Lipids in Health and Disease

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Lipid rafts: novel therapeutic targets for metabolic, neurodegenerative, oncological, and cardiovascular diseases

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Abstract

Lipid rafts are specialized microdomains within cellular membranes enriched with cholesterol and sphingolipids that play key roles in cellular organization, signaling, and homeostasis. This review highlights their involvement in protein clustering, energy metabolism, oxidative stress responses, inflammation, autophagy, and apoptosis. These findings clarify their influence on signaling, trafficking, and adhesion while interacting with the extracellular matrix, cytoskeleton, and ion channels, making them pivotal in the progression of various diseases. This review further addresses their contributions to immune responses, including autoimmune diseases, chronic inflammation, and cytokine storms. Additionally, their role as entry points for pathogens has been demonstrated, with raft-associated receptors being exploited by viruses and bacteria to increase infectivity and evade immune defenses. Disruptions in lipid raft dynamics are linked to oxidative stress and cellular signaling defects, which contribute to metabolic, neurodegenerative, and cardiovascular diseases. This review underscores their potential as therapeutic targets, discussing innovations such as engineered lipid raft transplantation. Advances in analytical techniques such as mass spectrometry have expanded our understanding of lipid raft composition and dynamics, opening new directions for research. By consolidating the current insights, we highlight the therapeutic potential of lipid rafts and highlight the need for further exploration of their molecular mechanisms.

Keywords Lipid rafts, Cellular crosstalk, Metabolic syndrome, Neurodegenerative disorders, Cardiovascular disease, Therapeutic targets

Introduction

Lipid rafts are specialized microdomains within the cell membrane with unique lipid compositions and organizations. They are characterized by high contents of cholesterol and sphingolipids, which distinguish them from the surrounding lipid bilayer. Understanding their dynamic nature is crucial for uncovering the mechanisms underlying both physiological and pathological conditions since they are multifaceted microdomains with significant implications for cellular homeostasis, disease progression, and therapeutic innovation [1].

Historically, the concept of lipid rafts originated from the fluid mosaic model proposed by Singer and Nicolson

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in 1972, which depicted biological membranes as fluid lipid layers with embedded proteins, allowing protein diffusion and interaction. This model revolutionized our understanding of cell membranes at the time. The term "lipid raft" was first introduced by Kai Simons and Elina Ikonen in their 1997 paper published in Nature [2–5]. They described these lipid rafts as microdomains within the cell membrane that are enriched in cholesterol and sphingolipids and play critical roles in cellular processes such as signal transduction and membrane trafficking. Subsequent research suggested the presence of dynamic phase behavior, excitability, and domain formation within membranes, highlighting the intricate and elastic nature of biological membranes. This research expanded the original fluid mosaic concept to include their ability to propagate nerve pulses and form ion-channel-like pores [2–5]. Early work on membrane-derived liposomes revealed the integral relationship between the structural and stability characteristics of lipid membranes. For example, a high cholesterol content helps maintain membrane fluidity and rigidity, which are crucial for membrane stability [6]. The stability and specific protein content of these materials potentially make them promising candidates as nanocarriers for drug delivery. Despite their importance, lipid rafts have been subject to skepticism due to technical challenges in isolating and studying these nanoscale structures. Ongoing debates concerning their stability, definition, and functional relevance persist.

Structural components of lipid rafts are correlated with their functions

Lipid rafts are characterized by a unique composition of cholesterol, sphingolipids, and specific proteins (Table 1). These domains create a more ordered and less fluid environment than the surrounding membrane does, which endows them with crucial physical and functional properties. They play essential roles in various cellular processes, such as signal transduction, membrane trafficking, and cell adhesion [7]. Biochemically, cholesterol is integral to lipid rafts and enhances lipid order and stability by interacting with sphingolipids and phospholipids. The rigid ring structure of cholesterol intercalates with the fatty acyl chains of sphingolipids and phospholipids, regulating membrane fluidity and preventing excessive lipid packing to maintain structural integrity. Sphingolipids, such as sphingomyelin and glycosphingolipids, contribute to tight packing and phase separation from more fluid, unsaturated phospholipid regions, ensuring the stability of these domains. The composition of lipid rafts varies dramatically across different tissues. For example, nervous tissue contains up to 10 times more glycolipids than extraneural tissues do, reflecting the specialized roles these lipids play in brain function and cellular interactions [8]. The molecular interactions between lipid rafts and other cellular components are crucial for their function. For example, cholesterol and sphingolipids within lipid rafts interact with signaling proteins to modulate their activity. Gangliosides, a subset of glycosphingolipids, not only serve as markers for lipid rafts but also bind to specific proteins, influencing signal transduction and cell adhesion [9–11]. These interactions are essential for various cellular processes, including immune responses and neuronal signaling. The distinct enrichment of cholesterol and glycosphingolipids enables rafts to regulate membrane protein function, with cholesterol-enriched rafts often associated with cellular signaling and glycosphingolipid-rich rafts implicated in neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD) [11, 12]. Lipid rafts are further enriched in specific proteins, such as glycosylphosphatidylinositol (GPI)-anchored proteins involved in immune cell signaling [13], and transmembrane proteins, such as growth factor receptors, G-protein coupled receptors, and ion channels, that enable precise signaling control [5].

Recent studies have demonstrated that lipid rafts serve as platforms for the assembly of signaling complexes. For example, the recruitment of Src family kinases to lipid rafts is essential for their activation and subsequent signal transduction. These kinases play pivotal roles in various signaling cascades, including those involved in cell growth and differentiation [14].

Moreover, lipid rafts facilitate the endocytosis and intracellular trafficking of proteins. Caveolin, a structural protein in caveolae, interacts with cholesterol and other lipids within rafts to organize these microdomains. Caveolae are involved in the endocytosis of various ligands,

Table 1 Key components of lipid rafts and their functions

Component	Function
Cholesterol	Regulates membrane fluidity and prevents excessive lipid packing to maintain stability.
Sphingolipids	Ensures tight packing, structural integrity, and phase separation.
Gangliosides	Modulates cell signaling and adhesion; serves as raft markers.
GPI-Anchored Proteins	Involved in immune cell signaling.
Transmembrane Proteins	Enable precise control of signaling events, e.g., growth factor receptors and ion channels.
Src Family Kinases	Facilitate signal transduction cascades.
Caveolin and Flotillin	Assist in organizing lipid rafts and forming caveolae.

including growth factor receptors, which are critical for cellular signaling [15, 16].

