, C. (2021). Pro-resolving lipid mediators: regulators of inflammation, metabolism and kidney function. *Nat Rev Nephrol, 17*(11), 725-739. doi:10.1038/s41581-021-00454-y
21. Brinkmann, V., Billich, A., Baumruker, T., Heining, P., Schmouder, R., Francis, G., Burtin, P. (2010). Fingolimod (FTY720): discovery and development of an oral drug to treat multiple sclerosis. *Nat Rev Drug Discov, 9*(11), 883-897. doi:10.1038/nrd3248
22. Briot, A., Civelek, M., Seki, A., Hoi, K., Mack, J. J., Lee, S. D., Fishbein, G. A. (2015). Endothelial NOTCH1 is suppressed by circulating lipids and antagonizes inflammation during atherosclerosis. *Journal of Experimental Medicine, 212*(12), 2147-2163. doi:https://doi.org/10.1084/jem.20150603
23. Brown, E. M., Clardy, J., & Xavier, R. J. (2023). Gut microbiome lipid metabolism and its impact on host physiology. *Cell Host Microbe, 31*(2), 173-186. doi:10.1016/j.chom.2023.01.009
24. Bruns-Numrich, A. (2025). Diet quality, nutritional status, and cardiovascular risk factors in a flexitarian cohort. doi:https://doi.org/10.1186/s40795-023-00799-6
25. Busanello, A., Menezes, V. M., Koller, O. G., Volz Andreia, A., & de Almeida, J. C. (2025). Effect of group-based nutritional education combined with individual standard care for outpatients with type 2 diabetes: study protocol for a randomized clinical trial 1. *Trials, 26*(1), 78. doi:10.1186/s13063-025-08720-1
26. Busch, D. J., Houser, J. R., Hayden, C. C., Sherman, M. B., Lafer, E. M., & Stachowiak, J. C. (2015). Intrinsically disordered proteins drive membrane curvature. *Nat Commun, 6*, 7875. doi:10.1038/ncomms8875
27. Byrne, E. F. X., Sircar, R., Miller, P. S., Hedger, G., Luchetti, G., Nachtergaele, S., Siebold, C. (2016). Structural basis of Smoothened regulation by its extracellular domains. *Nature, 535*(7613), 517-522. doi:10.1038/nature18934
28. Chandrasekharan, J. A., & Sharma-Walia, N. (2015). Lipoxins: nature's way to resolve inflammation. *J Inflamm Res, 8*, 181-192. doi:10.2147/JIR.S90380
29. Chaurasia, B., & Summers, S. A. (2021). Ceramides in Metabolism: Key Lipotoxic Players. *Annu Rev Physiol, 83*, 303-330. doi:10.1146/annurev-physiol-031620-093815
30. Chen, W., Wang, B., Liang, S., Zheng, L., Fang, H., Xu, S., Feng, W. (2025). Fullerenols as efficient ferroptosis inhibitor by targeting lipid peroxidation for preventing drug-induced acute kidney injury. *Journal of Colloid and Interface Science, 680*, 261-273. doi:https://doi.org/10.1016/j.jcis.2024.10.198
31. Chew, H., Solomon, V. A., & Fonteh, A. N. (2020). Involvement of Lipids in Alzheimer's Disease Pathology and Potential Therapies. *Front Physiol, 11*, 598. doi:10.3389/fphys.2020.00598
32. Chiang, N., & Serhan, C. N. (2020). Specialized pro-resolving mediator network: an update on production and actions. *Essays Biochem, 64*(3), 443-462. doi:10.1042/EBC20200018
33. Conway, A. E., White, A. A., Borish, L., Shaker, M., & Lee, M. W. (2024). Eicosanoids, innate immunity, and alarmins in aspirin-exacerbated respiratory disease. *Ann Allergy Asthma Immunol, 133*(1), 13-15. doi:10.1016/j.anai.2024.02.024
34. Cuffaro, F., Lamminpaa, I., Niccolai, E., & Amedei, A. (2024). Nutritional and Microbiota-Based Approaches in Amyotrophic Lateral Sclerosis: From Prevention to Treatment. *Nutrients, 17*(1). doi:10.3390/nu17010102
35. Czubowicz, K., Jesko, H., Wencel, P., Lukiw, W. J., & Strosznajder, R. P. (2019). The Role of Ceramide and Sphingosine-1-Phosphate in Alzheimer's Disease and Other Neurodegenerative Disorders. *Mol Neurobiol, 56*(8), 5436-5455. doi:10.1007/s12035-018-1448-3
36. Da Dalt, L., Cabodevilla, A. G., Goldberg, I. J., & Norata, G. D. (2023). Cardiac lipid metabolism, mitochondrial function, and heart failure. *Cardiovasc Res, 119*(10), 1905-1914. doi:10.1093/cvr/cvad100
37. Das, M., Sauceda, C., & Webster, N. J. G. (2021). Mitochondrial Dysfunction in Obesity and Reproduction. *Endocrinology, 162*(1). doi:10.1210/endocr/bqaa158
38. Davila-Roman, V. G., Vedala, G., Herrero, P., de las Fuentes, L., Rogers, J. G., Kelly, D. P., & Gropler, R. J. (2002). Altered myocardial fatty acid and glucose metabolism in idiopathic dilated cardiomyopathy. *J Am Coll Cardiol, 40*(2), 271-277. doi:10.1016/s0735-1097(02)01967-8