Dynamic nature of lipid rafts

Lipid rafts are not static structures; they exhibit fluidity and flexibility within the fluid mosaic model of the cell membrane. The evolution of the lipid raft model accounts for the dynamic and heterogeneous nature of membrane microdomains. This includes various types of membrane domains, such as lipid shells around specific proteins or protein clusters within the membrane [5, 17, 18]. Lateral movement allows the assembly and disassembly of raft domains for cellular functions [19]. Additionally, their ability to cluster or coalesce into larger domains in response to various stimuli significantly influences cellular processes, including signal transduction and membrane trafficking. For example, during immune stimuli, lipid rafts play a critical role in the activation of immune cells. Upon the binding of antigens to T-cell receptors (TCRs), the TCRs accumulate in lipid rafts, facilitating downstream signaling events essential for T-cell activation and immune responses [20]. The swift in-and-out movements of their associated proteins, e.g., receptor molecules and signaling proteins, essentially regulate the cellular signaling and dynamic responses to external stimuli [21]. The long-chain polyunsaturated fatty acids (LCPUFAs) significantly influence microviscosity fluidity at both the membrane plane and the hydrophobic core. Interestingly, LCPUFA supplementation restored the aging-related distorted lipid raft microviscosity in control mice to levels similar to those in younger mice. Despite the increased docosahexaenoic acid (DHA) content resulting from n-3 LCPUFA supplementation, lipid remodeling ensures that lipid raft fluidity is preserved within physiological ranges, suggesting that complex regulatory mechanisms maintain membrane functionality during aging [22].

Major roles in cellular events

Lipid rafts play crucial roles in cellular processes by organizing and regulating key molecular interactions. They mediate mitochondrial–endoplasmic reticulum (ER) crosstalk, influence receptor localization and activation in signaling pathways, and facilitate extracellular vesicle (EV) biogenesis. Additionally, lipid rafts contribute to extracellular matrix (ECM)-cytoskeleton communication and modulate ion channel functions, whereas heat shock proteins help maintain their stability under stress conditions. These multifaceted roles, summarized in Fig. 1, underscore the importance of lipid rafts in maintaining cellular balance and communication. The following sections explore each of these functions in detail, highlighting their molecular mechanisms and physiological relevance.

Lipid rafts control cellular fitness by mediating mitochondrial–endoplasmic reticulum crosstalk

Eukaryotic cells rely on intricate mechanisms to cope with internal and external stressors, including the unfolded protein response, autophagy, and mitochondrial adjustments. Within this framework, lipid rafts play a pivotal role in mediating communication between the ER and mitochondria. Notably, the ER lipid raft associated 1 protein (ERLIN1) regulates calcium flux between these organelles while degrading the inositol 1,4,5-triphosphate receptor (IP3R). This crucial process is modulated by the RNA demethylase ALKBH5 (α-ketoglutarate-dependent dioxygenase homolog 5), which influences ERLIN1-IP3R-dependent calcium signaling [23]. This modulation highlights the vital role of lipid rafts in orchestrating the communication between the ER and mitochondria to promote cell survival. They further operate as lighthouses, guiding signaling molecules, such as G protein-coupled receptors (GPCRs), ionotropic receptors, various kinases and phosphatases, to their destinations via specialized cellular communication [24]. Receptors localized within lipid rafts, such as receptor tyrosine kinases (RTKs), GPCRs [25], and T-cell receptors (TCRs) [26], undergo conformational changes upon ligand binding. This leads to receptor activation and the initiation of downstream signaling cascades. Additionally, the unique lipid raft composition confers the stability and functionality of these signaling complexes, enabling accurate spatiotemporal regulation of cellular responses that influence processes such as proliferation, differentiation, and apoptosis. The formation of signaling complexes within lipid rafts, known as signalosomes, represents a pivotal event in cellular signaling cascades. Signalosomes are multiprotein complexes that form within lipid rafts and play crucial roles in organizing and amplifying cellular signaling cascades [27]. Recent studies have demonstrated that the formation and function of signalosomes are intricately linked to the lipid raft environment. For example, disruptions in the structure and function of lipid rafts have been associated with various diseases, including AD and menopause-related neurodegeneration, where signalosome malfunctions have been observed [28]. On the other hand, the disruption of lipid rafts alters the spatial organization of receptors and signaling molecules, impairing receptor activation and signaling. Cholesterol depletion, a common approach for disrupting lipid rafts, attenuates receptor-mediated signaling pathways, underscoring the importance of lipid rafts in receptor activation. Alterations in cholesterol levels, net charge, and hydrophobicity within lipid rafts associated with fibroblast growth factor receptor 2 (FGFR2) have been observed, particularly in the absence of the adaptor protein GRB2. However, FGFR2 stimulation reduces receptor clustering

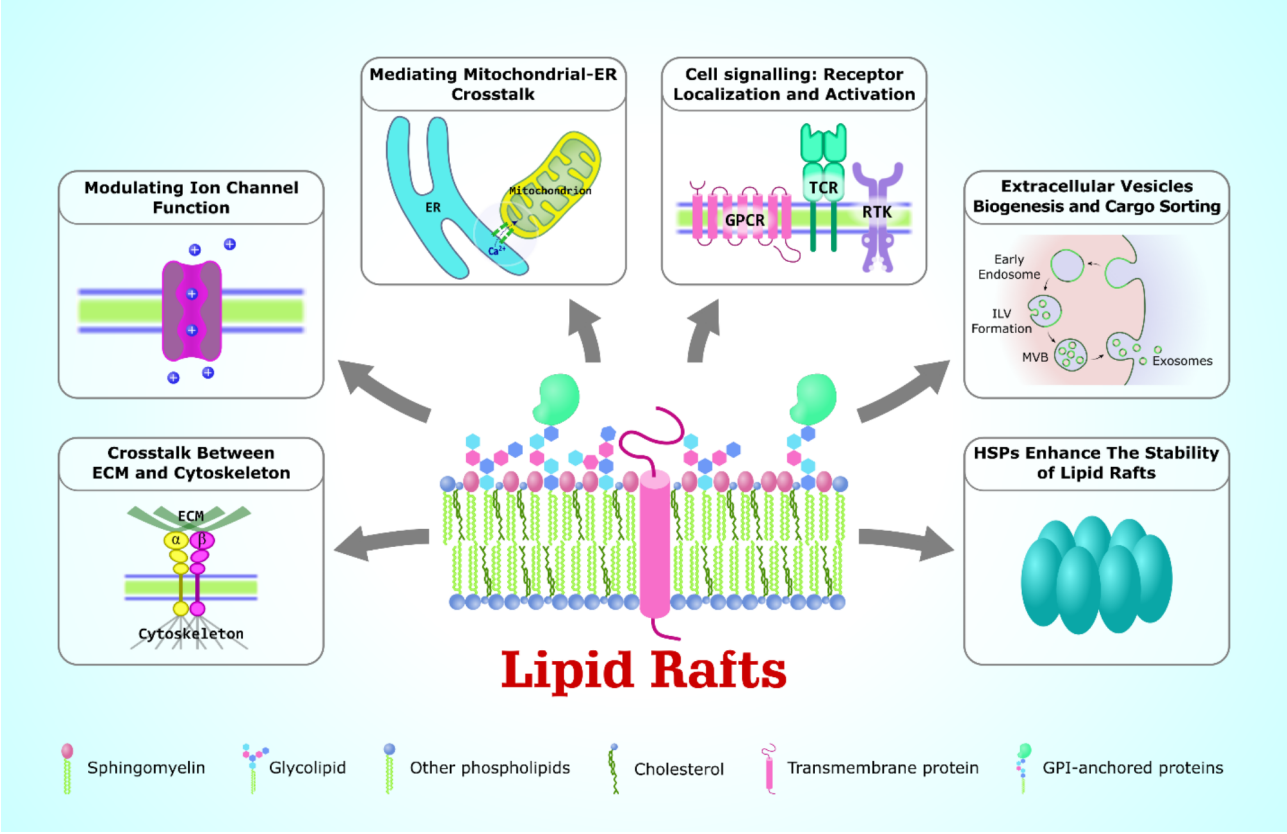

Fig. 1 Major roles of lipid rafts in cellular events. Graphical representation of lipid raft functions in cellular processes, including mitochondrial–ER crosstalk, receptor signaling, EV formation, ECM–cytoskeleton interactions, and ion channel modulation, while heat shock proteins confer raft stability during cellular stress