 doi:10.20944/preprints202506.2175.v1

39. Dawczynski, C., Drobner, T., Weidauer, T., Schlattmann, P., Kiehntopf, M., Weber, D., Lorkowski, S. (2025). Reduction of cardiovascular risk factors by the diet - Evaluation of the MoKaRi concept by a parallel-designed randomized study. *Lipids Health Dis, 24*(1), 88. doi:10.1186/s12944-025-02500-1
40. Diakos, N. A., Navankasattusas, S., Abel, E. D., Rutter, J., McCreath, L., Ferrin, P., Drakos, S. G. (2016). Evidence of Glycolysis Up-Regulation and Pyruvate Mitochondrial Oxidation Mismatch During Mechanical Unloading of the Failing Human Heart: Implications for Cardiac Reloading and Conditioning. *JACC Basic Transl Sci, 1*(6), 432-444. doi:10.1016/j.jacbts.2016.06.009
41. DiNicolantonio, J. J., & O'Keefe, J. H. (2022). Monounsaturated Fat vs Saturated Fat: Effects on Cardio-Metabolic Health and Obesity. *Mo Med, 119*(1), 69-73. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/36033137
42. Draper, E., DeCourcey, J., Higgins, S. C., Canavan, M., McEvoy, F., Lynch, M., Loscher, C. E. (2014). Conjugated linoleic acid suppresses dendritic cell activation and subsequent Th17 responses. *J Nutr Biochem, 25*(7), 741-749. doi:10.1016/j.jnutbio.2014.03.004
43. Duan, T., Ren, Z., Jiang, H., Ding, Y., Wang, H., & Wang, F. (2025). Gut microbiome signature in response to neoadjuvant chemoradiotherapy in patients with rectal cancer. *Front Microbiol, 16*, 1543507. doi:10.3389/fmicb.2025.1543507
44. Erb, M. L., & Moore, D. J. (2020). LRRK2 and the Endolysosomal System in Parkinson's Disease. *J Parkinsons Dis, 10*(4), 1271-1291. doi:10.3233/JPD-202138
45. Estes Raja Elizabeth, L. B., Khera Arnav , Davis Marie Ynez. (2021). Lipid Metabolism Influence on Neurodegenerative Disease Progression: Is the Vehicle as Important as the Cargo? *Front. Mol. Neurosci.* doi:https://doi.org/10.3389/fnmol.2021.788695
46. Fabbrini, M. S., & Vago, R. (2024). What does experimental pharmacology and drug discovery look like in 2035? In (Vol. 15, pp. 1504817): Frontiers Media SA.
47. Finck, B. N., & Kelly, D. P. (2002). Peroxisome proliferator-activated receptor alpha (PPARalpha) signaling in the gene regulatory control of energy metabolism in the normal and diseased heart. *J Mol Cell Cardiol, 34*(10), 1249-1257. doi:10.1006/jmcc.2002.2061
48. Fritzsche, M., Li, D., Colin-York, H., Chang, V. T., Moeendarbary, E., Felce, J. H., Eggeling, C. (2017). Self-organizing actin patterns shape membrane architecture but not cell mechanics. *Nat Commun, 8*, 14347. doi:10.1038/ncomms14347
49. Fukuishi, N. T., K.; Kurosaki, H.; Ono, S.; Asai, H. (2025). The Role of Endogenous Specialized Proresolving Mediators in Mast Cells and Their Involvement in Inflammation and Resolution. *Int. J. Mol. Sci.*
50. Funk, C. D. (2001). Prostaglandins and leukotrienes: advances in eicosanoid biology. *Science, 294*(5548), 1871-1875. doi:10.1126/science.294.5548.1871
51. Gaire, B. P., & Choi, J. W. (2021). Sphingosine 1-Phosphate Receptors in Cerebral Ischemia. *Neuromolecular Med, 23*(1), 211-223. doi:10.1007/s12017-020-08614-2
52. Galvagnion, C., Buell, A. K., Meisl, G., Michaels, T. C., Vendruscolo, M., Knowles, T. P., & Dobson, C. M. (2015). Lipid vesicles trigger alpha-synuclein aggregation by stimulating primary nucleation. *Nat Chem Biol, 11*(3), 229-234. doi:10.1038/nchembio.1750
53. Ghorbanzadeh, B., Azizolahi, B., Behmanesh, M. A., Forouhar, P., Foroughinia, A., & Nabizadeh, M. (2025). The role of opioid receptors in the anti-allodynic effect of local montelukast in a rat chronic constriction injury of sciatic nerve model. *Neurosci Lett, 851*, 138165. doi:10.1016/j.neulet.2025.138165
54. Giussani, P. A.-O., Prinetti, A. A.-O., & Tringali, C. A.-O. (2020). The role of Sphingolipids in myelination and myelin stability and their involvement in childhood and adult demyelinating disorders. (1471-4159 (Electronic)).
55. Glatz, J. F. C., & Luiken, J. (2018). Dynamic role of the transmembrane glycoprotein CD36 (SR-B2) in cellular fatty acid uptake and utilization. *J Lipid Res, 59*(7), 1084-1093. doi:10.1194/jlr.R082933
56. Gonzales, C. B., Seubert, J. M., & Paes, A. M. (2025). Editorial: Targeting mitochondria in aging and disease. *Front Pharmacol, 16*, 1589728. doi:10.3389/fphar.2025.1589728
57. Green, C. D., Maceyka, M., Cowart, L. A., & Spiegel, S. (2021). Sphingolipids in metabolic disease: The good, the bad, and the unknown. *Cell Metab, 33*(7), 1293-1306. doi:10.1016/j.cmet.2021.06.006