and dissociation, facilitating changes in receptor conformation and interactions with downstream signaling proteins within lipid rafts [29]. These findings highlight the role of lipid rafts as dynamic platforms for FGFR2 signaling regulation, suggesting that GRB2 prevents FGFR2 from accessing a signaling-competent lipid environment. Therefore, it is logical that any dysregulation of lipid raft-associated receptors has been implicated in various pathological conditions, including cancer, neurodegenerative diseases, and immune disorders [29, 30]. Additionally, posttranslational modifications such as palmitoylation or myristoylation target signaling proteins to lipid rafts, modulating their interactions and conformational changes within these microdomains [31]. A recent theoretical study highlighted their influence on substance trafficking and intracellular pathway activation through multiphysics coupling between phase kinetics and mechanical interactions [32]. These findings suggest strategies for controlling membrane selectivity and intracellular functions on the basis of mechanical principles.

Heat shock proteins and lipid rafts: key interactions for cellular stability and immune function

There is a significant relationship between HSPs and lipid rafts. HSPs, such as HSP70 and HSPB11, interact with lipid rafts through various mechanisms. HSPB11 binds to lipid membranes via cholesterol-dependent interactions, with increased efficiency in cholesterol-rich lipid rafts. HSPs stabilize lipid rafts and protect against stress-induced membrane defects. In particular, HSPB11 stabilizes mitochondrial membranes and lipid rafts, promoting cell survival under stress [33]. Furthermore, crucial immune response-related interactions with HSP70 enhance phagocytosis and antigen presentation by binding to lipid raft microdomains in macrophages [34]. Additionally, constitutively expressed HSPs, such as HSP90, HSC70, HSP60, and HSP40, usually adhere to neuronal lipid rafts, and their dissociation upon cholesterol depletion confirms this association [35]. These interactions support the role of HSPs in maintaining lipid raft integrity under stress conditions. Although efficient HSP glycosylation enhances its stability under stress conditions [36], it remains to be determined whether this stability translates to improved lipid raft stability and protection against stress-induced membrane defects.

Heat shock protein/lipid raft interactions and viral infection

Heat shock proteins (HSPs) play a conserved role associated with lipid rafts. Some viral pathogens have evolved to exploit the interaction between HSPs and lipid rafts (Fig. 2). During respiratory syncytial virus infection, confocal microscopy was used to confirm the association of HSP70 and the viral polymerase complex with the lipid rafts located in the viral inclusion bodies. Moreover, blocking HSP70 with a specific antibody reduced polymerase activity in a dose-dependent manner. These findings confirm the dependence of viral polymerase on HSP70 after its recruitment to lipid rafts associated with viral inclusion bodies [37]. In Japanese encephalitis virus (JEV), a member of Flaviviridae, preincubating Huh7 cells with anti-HSP70 antibodies reduced the number of JEV-positive cells in a dose-dependent manner, indicating that HSP70 is required for viral binding. Further membrane fractionation revealed that HSP70 and JEV E protein (the main spike protein) were colocalized in the raft-rich fractions. Moreover, raft disruption by cholesterol depletion shifted the HSP70/JEV E protein complex to a nonraft region of the membrane, with a subsequent reduction in viral entry without affecting viral binding. These reports emphasize the importance of localizing HSP70 in raft regions for viral entry [38]. Similar findings were revealed for another member of Flaviviridae, dengue virus. The entry of the virus requires the localization of both HSP70 and HSP90 in the lipid raft region [39].

Extracellular vesicles and lipid rafts: mechanisms and therapeutic potential

The impact of lipid rafts on the formation and function of EVs, such as exosomes, is an emerging area of research with significant implications for intercellular communication. Lipid rafts play central roles in the biogenesis, regulation, and cargo sorting processes of these vesicles, thereby regulating a variety of physiological and pathological processes. During biogenesis, lipid rafts support