 doi:10.20944/preprints202506.2175.v1

58. Haapala, E. A. (2025). Identifying adolescents with increased cardiometabolic risk—Simple, but challenging. *Jornal de Pediatria, 101*(1), 1-3. doi:10.1001/jamanetworkopen.2024.60012
59. Haidar, M., Loix, M., Bogie, J. F. J., & Hendriks, J. J. A. (2021). Lipophagy: a new player in CNS disorders. *Trends Endocrinol Metab, 32*(11), 941-951. doi:10.1016/j.tem.2021.08.010
60. Han, X., M Holtzman D Fau - McKeel, D. W., Jr., McKeel Dw Jr Fau - Kelley, J., Kelley J Fau - Morris, J. C., & Morris, J. C. (2002). Substantial sulfatide deficiency and ceramide elevation in very early Alzheimer's disease: potential role in disease pathogenesis. (0022-3042 (Print)).
61. Hannun, Y. A., & Obeid, L. M. (2018). Sphingolipids and their metabolism in physiology and disease. *Nature Reviews Molecular Cell Biology, 19*(3), 175-191. doi:10.1038/nrm.2017.107
62. Hao, Z., Guan, W., Wei, W., Li, M., Xiao, Z., Sun, Q., Xin, W. (2025). Unlocking the therapeutic potential of tumor-derived EVs in ischemia-reperfusion: a breakthrough perspective from glioma and stroke. *J Neuroinflammation, 22*(1), 84. doi:10.1186/s12974-025-03405-7
63. Hartsoe, P., Holguin, F., & Chu, H. W. (2024). Mitochondrial Dysfunction and Metabolic Reprogramming in Obesity and Asthma. *Int J Mol Sci, 25*(5). doi:10.3390/ijms25052944
64. Hellstrom, A., Hellstrom, W., Hellgren, G., L, E. H. S., Puttonen, H., Fyhr, I. M., Klevebro, S. (2020). Docosahexaenoic Acid and Arachidonic Acid Levels Are Associated with Early Systemic Inflammation in Extremely Preterm Infants. *Nutrients, 12*(7). doi:10.3390/nu12071996
65. Hodges, R. R., Li, D., Shatos, M. A., Bair, J. A., Lippestad, M., Serhan, C. N., & Dartt, D. A. (2017). Lipoxin A(4) activates ALX/FPR2 receptor to regulate conjunctival goblet cell secretion. *Mucosal Immunol, 10*(1), 46-57. doi:10.1038/mi.2016.33
66. Huang, J., Yancey, P. G., Tao, H., Borja, M. S., Smith, L. E., Kon, V., Linton, M. F. (2020). Reactive Dicarbonyl Scavenging Effectively Reduces MPO-Mediated Oxidation of HDL and Restores PON1 Activity. *Nutrients, 12*(7). doi:10.3390/nu12071937
67. Huang, P., Nedelcu, D., Watanabe, M., Jao, C., Kim, Y., Liu, J., & Salic, A. (2016). Cellular Cholesterol Directly Activates Smoothened in Hedgehog Signaling. *Cell, 166*(5), 1176-1187 e1114. doi:10.1016/j.cell.2016.08.003
68. Ikuno, M., Yamakado, H., Akiyama, H., Parajuli, L. K., Taguchi, K., Hara, J., Takahashi, R. (2019). GBA haploinsufficiency accelerates alpha-synuclein pathology with altered lipid metabolism in a prodromal model of Parkinson's disease. *Hum Mol Genet, 28*(11), 1894-1904. doi:10.1093/hmg/ddz030
69. Ito, A., Hong, C., Rong, X., Zhu, X., Tarling, E. J., Hedde, P. N., Tontonoz, P. (2015). LXRs link metabolism to inflammation through Abca1-dependent regulation of membrane composition and TLR signaling. *Elife, 4*, e08009. doi:10.7554/eLife.08009
70. Jia, H., Bian, C., & Chang, Y. (2025). Exploring the molecular interactions between ferroptosis and the Wnt/β-catenin signaling pathway: Implications for cancer and disease therapy. *Critical Reviews in Oncology/Hematology, 210*, 104674. doi:https://doi.org/10.1016/j.critrevonc.2025.104674
71. Jiang, M., Huang, J., Guo, X., Fu, W., Peng, L., Wang, Y., Xiao, Y. (2025). HIF-3alpha/PPAR-gamma Regulates Hypoxia Tolerance by Altering Glycolysis and Lipid Synthesis in Blunt Snout Bream (Megalobrama amblycephala). *Int J Mol Sci, 26*(6). doi:10.3390/ijms26062613
72. Joseph, S. B., Castrillo, A., Laffitte, B. A., Mangelsdorf, D. J., & Tontonoz, P. (2003). Reciprocal regulation of inflammation and lipid metabolism by liver X receptors. *Nat Med, 9*(2), 213-219. doi:10.1038/nm820
73. Kasatkina, L. A., Rittchen, S., & Sturm, E. M. (2021). Neuroprotective and immunomodulatory action of the endocannabinoid system under neuroinflammation. *International journal of molecular sciences, 22*(11), 5431. doi:https://doi.org/10.3390/ijms22115431
74. Khan, R. S., Lin, Y., Hu, Y., Son, N. H., Bharadwaj, K. G., Palacios, C., Goldberg, I. J. (2013). Rescue of heart lipoprotein lipase-knockout mice confirms a role for triglyceride in optimal heart metabolism and function. *Am J Physiol Endocrinol Metab, 305*(11), E1339-1347. doi:10.1152/ajpendo.00349.2013
75. Kim, D. H., Go, H. S., Jeon, E. J., Nguyen, T. Q. T., Kim, D. Y., Park, H., Cho, K. A. (2025). The Impact of Toll-Like Receptor 5 on Liver Function in Age-Related Metabolic Disorders. *Aging Cell*, e70009. doi:10.1111/acel.70009
76. Kim, M. J., Jeon, S., Burbulla, L. F., & Krainc, D. (2018). Acid ceramidase inhibition ameliorates α-synuclein accumulation upon loss of GBA1 function. (1460-2083 (Electronic)).

 doi:10.20944/preprints202506.2175.v1

77. Kliewer, S. A., Sundseth Ss Fau - Jones, S. A., Jones Sa Fau - Brown, P. J., Brown Pj Fau - Wisely, G. B., Wisely Gb Fau - Koble, C. S., Koble Cs Fau - Devchand, P., Lehmann, J. M. (1997). Fatty acids and eicosanoids regulate gene expression through direct interactions with peroxisome proliferator-activated receptors alpha and gamma. (0027-8424 (Print)).
78. Kolivas, D., Fraser, L., Schweitzer, R., Brukner, P., & Moschonis, G. (2025). A 6-Month mHealth Low-Carbohydrate Dietary Intervention Ameliorates Glycaemic and Cardiometabolic Risk Profile in People with Type 2 Diabetes. *Nutrients, 17*(6). doi:10.3390/nu17060937
79. Krishnamurthy, H. K., Rajavelu, I., Reddy, S., Pereira, M., Jayaraman, V., Krishna, K., Rajasekaran, J. J. (2024). Association of Apolipoprotein E (APOE) Polymorphisms With Serological Lipid and Inflammatory Markers. *Cureus, 16*(5), e60721. doi:10.7759/cureus.60721
80. Kroglund, I. B., Ciesielski, T. M., Østnes, J. E., Patten, M. A., Borgå, K., & Jaspers, V. L. (2025). Trace, macro and rare earth elements in a sedentary avian predator: Relationships with age and dietary tracers. *Environmental research, 275*, 121381. doi:https://doi.org/10.1016/j.envres.2025.121381
81. Kumar, N. A.-O., Contaifer, D., Madurantakam, P., Carbone, S. A.-O., Price, E. T., Van Tassell, B., Wijesinghe, D. A.-O. (2019). Dietary Bioactive Fatty Acids as Modulators of Immune Function: Implications on Human Health. LID - 10.3390/nu11122974 [doi] LID - 2974. (2072-6643 (Electronic)).
82. Kurzawa-Akanbi, M. A.-O., Tammireddy, S., Fabrik, I., Gliaudelytė, L., Doherty, M. K., Heap, R., Morris, C. M. (2021). Altered ceramide metabolism is a feature in the extracellular vesicle-mediated spread of alpha-synuclein in Lewy body disorders. (1432-0533 (Electronic)).
83. Lai, C. Q., Gervis, J. E., Parnell, L. D., Lichtenstein, A. H., & Ordovas, J. M. (2025). Changes in triglyceride-rich lipoprotein particle profiles in response to one-week on a low fat or Mediterranean diet by TCF7L2 rs7903146 genotype: a randomized crossover dietary intervention trial. *Genes Nutr, 20*(1), 4. doi:10.1186/s12263-025-00763-y
84. Laparra Llopis, J. M., Brown, D., & Saiz, B. (2020). Chenopodium Quinoa and Salvia Hispanica Provide Immunonutritional Agonists to Ameliorate Hepatocarcinoma Severity under a High-Fat Diet. *Nutrients, 12*(7). doi:10.3390/nu12071946
85. Laude, A. J., & Prior, I. A. (2004). Plasma membrane microdomains: organization, function and trafficking. *Mol Membr Biol, 21*(3), 193-205. doi:10.1080/09687680410001700517
86. Lee, C. S., Zhai, Y., Shang, R., Wong, T., Mattison, A. J., Cen, H. H., Rodrigues, B. (2022). Flow-Induced Secretion of Endothelial Heparanase Regulates Cardiac Lipoprotein Lipase and Changes Following Diabetes. *J Am Heart Assoc, 11*(23), e027958. doi:10.1161/JAHA.122.027958
87. Lee, J. H., Jung, I. R., Tu-Sekine, B., Jin, S., Anokye-Danso, F., Ahima, R. S., & Kim, S. F. (2025). Loss of Skeletal Muscle Inositol Polyphosphate Multikinase Disrupts Glucose Regulation and Limits Exercise Capacity. *Int J Mol Sci, 26*(6). doi:10.3390/ijms26062395
88. Leitao, C., Mignano, A., Estrela, M., Fardilha, M., Figueiras, A., Roque, F., & Herdeiro, M. T. (2022). The Effect of Nutrition on Aging-A Systematic Review Focusing on Aging-Related Biomarkers. *Nutrients, 14*(3). doi:10.3390/nu14030554
89. Levy, B. D., Clish, C. B., Schmidt, B., Gronert, K., & Serhan, C. N. (2001). Lipid mediator class switching during acute inflammation: signals in resolution. *Nat Immunol, 2*(7), 612-619. doi:10.1038/89759
90. Liang, Y., Zhao, X., Jin, G., & Hou, T. (2025). Selenium- and zinc-biofortified bean sprouts improve cognitive dysfunction in aging mice by reducing oxidative stress. *J Food Sci, 90*(3), e70093. doi:10.1111/1750-3841.70093
91. Lin, K. J., Chen, S. D., Lin, K. L., Liou, C. W., Lan, M. Y., Chuang, Y. C., Lin, T. K. (2022). Iron Brain Menace: The Involvement of Ferroptosis in Parkinson Disease. *Cells, 11*(23). doi:10.3390/cells11233829
92. Liu, C. C., Liu, C. C., Kanekiyo, T., Xu, H., & Bu, G. (2013). Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy. *Nat Rev Neurol, 9*(2), 106-118. doi:10.1038/nrneurol.2012.263
93. Liu, J. (2025). Prostaglandins and other lipids as therapeutic targets and prognostic biomarkers in rheumatoid arthritis. *Thesis*. doi:https://doi.org/10.69622/28034714.v2
94. Liu, P., Chen, H., Jiang, X., & Diaz-Cidoncha Garcia, J. (2025). Impact of exercise training in a hypobaric/normobaric hypoxic environment on body composition and glycolipid metabolism in

 doi:10.20944/preprints202506.2175.v1

individuals with overweight or obesity: a systematic review and meta-analysis. *Front Physiol, 16*, 1571730. doi:10.3389/fphys.2025.1571730