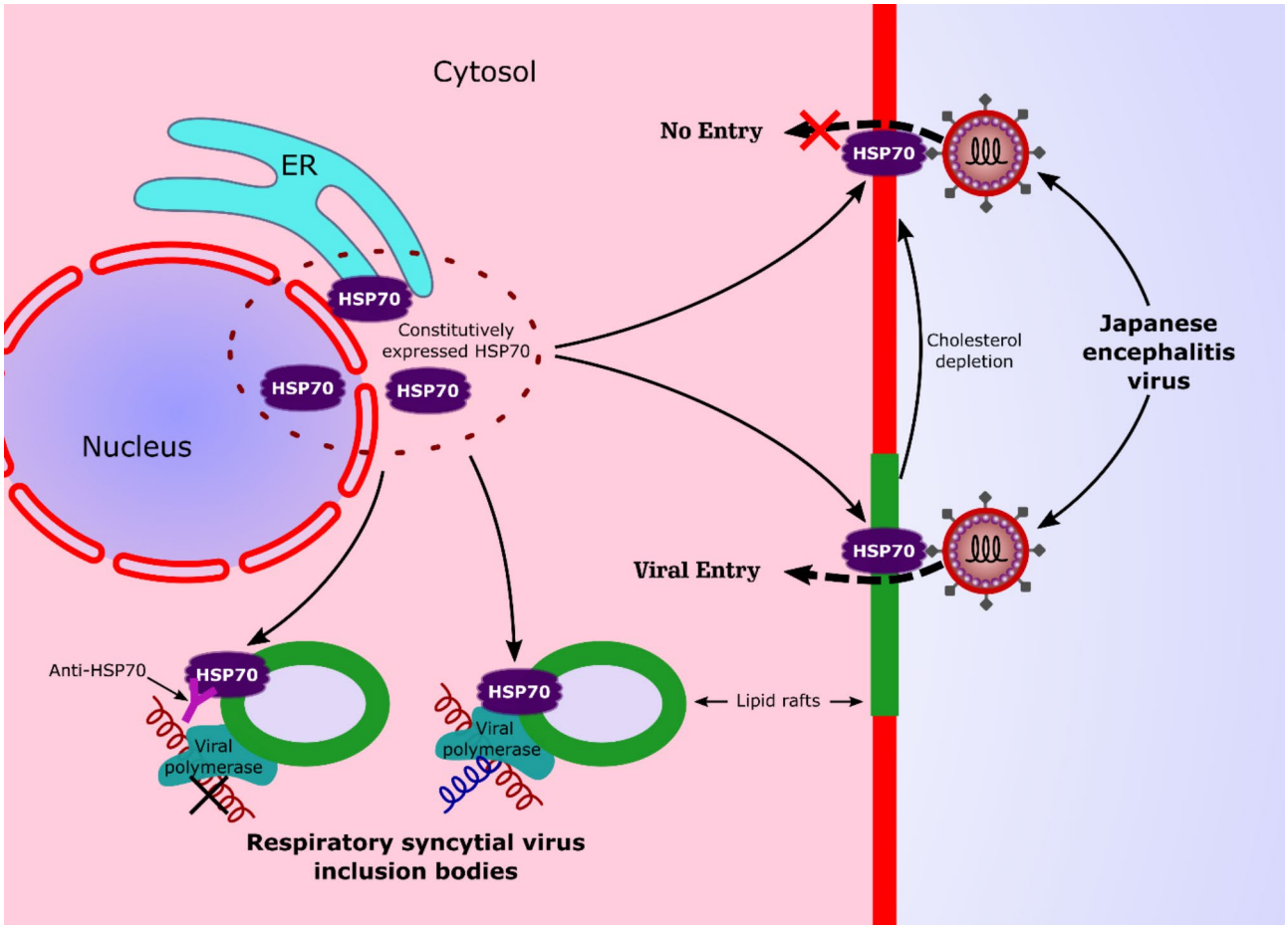

Fig. 2 Heat shock protein–lipid raft interaction and viral infection. Respiratory syncytial virus infection is associated with the formation of inclusion bodies, which are essential for viral replication and polymerase activity. These inclusion bodies are rich in lipid rafts and HSP70. Blocking HSP70 with a specific antibody reduced viral polymerase activity in a dose-dependent manner. Among Japanese encephalitis viruses, HSP70 is an integral part of the viral binding and entry mechanism. Disruption of lipid rafts by cholesterol depletion shifts the virus/HSP70 complex to a nonraft region of the membrane and prevents viral entry without affecting its binding to HSP70

the formation and budding of EVs from the cell membrane while facilitating the assembly of proteins and lipids necessary for vesicle formation [5]. Recent research has shown that cilia elongation in polarized epithelia is promoted during ciliogenesis. For example, apically secreted Gal8 binds to lipid raft components in the transition zone of the primary cilia membrane, influencing the molecular inflow and outflow of the cilia axoneme [40]. This interaction signifies the role of lipid rafts in cellular morphogenesis and has therapeutic potential in the treatment of ciliopathies.

Cholesterol- and sphingolipid-enriched lipid rafts create distinct membrane environments to facilitate the clustering of cargo molecules, including proteins and nucleic acids, before they are sorted into EVs [41]. Moreover, proteins linked to lipid rafts, either through lipid modifications or interactions between proteins, are selectively incorporated into EVs. Posttranslational modifications, such as palmitoylation and glycosylation, strengthen protein associations with lipid rafts, thereby guiding their localization and promoting their recruitment by lipid rafts for incorporation into EVs [42, 43]. This recruitment process involves specific proteins from the endosomal sorting complex required for transport, further ensuring efficient protein sorting into EVs [44]. Therefore, lipid rafts play essential roles in coordinating the regulatory mechanisms that facilitate intercellular communication during EV biogenesis.

Lipid raft-derived mamocrine exosomes: nanovehicles for transmaternal epigenetics

Because the lipid composition of exosomes mirrors that of the resulting lipid rafts, this relationship highlights their common role in forming and functioning as exosomes. In particular, exosomes derived from mammary sources, such as dromedary milk, have attracted interest for their potential health benefits. Previous research highlighted their role as nanovehicles for mammary transcriptomes and their influence on transmaternal epigenetics, suggesting potential intergenerational health benefits [45–48]. Interestingly, dromedary milk exosomes have demonstrated significant antiproliferative effects on various cancer cell lines, including HepaRG, MCF7, Hl60, and PANC12. Moreover, they also exhibit bacteriostatic and fungistatic effects [49].

Diseases where EVs and lipid rafts play key roles

EVs are involved in a variety of diseases because of their role in intercellular communication and cargo transport. Lipid rafts facilitate biogenesis, cargo selection, and the release of EVs by providing a lipid environment enriched with cholesterol and sphingolipids, which promotes membrane curvature and vesicle budding. The structural organization of lipid rafts enables the selective recruitment of key proteins, such as tetraspanins, caveolins, and flotillins, which regulate EV formation and cargo loading [50]. This dynamic process influences the functional properties of EVs in various diseases. For example, in inflammatory conditions such as rheumatoid arthritis and inflammatory bowel disease, lipid raft-enriched EVs propagate inflammatory mediators, exacerbating disease progression. In cardiovascular diseases, lipid rafts contribute to the formation of EVs that mediate endothelial dysfunction and leukocyte recruitment, key factors in the progression of atherosclerosis [51]. In neurodegenerative disorders such as AD, EVs derived from lipid raft domains transport toxic proteins such as amyloid-beta, facilitating disease propagation [52]. Furthermore, in metabolic disorders such as diabetes and nonalcoholic fatty liver disease (NAFLD), lipid raft-associated EVs influence insulin resistance and hepatic lipid metabolism, contributing to metabolic dysfunction [53, 54].

Crosstalk with the exo- and/or cytoskeleton

Lipid rafts play crucial roles in cancer progression by mediating interactions between the extracellular matrix (ECM) and the cytoskeleton. Recent investigations [47] have highlighted how lipid rafts regulate the clustering of adhesion molecules, such as β1 and β3 integrins, at the leading edge of migrating cells. This clustering is essential for facilitating cell–ECM interactions and cytoskeletal organization, which are necessary for lamellipodia formation and tumor cell migration [55]. Lipid rafts organize key signaling proteins, integrins, and cytoskeletal regulators, playing pivotal roles in controlling processes such as actin polymerization, microtubule stability, and cellular movement. The interaction between lipid rafts and the underlying cytoskeleton is vital for maintaining cellular polarity, regulating adhesion to the ECM, and driving migration. Disruption of lipid raft integrity impairs the localization and function of these critical signaling molecules, leading to altered cell motility, which can influence disease progression, including cancer metastasis. This dynamic relationship enables cells to adapt to changing extracellular conditions and respond to stimuli such as shear stress, receptor activation, and nutrient demand [56].

Recent studies have also shown that nanoparticles can destabilize lipid rafts, disrupting tumor cell adhesion and migration, which may reduce metastatic potential by impairing epithelial-to-mesenchymal transition, a process heavily dependent on lipid raft-mediated signaling [20, 57]. Additionally, lipid rafts regulate matrix metalloproteinases, critical enzymes responsible for ECM degradation and tumor invasion [58]. Targeting lipid raft integrity through manipulation of sphingolipid and cholesterol contents or by using antibodies against gangliosides has emerged as a promising strategy in preclinical

models to modulate growth factor signaling within lipid rafts, offering therapeutic potential in cancer metastasis [59]. Thus, a deeper understanding of lipid raft–ECM interactions could unveil valuable therapeutic targets for cancer treatment.

Furthermore, lipid rafts are crucial for cytoskeletal dynamics. The enrichment of specific lipids, particularly sphingolipids, promotes lateral segregation of membrane components, including cytoskeleton-associated proteins. This segregation creates microenvironments that facilitate the recruitment and activation of cytoskeletal regulators, such as Rho GTPases, which govern critical processes such as cell migration and division [53]. Lipid rafts serve as scaffolds for recruiting and assembling cytoskeletal components, such as actin-binding proteins and microtubule-associated factors, to facilitate cytoskeleton spatial organization. This interaction results in precise changes in cellular morphology and motility [54, 55]. The importance of lipid raft–cytoskeleton interactions extends beyond individual cells, orchestrating complex processes such as tissue morphogenesis, immune cell activation, and neuronal synapse formation. Dysregulation of these interactions underlies pathological conditions, including cancer metastasis, neurodegenerative diseases, and cardiovascular disorders [56–58], demonstrating the therapeutic potential of targeting these interactions for disease intervention.

Moreover, caveolae, specialized lipid rafts enriched in cholesterol and glycosphingolipids, have distinct protein compositions, including caveolins and cavins, and are involved in regulating critical cellular processes [24, 48, 49]. The endothelial glycocalyx, which interacts with lipid rafts, contributes to vascular homeostasis and stability [50]. Furthermore, lipid raft-associated glycosaminoglycans (GAGs) play important roles in the bioactivity of fibroblast growth factor-2 (FGF-2), promoting angiogenesis and protecting FGF-2 from enzymatic degradation [49, 51]. These findings suggest that lipid rafts, particularly caveolae, may be involved in vascular pathologies such as eclampsia, a severe pregnancy complication associated with impaired placenta–fetal communication. Our previous work [52] highlighted significant differences in GAG sulfation patterns and the mRNA levels of GAG O-sulfotransferases in preeclampsia, indicating a link between altered placental GAGs and preeclampsia. Since lipid rafts are crucial for maintaining blood vessel stability, alterations in the context of GAG changes may contribute to the onset of eclampsia.

In addition, caveolae-mediated signaling has been shown to confer cardioprotection during ischemia–reperfusion injury. A study examining the involvement of the actin cytoskeleton during postconditioning revealed that disruption of the cytoskeleton in rat hearts subjected to I/R resulted in significant loss of cardioprotection, along with morphological alterations in cardiac tissue and compromised mitochondrial function [59]. These findings underscore the importance of the actin cytoskeleton in facilitating caveolae-mediated signaling and illustrate the role of lipid rafts in cardioprotection following reperfusion injury. The intricate interplay between lipid rafts and cytoskeletal dynamics is critical for maintaining both cellular physiology and pathology, precisely shaping the cellular landscape while regulating cytoskeletal organization in both spatial and temporal contexts.

Lipid rafts also influence ion channel behavior. Simulated membrane systems capable of forming raft-like domains enriched in cholesterol have demonstrated that lipid lateral phase separation significantly affects ion channel kinetics [60, 61]. These findings confirm the modulatory effect of lipid rafts on ion channels, suggesting that lipid rafts play additional roles in cellular signaling. Additionally, lipid rafts serve as scaffolds for various membrane proteins, including voltage-gated sodium channels (VGSCs), which are essential for neuronal excitability. Anesthetics target lipid rafts to exert their effects on the nervous system, with local anesthetics blocking VGSC pores and disrupting lipid raft packing, whereas inhalation anesthetics induce changes in raft size and composition. These alterations facilitate substrate access, contributing to lipid-driven anesthesia [62]. Therefore, lipid rafts, through their interactions with the cytoskeleton and their role in mediating critical cellular processes, clearly hold significant therapeutic potential. Understanding the intricate crosstalk among lipid rafts, the ECM, and cytoskeletal dynamics offers promising avenues for developing interventions for cancer metastasis, cardiovascular diseases, and other pathologies.

Lipid rafts and blood barriers

The integrity of cellular and tissue barriers is a key indicator of health. These barriers block harmful environmental elements (barrier function) and allow the passage of essential ions, signaling molecules, and nutrients to maintain the internal environment (transport function). Numerous cellular and subcellular barriers exist, and some are interconnected. The principal physiological barriers include the blood–retinal barrier (BRB), blood–brain barrier (BBB), blood–testis barrier (BTB), renal glomerular/tubular barrier, intestinal barrier, pulmonary blood–alveolar barrier, blood–placental barrier, and skin barrier [60]. Most of these blood barriers utilize lipid rafts to protect against harmful substances while permitting nutrient transport. In the BBB, which safeguards the brain from pathogens and toxins while regulating the transport of essential molecules, lipid rafts in endothelial cells play a selective role in signal transduction, enabling effective communication between the brain and peripheral blood circulation [61]. They also mediate the transport

of molecules across the BBB via endocytosis and transcytosis and further contribute to tight junction stability, which is crucial for maintaining selective permeability and protection against the development of neurodegenerative diseases [62]. Moreover, their ability to modulate caveolin-1 and claudin-5 helps preserve BBB integrity and proper neural function by preventing increased tissue permeability [63]. The BRB protects the neural retina, with lipid rafts in retinal pigment epithelium and endothelial cells playing crucial roles in nutrient exchange and waste removal. This supports retinal function, signal transduction, and inflammation regulation, especially in conditions like diabetic retinopathy. Vascular endothelial growth factor enhances caveolae-mediated endocytosis, increasing BRB permeability. Downregulation of caveolae and caveolin-1 often leads to reduced tight junction protein levels and higher permeability, highlighting their role in paracellular transport. Caveolae also aid oncotic pressure gradients by transcytosing albumin, forming caveolin-1 clusters that facilitate transcytosis [64]. Furthermore, lipid rafts indirectly increase bacterial entry during gut infection. Cholesterol- and sphingolipid-enriched rafts trigger inflammation through NOD2 and NF-κB activation. In contrast, lowering cholesterol levels with simvastatin reduces infection. These findings demonstrate the role of lipid rafts in the response to bacterial invasion and gut protection [65]. The BTB is crucial for spermatogenesis, dividing the seminiferous epithelium into basal and adluminal compartments. Unlike most barriers, the BTB includes tight junctions, ectoplasmic specializations, desmosomes, and gap junctions, creating a unique environment for meiosis and spermiogenesis. Lipid rafts regulate BTB integrity by facilitating the selective movement of nutrients and signaling molecules, supporting the development of spermatocytes into mature spermatozoa [66, 67].

Lipid rafts: guardians of cellular homeostasis

Recent research highlights their significant involvement in maintaining cellular homeostasis and influencing processes such as energy metabolism, oxidative stress responses, inflammation, autophagy, and apoptosis.

Roles in protein crumbling and cellular dysfunction

The role of lipid rafts in protein misfolding and aggregation as consequences of the pathogenesis of neurodegenerative diseases has been resolved [68]. Accumulated evidence from structural biology, biophysics, and cell biology reveals how lipid raft composition and dynamics affect protein structure and function, leading to cellular dysfunction [69, 70]. Dysregulated lipid raft-mediated protein misfolding is linked to neurodegenerative disorders, disrupting cellular homeostasis and inducing neuronal toxicity. They also facilitate the aggregation of disease-associated proteins and promote their downstream signaling pathways [71].