95. Liu, Z., Chen, M., Zheng, W., Zhan, X., Sui, W., Huang, H., Zhao, W. (2025). Effect of gut symbiotic bacteria Akkermansia muciniphila on aging-related obesity. *Biochem Biophys Res Commun, 756*, 151606. doi:10.1016/j.bbrc.2025.151606
96. Luchetti, G., Sircar, R., Kong, J. H., Nachtergaele, S., Sagner, A., Byrne, E. F., Rohatgi, R. (2016). Cholesterol activates the G-protein coupled receptor Smoothened to promote Hedgehog signaling. *Elife, 5*. doi:10.7554/eLife.20304
97. Maceyka, M., Harikumar, K. B., Milstien, S., & Spiegel, S. (2012). Sphingosine-1-phosphate signaling and its role in disease. *Trends Cell Biol, 22*(1), 50-60. doi:10.1016/j.tcb.2011.09.003
98. Matera, M. G., Cazzola, M., Rogliani, P., & Patella, V. (2025). An update on long-acting muscarinic agents for asthma therapy. *Expert Review of Respiratory Medicine, 19*(5), 407-421. doi:https://doi.org/10.1080/17476348.2025.2484289
99. McIsaac, S. M., Stadnyk, A. W., & Lin, T. J. (2012). Toll-like receptors in the host defense against Pseudomonas aeruginosa respiratory infection and cystic fibrosis. *J Leukoc Biol, 92*(5), 977-985. doi:10.1189/jlb.0811410
100. Mesmin, B. (2025). Editorial on Special Collection in Contact: Lipid Transfer Proteins: From Molecular Mechanisms to Functional Validation. *Contact (Thousand Oaks), 8*, 25152564251322628. doi:10.1177/25152564251322628
101. Mielke, M. M., Bandaru, V. V., Haughey, N. J., Xia, J., Fried, L. P., Yasar, S., Carlson, M. C. (2012). Serum ceramides increase the risk of Alzheimer disease: the Women's Health and Aging Study II. *Neurology, 79*(7), 633-641. doi:10.1212/WNL.0b013e318264e380
102. Mielke, M. M., Haughey, N. J., Bandaru, V. V., Schech, S., Carrick, R., Carlson, M. C., Lyketsos, C. G. (2010). Plasma ceramides are altered in mild cognitive impairment and predict cognitive decline and hippocampal volume loss. *Alzheimers Dement, 6*(5), 378-385. doi:10.1016/j.jalz.2010.03.014
103. Milovanovic, D., Honigmann, A., Koike, S., Göttfert, F., Pähler, G., Junius, M., Jahn, R. (2015). Hydrophobic mismatch sorts SNARE proteins into distinct membrane domains. *Nature Communications, 6*(1), 5984. doi:10.1038/ncomms6984
104. Miranda, A. M., Lasiecka, Z. M., Xu, Y., Neufeld, J., Shahriar, S., Simoes, S., Di Paolo, G. (2018). Neuronal lysosomal dysfunction releases exosomes harboring APP C-terminal fragments and unique lipid signatures. *Nat Commun, 9*(1), 291. doi:10.1038/s41467-017-02533-w
105. Mohammed, S., Ohene-Marfo, P., Jiang, C., Peng, Z., Thadathil, N., Tran, A., Deepa, S. S. (2025). Impact of Mlkl or Ripk3 deletion on age-associated liver inflammation, metabolic health, and lifespan. *Geroscience*. doi:10.1007/s11357-025-01553-5
106. Monaghan, R. M. (2025). The fundamental role of mitochondria-endoplasmic reticulum contacts in ageing and declining healthspan. *Open Biol, 15*(2), 240287. doi:10.1098/rsob.240287
107. Murashige, D., Jang, C., Neinast, M., Edwards, J. J., Cowan, A., Hyman, M. C., Arany, Z. (2020). Comprehensive quantification of fuel use by the failing and nonfailing human heart. *Science, 370*(6514), 364-368. doi:10.1126/science.abc8861
108. Murphy, K. E., Gysbers Am Fau - Abbott, S. K., Abbott Sk Fau - Tayebi, N., Tayebi N Fau - Kim, W. S., Kim Ws Fau - Sidransky, E., Sidransky E Fau - Cooper, A., Halliday, G. M. (2014). Reduced glucocerebrosidase is associated with increased α-synuclein in sporadic Parkinson's disease. (1460-2156 (Electronic)).
109. Mutlu, A. S., Duffy, J., & Wang, M. C. (2021). Lipid metabolism and lipid signals in aging and longevity. *Dev Cell, 56*(10), 1394-1407. doi:10.1016/j.devcel.2021.03.034
110. Naik, R. A., Mir, M. N., Malik, I. A., Bhardwaj, R., Alshabrmi, F. M., Mahmoud, M. A., Singh, S. K. (2025). The Potential Mechanism and the Role of Antioxidants in Mitigating Oxidative Stress in Alzheimer's Disease. *Front Biosci (Landmark Ed), 30*(2), 25551. doi:10.31083/FBL25551
111. Neff, R. J., & Radka, C. A.-O. (2025). Exploring Oxylipins in Host-Microbe Interactions and Their Impact on Infection and Immunity. LID - 10.3390/cimb47030190 [doi] LID - 190. (1467-3045 (Electronic)).
112. Neglia, D., De Caterina, A., Marraccini, P., Natali, A., Ciardetti, M., Vecoli, C., Recchia, F. A. (2007). Impaired myocardial metabolic reserve and substrate selection flexibility during stress in patients with

 doi:10.20944/preprints202506.2175.v1

idiopathic dilated cardiomyopathy. *Am J Physiol Heart Circ Physiol, 293*(6), H3270-3278. doi:10.1152/ajpheart.00887.2007

113. Nixon, R. A. (2013). The role of autophagy in neurodegenerative disease. *Nat Med, 19*(8), 983-997. doi:10.1038/nm.3232
114. Odehnalová, N., Šandriková, V., Hromadka, R., Skaličková, M., Dytrych, P., Hoskovec, D., Vašáková, M. K. (2025). The potential of exosomes in regenerative medicine and in the diagnosis and therapies of neurodegenerative diseases and cancer. *Frontiers in Medicine, 12*, 1539714. doi:https://doi.org/10.3389/fmed.2025.1539714
115. Ogiso, H., Taniguchi, M., & Okazaki, T. (2015). Analysis of lipid-composition changes in plasma membrane microdomains. *J Lipid Res, 56*(8), 1594-1605. doi:10.1194/jlr.M059972
116. Ortiz-Munoz, G., Mallavia, B., Bins, A., Headley, M., Krummel, M. F., & Looney, M. R. (2014). Aspirin-triggered 15-epi-lipoxin A4 regulates neutrophil-platelet aggregation and attenuates acute lung injury in mice. *Blood, 124*(17), 2625-2634. doi:10.1182/blood-2014-03-562876
117. Pahal, S., Mainali, N., Balasubramaniam, M., Shmookler Reis, R. J., & Ayyadevara, S. (2025). Mitochondria in aging and age-associated diseases. *Mitochondrion, 82*, 102022. doi:10.1016/j.mito.2025.102022
118. Papp, T. E., Zeng, J., Shahnawaz, H., Akyianu, A., Breda, L., Yadegari, A., Parhiz, H. (2025). CD47 peptide-cloaked lipid nanoparticles promote cell-specific mRNA delivery. *Mol Ther*. doi:10.1016/j.ymthe.2025.03.018
119. Paredes, S. D., Hernandez-Cortes, J., Falahat, F., Rancan, L., Arias-Diaz, J., & Vara, E. (2024). Protective Effect of Pentoxifylline on the Development of Acute Gastric Mucosal Injury in a Model of LPS-Induced Sepsis. *Antioxidants (Basel), 13*(12). doi:10.3390/antiox13121481
120. Parvez, S., Bhavani, K. S., Gupta, C. C., Werz, O., & Aparoy, P. (2025). Molecular dynamics simulations to decipher the hotspots at the allosteric site of human 5-lipoxygenase. *Journal of Molecular Graphics and Modelling, 136*, 108940. doi:https://doi.org/10.1016/j.jmgm.2024.108940
121. Pils, V., Terlecki-Zaniewicz, L., Schosserer, M., Grillari, J., & Lammermann, I. (2021). The role of lipid-based signalling in wound healing and senescence. *Mech Ageing Dev, 198*, 111527. doi:10.1016/j.mad.2021.111527
122. Rahmawati, S. I., Indriani, D. W., Ningsih, F. N., Hardhiyuna, M., Firdayani, F., Ahmadi, P., Putra, M. Y. (2024). Dual anti-inflammatory activities of COX-2/5-LOX driven by kratom alkaloid extracts in lipopolysaccharide-induced RAW 264.7 cells. *Sci Rep, 14*(1), 28993. doi:10.1038/s41598-024-79229-x
123. Randall, A. S., Liu, C. H., Chu, B., Zhang, Q., Dongre, S. A., Juusola, M., Hardie, R. C. (2015). Speed and sensitivity of phototransduction in Drosophila depend on degree of saturation of membrane phospholipids. *J Neurosci, 35*(6), 2731-2746. doi:10.1523/JNEUROSCI.1150-14.2015
124. Reilly, I., Doran, J. B., Smith, B., & FitzGerald, G. A. (1986). Increased thromboxane biosynthesis in a human preparation of platelet activation: biochemical and functional consequences of selective inhibition of thromboxane synthase. *Circulation, 73*(6), 1300-1309. doi:https://doi.org/10.1161/01.CIR.73.6.1300
125. Rossetti, R. G., Seiler, C. M., DeLuca, P., Laposata, M., & Zurier, R. B. (1997). Oral administration of unsaturated fatty acids: effects on human peripheral blood T lymphocyte proliferation. *J Leukoc Biol, 62*(4), 438-443. doi:10.1002/jlb.62.4.438
126. Russo, A., Putaggio, S., Tellone, E., Calderaro, A., Cirmi, S., Lagana, G., Patane, G. T. (2025). Emerging Ferroptosis Involvement in Amyotrophic Lateral Sclerosis Pathogenesis: Neuroprotective Activity of Polyphenols. *Molecules, 30*(6). doi:10.3390/molecules30061211
127. Savica, R., Murray, M. E., Persson, X. M., Kantarci, K., Parisi, J. E., Dickson, D. W., Mielke, M. M. (2016). Plasma sphingolipid changes with autopsy-confirmed Lewy Body or Alzheimer's pathology. *Alzheimers Dement (Amst), 3*, 43-50. doi:10.1016/j.dadm.2016.02.005
128. Schoeniger, A., Fuhrmann, H., & Schumann, J. (2016). LPS- or Pseudomonas aeruginosa-mediated activation of the macrophage TLR4 signaling cascade depends on membrane lipid composition. *PeerJ, 4*, e1663. doi:10.7717/peerj.1663
129. Schulze, P. C., Drosatos, K., & Goldberg, I. J. (2016). Lipid Use and Misuse by the Heart. *Circ Res, 118*(11), 1736-1751. doi:10.1161/CIRCRESAHA.116.306842