Integrative role in autophagy and cellular homeostasis

Lipid rafts play essential roles in autophagy, a cellular process essential for degrading and recycling damaged organelles and proteins. This is accomplished by facilitating the assembly and regulation of autophagy-related signaling complexes, impacting cellular responses to diverse stimuli and therefore offering insights into therapeutic interventions that can be used to modulate disease mechanisms and cellular homeostasis [72]. Targeting lipid rafts by modulating their composition or disrupting their integrity provides a valuable framework for elucidating the pathophysiology of metabolic disorders such as obesity and type 2 diabetes mellitus (T2DM) [73]. Moreover, the lipid rafts are crucial for the formation of EVs, including transport, endocytic, exocytic, synaptic, and virus-associated vesicles. By regulating autophagy-related signaling complexes, they influence the generation and release of extracellular macrovesicles. These vesicles are key in intercellular communication and biomolecule transport, providing new insights into cellular communication and potential therapeutic targets, highlighting their significance in health and disease [74].

Lipid rafts in energy stress, oxidative balance, and cellular resilience

Lipid rafts play crucial roles in cellular responses to metabolic stress, oxidative damage, and nutrient deprivation, shaping key pathways involved in survival and disease progression. Acute energy overload disrupts lipid raft integrity, altering lipid composition, increasing oxidative stress, and triggering inflammation—mechanisms implicated in apoptosis and metabolic disorders [82–85]. Conversely, lipid rafts are essential for cellular adaptation to starvation, influencing survival through lipid reserves and protein–lipid interactions [86]. Understanding their role in nutrient scarcity may provide therapeutic insights into enhancing cellular resilience and mitigating disease progression [87].

Under oxidative stress, lipid rafts regulate redox-sensitive signaling pathways, orchestrating antioxidant defense mechanisms to counteract oxidative damage [88]. They fine-tune cellular responses through spatial–temporal control of signaling molecules, maintaining redox balance while mitigating oxidative stress-induced cellular dysfunction [77]. However, excessive oxidative stress disrupts raft organization via lipid peroxidation, impairing their role in cellular signaling [89]. These disruptions also affect immune function, weakening responses to external stressors such as infections and xenobiotics and exacerbating inflammatory conditions [90].

By modulating lipid raft composition and targeting associated signaling pathways, potential therapeutic strategies can be developed to counteract metabolic dysfunction, oxidative stress, and inflammation, thereby promoting cellular homeostasis and disease resistance.

Lipid rafts in immune regulation: implications for autoimmune and inflammatory diseases

Inflammation is a vital immune response to infections, cellular damage, or injury. While typically self-limiting, prolonged immune activation leads to chronic inflammation and irreversible tissue damage, a hallmark of autoimmune disorders such as type 1 diabetes, multiple sclerosis, psoriasis, inflammatory bowel disease, and Grave's disease [20]. Lipid rafts play a central role in modulating immune signaling, influencing both innate and adaptive immunity, and are emerging as potential therapeutic targets [91].

A prime example is antiphospholipid syndrome (APS), an autoimmune disorder often linked to systemic lupus erythematosus characterized by a hypercoagulable state that predisposes individuals to vascular thrombosis and obstetric complications [92, 93]. The interaction between antiphospholipid antibodies and lipid raft-associated receptors initiates pathological signaling cascades, amplifying thromboinflammatory responses [94]. Notably, anti-β2 glycoprotein 1 antibodies exploit lipid rafts to modulate LRP8/ApoER2 signaling and nitric oxide production, contributing to endothelial dysfunction and thrombosis [95]. Given their role in APS pathogenesis, lipid raft-targeted therapies, such as statins and beta-cyclodextrins, have shown promise in disrupting these pathogenic processes by modulating cholesterol levels and interfering with lipid raft-mediated antibody signaling [96]. Additionally, lipid raft regulation of key cardiovascular pathways, including tissue factor production and endothelial nitric oxide synthase (eNOS) activity, underscores their potential as therapeutic targets in APS-associated vascular diseases [97, 98].

In addition to APSs, lipid rafts significantly influence immune cell function in autoimmune disorders by modulating antigen presentation, cytokine secretion, and T and B-cell activation. Dysregulation of these processes results in inappropriate immune responses, fostering autoantibody production and tissue destruction [24, 91, 114, 115]. Moreover, alterations in lipid raft composition impact immune cell behavior, exacerbating autoimmune pathologies [115]. A recent study demonstrated that lipid rafts modulate interferon alpha (IFN-α) signaling in paroxysmal nocturnal hemoglobinuria cells, identifying cavin1 as a potential target for suppressing IFN-α-driven inflammation. This finding highlights how immune cells exploit lipid rafts for survival in unfavorable environments, offering new avenues for autoimmune disease treatment [21].

Understanding the role of lipid rafts in immune signaling has profound implications for immunotherapy and vaccine development [75]. Targeting lipid raft dynamics could provide innovative strategies to regulate immune responses, mitigate chronic inflammation, and develop novel treatments for autoimmune and inflammatory diseases.

Lipid rafts in metabolic syndrome and fatty liver disease: insights into obesity, diabetes, and therapeutic strategies

Metabolic syndrome (MS), characterized by insulin resistance, obesity, hypertension, and dyslipidemia, has been increasingly linked to the functional dynamics of lipid rafts. Owing to their structural composition, lipid rafts facilitate the organization and function of insulin receptors and other critical proteins involved in metabolic pathways. Disruption of lipid raft integrity impairs insulin receptor function with the development of insulin resistance, a hallmark of MS [24, 59]. Furthermore, lipid raft-associated proteins, such as caveolins and flotillins, modulate glucose uptake and lipid metabolism, and alterations in their expression during obesity and T2DM exacerbate metabolic dysfunctions [16, 76]. There is another close link between lipid rafts and MS-related inflammatory responses. Lipid raft recruitment of inflammatory receptors and signaling molecules can amplify inflammatory pathways, contributing to the chronic low-grade inflammation observed in MS [77]. Therefore, targeting lipid raft composition might offer novel strategies to mitigate insulin resistance, improve metabolic health, and reduce the risk of associated cardiovascular diseases [78]. At the adipocyte level, lipid raft alterations associated with metabolic dysregulation and inflammation in obesity and T2DM impact key metabolic processes, including fatty acid translocation, lipid biosynthesis, and storage, ultimately contributing to metabolic imbalances. Furthermore, the orchestration of adipogenesis and adipocyte maturation involves lipid raft-dependent signaling cascades, such as the recruitment of the fatty acid translocase FAT/CD36 and the activation of the peroxisome proliferator-activated receptor gamma and extracellular signal-regulated kinase pathways [24]. The modulation of lysophosphatidylcholine acyltransferase 3 (LPCAT3), a crucial phosphatidylcholine-synthesizing enzyme in adipose tissue, has gained considerable attention in the context of insulin resistance in T2DM patients. LPCAT3-deficient mice exhibit increased insulin sensitivity, suggesting that LPCAT3 may modulate membrane phospholipid saturation [16]. Furthermore, high-content imaging studies revealed an increase in lipid raft clustering in endothelial cells, particularly in the diabetic aorta,

suggesting their role in vascular complications associated with T2DM. Further exploration of 'metabolic memory' in chronic diabetic complications is another promising avenue to interpret the intricate interplay between lipid rafts and disease pathogenesis [79].

Similarly, fatty liver disease (hepatic steatosis), whether nonalcoholic (NAFLD) or alcohol-induced, also involves lipid dysregulation, with lipid raft-mediated cellular signaling playing a crucial role in its progression [103]. Shared mechanisms such as mitochondrial dysfunction and ER stress contribute to disease pathology [104, 105]. Notably, DHA, an n-3 polyunsaturated fatty acid, has been shown to mitigate ethanol-induced oxidative stress and cell death by modifying lipid rafts, underscoring its potential as a therapeutic target [106]. Lipid rafts further mediate the therapeutic benefits of ursodeoxycholyl lysophosphatidylethanolamide (UDCA-LPE), a potent hepatoprotective compound with antifibrogenic properties. UDCA-LPE interacts with these membrane microdomains to modulate integrin signaling, which is essential in processes such as hepatic fibrosis [80]. They mediate the link between fatty liver disease and insulin resistance by influencing insulin signaling. Alterations in lipid raft composition, such as those caused by hexosaminidase A, negatively impact glucose uptake and tissue insulin sensitivity [81]. Moreover, the impact of lipid rafts bridges MS to distant organs such as the eye. The recently resolved role of lipid raft-associated lipid metabolism in the pathogenesis of retinal diseases has expanded our understanding of its therapeutic potential in both metabolic and retinal conditions [82, 83]. The term inflammarafts has emerged to reveal the role of enlarged lipid rafts charged with inflammatory receptors and adaptor proteins, such as toll-like receptor 4 (TLR4), in inflamed cells [84]. Increased lipid raft density, elevated cholesterol levels, and prolonged presence of inflammatory receptors within these rafts occur during inflammation [85]. Furthermore, there is a marked recruitment of TLR4 into lipid rafts via the ATP-binding cassette transporter A1 (ABCA1)-dependent cholesterol efflux pathway following lipopolysaccharide exposure in macrophages and microglia [76, 82, 86].

Interplay of lipid rafts in cellular fate: balancing apoptosis and cancer

Lipid rafts play crucial roles in balancing apoptosis and cancer [87]. During apoptosis, lipid rafts facilitate the organization of death receptors required for the apoptotic cascade. A higher concentration of signaling molecules within lipid rafts indicates greater amplification of the death signal with efficient execution of apoptosis [88]. Conversely, lipid rafts promote cell survival and proliferation in cancer, which is mediated by altered normal apoptotic signaling, with the overexpression of raft-associated proteins such as flotillins. This dysregulation tips the balance in favor of cell survival and proliferation [89]. An altered composition is commonly observed in various types of cancer, recognized by the hyperactivation of critical oncogenes, including epidermal growth factor receptor (EGFR), Src family kinases, and other tyrosine kinases. This dysregulation of lipid raft architecture plays a significant role in enhancing oncogenic signaling pathways, contributing to cancer development and sustenance [24, 90].

Apoptosis signaling pathways

Lipid rafts harbor death receptors such as the death receptor (FAS) and TNFR1, which are pivotal for the initiation of apoptosis (Fig. 3) [20]. Ligand binding leads to the formation of a death-inducing signaling complex (DISC) within lipid rafts, recruiting caspases to initiate the apoptotic cascade [88]. This process enhances the formation of the DISC by recruiting FAS-associated death domain protein (FADD) and procaspase-8. When multiple DISC complexes aggregate within raft platforms, they form a cluster known as the cluster of apoptotic signaling molecule-enriched rafts (CASMER), which is highly effective in triggering apoptosis. Furthermore, lipid rafts organize and regulate key apoptotic proteins, serving as platforms for the recruitment and activation of various apoptotic proteins, including caspases and proapoptotic kinases, facilitating efficient apoptosis [16]. In the mitochondrial apoptosis pathway, however, lipid rafts harbor Bcl-2 family proteins that regulate mitochondrial integrity. Therefore, the disruption of lipid rafts potentially alters the interactions between pro- and antiapoptotic Bcl-2 family members, affecting mitochondrial membrane permeabilization and the release of apoptotic factors, thus playing a key role in regulating apoptosis [24]. Additionally, lipid rafts are crucial in generating ceramide through sphingomyelinase activity, which significantly influences cancer cell apoptosis. Upon activation, sphingomyelinases hydrolyze sphingomyelin to produce ceramide within these microdomains. This accumulation initiates apoptotic signaling by forming ceramide-rich platforms that cluster proapoptotic proteins and receptors, increasing signaling efficiency. Ceramide activates caspases, modulates Bcl-2 family proteins, and disrupts survival pathways such as the PI3K/AKT and ERK pathways, tipping the balance toward cell death. Therefore, improved regulation of lipid raft-mediated ceramide production affords potential cancer therapies that target sphingomyelinase activity or increase ceramide accumulation, promoting apoptosis in cancer cells [91]. Despite their role in apoptosis, lipid rafts also facilitate survival signaling under certain conditions. They also support the transmission of survival signals, such as those mediated by insulin-like growth factor (IGF). Upon activation