 doi:10.20944/preprints202506.2175.v1

130. Schumann, J., Leichtle A Fau - Thiery, J., Thiery J Fau - Fuhrmann, H., & Fuhrmann, H. (2015). Fatty acid and peptide profiles in plasma membrane and membrane rafts of PUFA supplemented RAW264.7 macrophages. (1932-6203 (Electronic)).
131. Schwab, J. M., Chiang, N., Arita, M., & Serhan, C. N. (2007). Resolvin E1 and protectin D1 activate inflammation-resolution programmes. *Nature, 447*(7146), 869-874. doi:10.1038/nature05877
132. Serhan, C. N., Chiang, N., & Dalli, J. (2015). The resolution code of acute inflammation: Novel pro-resolving lipid mediators in resolution. *Semin Immunol, 27*(3), 200-215. doi:10.1016/j.smim.2015.03.004
133. Serhan, C. N., & Levy, B. D. (2018). Resolvins in inflammation: emergence of the pro-resolving superfamily of mediators. *J Clin Invest, 128*(7), 2657-2669. doi:10.1172/JCI97943
134. Serna, M. F., Mosquera Escudero, M., & García-Perdomo, H. A. (2023). Lipoxins and their relationship with inflammation-associated diseases. A systematic review. *Obesity Research & Clinical Practice, 17*(4), 298-307. doi:https://doi.org/10.1016/j.orcp.2023.06.001
135. Shang, R., & Rodrigues, B. (2021). Lipoprotein Lipase and Its Delivery of Fatty Acids to the Heart. *Biomolecules, 11*(7). doi:10.3390/biom11071016
136. Shao, F., Wang, X., Wu, H., Wu, Q., & Zhang, J. (2022). Microglia and Neuroinflammation: Crucial Pathological Mechanisms in Traumatic Brain Injury-Induced Neurodegeneration. *Front Aging Neurosci, 14*, 825086. doi:10.3389/fnagi.2022.825086
137. Sharma, R., & Diwan, B. (2023). Lipids and the hallmarks of ageing: From pathology to interventions. *Mech Ageing Dev, 215*, 111858. doi:10.1016/j.mad.2023.111858
138. Shen, Y., Zhang, C., Jiang, X., Li, X., Chen, B., & Jiang, W. (2025). Capsiate attenuates atherosclerosis by activating Nrf2/GPX4 pathway and reshaping the intestinal microbiota in ApoE(-/-) mice. *Microbiol Spectr, 13*(4), e0315524. doi:10.1128/spectrum.03155-24
139. Simons, K., & Toomre, D. (2000). Lipid rafts and signal transduction. *Nat Rev Mol Cell Biol, 1*(1), 31-39. doi:10.1038/35036052
140. Son, N. H., Basu, D., Samovski, D., Pietka, T. A., Peche, V. S., Willecke, F., Goldberg, I. J. (2018). Endothelial cell CD36 optimizes tissue fatty acid uptake. *J Clin Invest, 128*(10), 4329-4342. doi:10.1172/JCI99315
141. Son, N. H., Park, T. S., Yamashita, H., Yokoyama, M., Huggins, L. A., Okajima, K., Goldberg, I. J. (2007). Cardiomyocyte expression of PPARgamma leads to cardiac dysfunction in mice. *J Clin Invest, 117*(10), 2791-2801. doi:10.1172/JCI30335
142. Spiegel, S., & Milstien, S. (2003). Sphingosine-1-phosphate: an enigmatic signalling lipid. *Nat Rev Mol Cell Biol, 4*(5), 397-407. doi:10.1038/nrm1103
143. Srivastava, S. P., Kopasz-Gemmen, O., Thurman, A., Rajendran, B. K., Selvam, M. M., Kumar, S., Inoki, K. (2025). The molecular determinants regulating redox signaling in diabetic endothelial cells. *Front Pharmacol, 16*, 1563047. doi:10.3389/fphar.2025.1563047
144. Stern, S. T., & Johnson, D. N. (2008). Role for nanomaterial-autophagy interaction in neurodegenerative disease. *Autophagy, 4*(8), 1097-1100. doi:10.4161/auto.7142
145. Sugiura, Y., Ikeda, K., & Nakano, M. (2015). High Membrane Curvature Enhances Binding, Conformational Changes, and Fibrillation of Amyloid-beta on Lipid Bilayer Surfaces. *Langmuir, 31*(42), 11549-11557. doi:10.1021/acs.langmuir.5b03332
146. Sui, Y. H., Luo, W. J., Xu, Q. Y., & Hua, J. (2016). Dietary saturated fatty acid and polyunsaturated fatty acid oppositely affect hepatic NOD-like receptor protein 3 inflammasome through regulating nuclear factor-kappa B activation. (2219-2840 (Electronic)).
147. Sureda, A., Martorell, M., Bibiloni, M. d. M., Bouzas, C., Gallardo-Alfaro, L., Mateos, D., Pons, A. (2020). Effect of free fatty acids on inflammatory gene expression and hydrogen peroxide production by ex vivo blood mononuclear cells. *Nutrients, 12*(1), 146. doi:doi:10.3390/nu12010146
148. Tabeling, C., Yu, H., Wang, L., Ranke, H., Goldenberg, N. M., Zabini, D., Kuebler, W. M. (2015). CFTR and sphingolipids mediate hypoxic pulmonary vasoconstriction. *Proc Natl Acad Sci U S A, 112*(13), E1614-1623. doi:10.1073/pnas.1421190112
149. Takasaki, J., Kawauchi, Y., Yasunaga, T., & Masuho, Y. (1996). Human type II phospholipase A2-induced Mac-1 expression on human neutrophils. *J Leukoc Biol, 60*(2), 174-180. doi:10.1002/jlb.60.2.174

 doi:10.20944/preprints202506.2175.v1

150. Tang, Y., Pan, W., Ding, W., Pan, X., Zhu, J., Chen, H., Zhang, B. (2025). Prostaglandin E2 alleviates inflammatory response and lung injury through EP4/cAMP/IKK/NF-kappaB pathway. *Biochim Biophys Acta Mol Basis Dis, 1871*(5), 167801. doi:10.1016/j.bbadis.2025.167801
151. Taniguchi, M., & Okazaki, T. (2020). Ceramide/sphingomyelin rheostat regulated by sphingomyelin synthases and chronic diseases in murine models. *Journal of Lipid and Atherosclerosis, 9*(3), 380. doi:10.12997/jla.2020.9.3.380
152. Tomishige, M., Sako, Y., & Kusumi, A. (1998). Regulation mechanism of the lateral diffusion of band 3 in erythrocyte membranes by the membrane skeleton. *J Cell Biol, 142*(4), 989-1000. doi:10.1083/jcb.142.4.989
153. Tomishige, N., Takahashi, K., Pollet, B., Richert, L., Mély, Y., & Kobayashi, T. (2024). Using lipid binding proteins and advanced microscopy to study lipid domains. In *Methods in Enzymology* (Vol. 700, pp. 217-234): Elsevier.
154. Turek, J. J., Schoenlein, I. A., Clark, L. K., & Van Alstine, W. G. (1994). Dietary polyunsaturated fatty acid effects on immune cells of the porcine lung. *J Leukoc Biol, 56*(5), 599-604. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/7964168
155. Umbarawan, Y., Syamsunarno, M. R. A. A., Koitabashi, N., Obinata, H., Yamaguchi, A., Hanaoka, H., Iso, T. (2018). Myocardial fatty acid uptake through CD36 is indispensable for sufficient bioenergetic metabolism to prevent progression of pressure overload-induced heart failure. *Scientific Reports, 8*(1), 12035. doi:10.1038/s41598-018-30616-1
156. Van der Pouw Kraan, T., Boeije, L., Smeenk, R., Wijdenes, J., & Aarden, L. A. (1995). Prostaglandin-E2 is a potent inhibitor of human interleukin 12 production. *The Journal of experimental medicine, 181*(2), 775-779. doi:https://doi.org/10.1084/jem.181.2.775
157. Vanhaesebroeck, B., Guillermet-Guibert, J., Graupera, M., & Bilanges, B. (2010). The emerging mechanisms of isoform-specific PI3K signalling. *Nature reviews Molecular cell biology, 11*(5), 329-341. doi:https://doi.org/10.1038/nrm2882
158. Wang, G., & Bieberich, E. (2018). Sphingolipids in neurodegeneration (with focus on ceramide and S1P). *Adv Biol Regul, 70*, 51-64. doi:10.1016/j.jbior.2018.09.013
159. Wang, P., Li, J. X., Kong, Y. Y., Zheng, S. L., & Miao, C. Y. (2025). Nicotinamide Mononucleotide and Nicotinamide Riboside Improve Dyslipidemia and Fatty Liver but Promote Atherosclerosis in Apolipoprotein E Knockout Mice. *Pharmaceuticals (Basel), 18*(3). doi:10.3390/ph18030281
160. Wang, W., Zhang, L., Battiprolu, P. K., Fukushima, A., Nguyen, K., Milner, K., Lopaschuk, G. D. (2019). Malonyl CoA Decarboxylase Inhibition Improves Cardiac Function Post-Myocardial Infarction. *JACC Basic Transl Sci, 4*(3), 385-400. doi:10.1016/j.jacbts.2019.02.003
161. Wang, W., Zhao, Y., & Zhu, G. (2023). The role of sphingosine-1-phosphate in the development and progression of Parkinson's disease. *Front Cell Neurosci, 17*, 1288437. doi:10.3389/fncel.2023.1288437
162. Wang, X., Ma, D. W., Kang, J. X., & Kulka, M. (2015). n-3 Polyunsaturated fatty acids inhibit Fc epsilon receptor I-mediated mast cell activation. *J Nutr Biochem, 26*(12), 1580-1588. doi:10.1016/j.jnutbio.2015.07.027
163. Wang, Y., Hu, Q., Chen, B., & Ma, D. (2025). Effects of Liupao Tea with Different Years of Aging on Glycolipid Metabolism, Body Composition, and Gut Microbiota in Adults with Obesity or Overweight: A Randomized, Double-Blind Study. *Foods, 14*(5). doi:10.3390/foods14050866
164. Wei, J., Wong, L. C., & Boland, S. (2023). Lipids as emerging biomarkers in neurodegenerative diseases. *International journal of molecular sciences, 25*(1), 131. doi:https://doi.org/10.3390/ijms25010131
165. Wen, H., Gris, D., Lei, Y., Jha, S., Zhang, L., Huang, M. T., Ting, J. P. (2011). Fatty acid-induced NLRP3-ASC inflammasome activation interferes with insulin signaling. *Nat Immunol, 12*(5), 408-415. doi:10.1038/ni.2022
166. Wong, H. S., Dighe, P. A., Mezera, V., Monternier, P. A., & Brand, M. D. (2017). Production of superoxide and hydrogen peroxide from specific mitochondrial sites under different bioenergetic conditions. *J Biol Chem, 292*(41), 16804-16809. doi:10.1074/jbc.R117.789271
167. Wu, S., Liu, X., Yang, H., Ma, W., & Qin, Z. (2023). The effect of lipid metabolism on age-associated cognitive decline: Lessons learned from model organisms and human. *IBRO Neurosci Rep, 15*, 165-169. doi:10.1016/j.ibneur.2023.08.2194

 doi:10.20944/preprints202506.2175.v1

168. Xie, Y., Zeng, Q., Chen, Z., Song, J., Wang, F., Liu, D., Huang, Q. (2025). Dysregulation of sphingolipid metabolism contributes to the pathogenesis of chronic myeloid leukemia. *Cell Death Dis, 16*(1), 282. doi:10.1038/s41419-025-07594-0
169. Yakah, W., Ramiro-Cortijo, D., Singh, P., Brown, J., Stoll, B., Kulkarni, M., Martin, C. R. (2021). Parenteral Fish-Oil Containing Lipid Emulsions Limit Initial Lipopolysaccharide-Induced Host Immune Responses in Preterm Pigs. *Nutrients, 13*(1). doi:10.3390/nu13010205
170. Yu, G., Yang, Z., Peng, T., & Lv, Y. (2021). Circular RNAs: Rising stars in lipid metabolism and lipid disorders. *Journal of cellular physiology, 236*(7), 4797-4806. doi:https://doi.org/10.1002/jcp.30200
171. Yu, H., Guo, Y., Mi, L., Wang, X., Li, L., & Gao, W. (2011). Mitofusin 2 inhibits angiotensin II-induced myocardial hypertrophy. *J Cardiovasc Pharmacol Ther, 16*(2), 205-211. doi:10.1177/1074248410385683
172. Zapata-Gonzalez, F., Rueda F Fau - Petriz, J., Petriz J Fau - Domingo, P., Domingo P Fau - Villarroya, F., Villarroya F Fau - Diaz-Delfin, J., Diaz-Delfin J Fau - de Madariaga, M. A., Domingo, J. C. (2008). Human dendritic cell activities are modulated by the omega-3 fatty acid, docosahexaenoic acid, mainly through PPAR(gamma):RXR heterodimers: comparison with other polyunsaturated fatty acids. (0741-5400 (Print)).
173. Zeb, F., Osaili, T., Naqeeb, H., Faris, M. E., Cheikh Ismail, L., Obaid, R. S., Alam, I. (2025). Scientific basis of dietary inflammatory index (DII): A dietary tool to metabolic syndrome risk. *Clinical Nutrition Open Science, 61*, 138-161. doi:https://doi.org/10.1016/j.nutos.2025.04.002
174. Zhang, Q., Lan, H., Ma, K., Ji, F., & Li, Q. (2025). Comprehensive Quantitative Score and Metabonomics Analysis of the Effect of Centenarians' Diet Patterns on Aging Mice. *Food Science and Human Wellness*. doi:10.26599/FSHW.2025.9250545
175. Zhao, X., Zhang, S., Sanders, A. R., & Duan, J. (2023). Brain Lipids and Lipid Droplet Dysregulation in Alzheimer's Disease and Neuropsychiatric Disorders. *Complex Psychiatry, 9*(1-4), 154-171. doi:10.1159/000535131