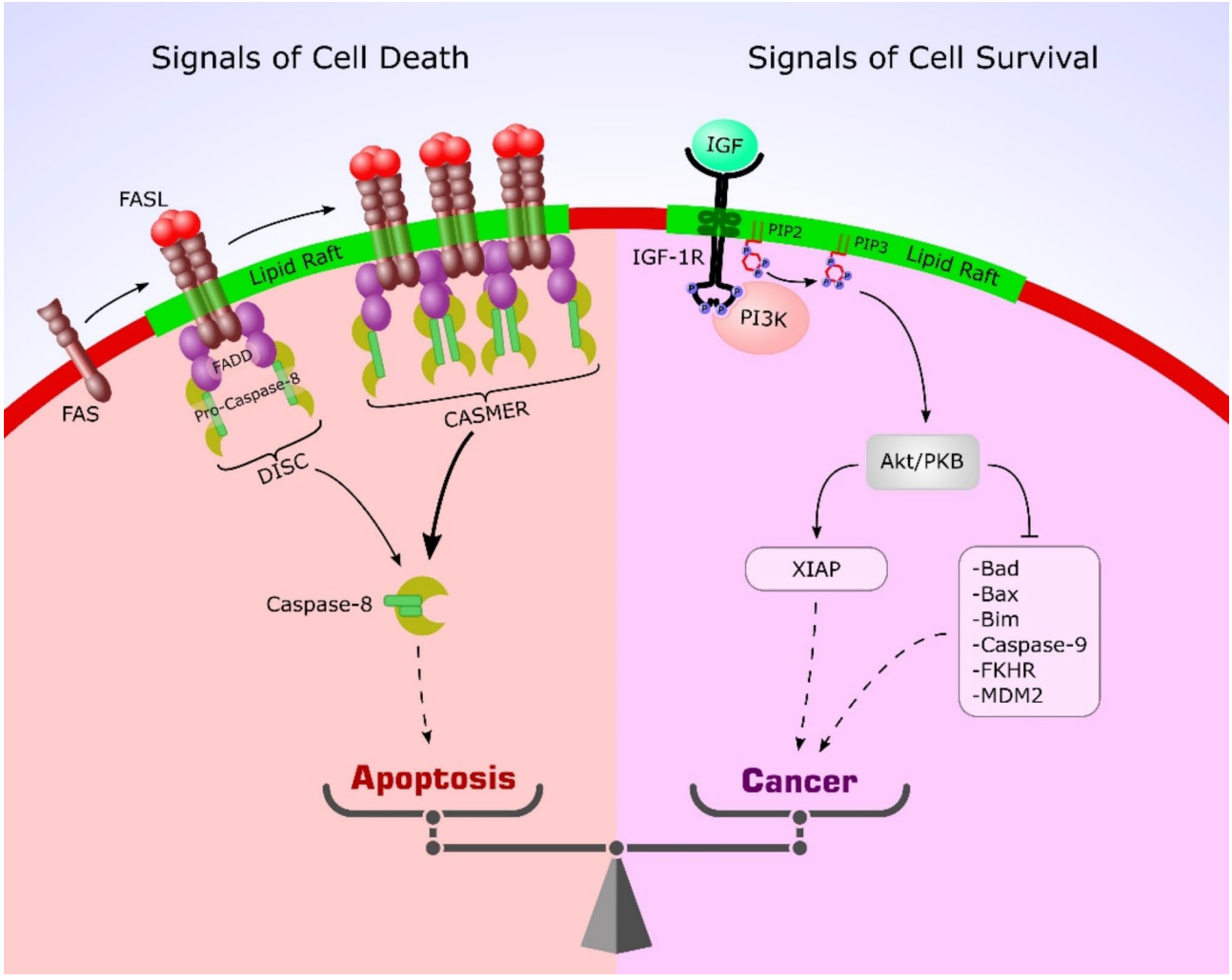

Fig. 3 Lipid rafts balance apoptosis and cancer. Lipid rafts harbor and affect the major receptors involved in cell death and survival signaling. Recruitment and accumulation of the FAS death receptor in lipid rafts upon apoptotic signals through FAS ligands enhances the formation of the DISC by recruiting FADD and pro-caspase-8. When several DISC signaling complexes are brought together in raft platforms, they form a CASMER that is more potent in inducing apoptosis. On the other hand, lipid rafts facilitate the transmission of survival signals such as IGF. When the IGF-1 receptor (IGF-1R) is stimulated by IGF, it activates PI3K, which phosphorylates colocalized PIP2 and produces PIP3, which activates PKB. Then, Akt/PKB phosphorylates and inhibits pro-apoptotic mediators such as BAD, BIM, caspase-9, FKHR, and MDM2 or activates prosurvival mediators such as XIAP

by IGF, the IGF-1 receptor (IGF-1R) within lipid rafts activates phosphoinositide 3-kinase (PI3K), leading to the phosphorylation of colocalized phosphatidylinositol 4,5-bisphosphate (PIP2) and the subsequent production of phosphatidylinositol (3,4,5)-trisphosphate (PIP3). This, in turn, activates Akt/protein kinase B (PKB), which phosphorylates and inhibits various proapoptotic mediators, such as BCL2-associated agonist of cell death (BAD), BCL2-associated X protein (BAX), Bcl-2 interacting mediator of cell death (BIM), caspase-9, Forkhead protein (FKHR), and mouse double-minute-2 homolog (MDM2). Additionally, Akt/PKB promotes the activation of prosurvival mediators, including X-linked inhibitor of apoptosis protein (XIAP) [20].

The role of lipid rafts in cancer development, drug resistance, and therapeutic potential

Lipid rafts, particularly those enriched in cholesterol within the plasma membrane and mitochondria, play pivotal roles in cancer cell survival and drug resistance. By promoting dysregulated signaling pathways, these microdomains facilitate increased cell proliferation, survival, migration, and metastasis, thereby contributing to the aggressive behavior of cancer cells [16, 92, 93]. Furthermore, the dynamic nature of lipid rafts aids in the formation of invadopodia, specialized protrusions that exacerbate cancer cell invasion and metastasis, indicating their critical involvement in tumor progression [91]. By driving these hallmarks of cancer, lipid rafts significantly influence the tumor microenvironment by regulating

cholesterol and lipid distribution. This regulation impacts oxidative stress and ferroptosis, a form of programmed cell death that is particularly effective against treatment-resistant cancer cells. Disruption of the structure and function of lipid rafts enhances ferroptosis and therefore provides a promising strategy to improve therapeutic outcomes and overcome resistance to conventional cancer treatments [94]. The rafts also serve as platforms for drug-resistance proteins, including efflux pumps like P-glycoproteins clustered within caveolae, which actively expel chemotherapeutic agents and diminish treatment efficacy. Targeting lipid raft-associated signaling, such as EGFR, IGF1R, and notably HER2, offers a promising therapeutic strategy. Statins, which deplete membrane cholesterol, disrupt raft integrity and inhibit these signaling pathways—including HER2-driven oncogenic signaling—thereby restoring drug sensitivity in cancer cells [95–97]. Additionally, lipid raft-associated proteins such as caveolin and flotillin have emerged as valuable prognostic markers and potential therapeutic targets, further underscoring their importance in cancer biology [98]. Collectively, these findings reveal the intricate balance orchestrated by lipid rafts between promoting cancer progression and offering therapeutic opportunities. Understanding and exploiting this duality could open avenues for innovative strategies to favor apoptosis and improve cancer treatment outcomes.

Lipid rafts in neuroscience and neurodegenerative diseases

Lipid rafts are currently gaining significant interest in the fields of neuroscience and neurodegenerative diseases because of their influence on neuronal function and disease progression. They contribute to brain health, and dysregulation of their dynamics has been implicated in several neurodegenerative diseases [99]. Early alterations in the composition of lipid rafts often signal the onset of disease-related neuropathological changes [100]. Alterations in lipid profiles in diseases such as amyotrophic lateral sclerosis (ALS) result not only from oxidative stress but also from lipid metabolism abnormalities and raft membrane biogenesis [101]. On the other hand, sex differences in neurodegenerative diseases related to oxidative stress may be influenced by androgens, such as testosterone, which increase oxidative stress via the membrane androgen receptor (mAR) located in lipid rafts. Disrupting the interaction between mAR and lipid rafts can mitigate androgen-induced neurotoxicity [102]. Notably, AD, PD, and prion diseases are associated with cholesterol as a primary component of lipid rafts. Lipid rafts are essential for neuronal signaling and synapse formation. The "aging" of lipid rafts in nerve cells is an initial step in the onset of neurodegenerative diseases such as AD. During the aging process, these lipid rafts can undergo alterations in lipid and protein composition, potentially impacting cellular signaling pathways and membrane dynamics. These changes are significant because they may contribute to the onset and progression of age-related diseases, including neurodegenerative disorders [102]. Age-related modifications in lipid rafts alter the interactions and distribution of signaling molecules, including glutamate receptors and ion channels involved in memory formation, ultimately contributing to cognitive decline [22]. The disruption of lipid rafts can affect immune responses and contribute to the neuroinflammation observed in AD. This neuroinflammation is particularly driven by dysfunction of complement-regulatory proteins, which is linked to the compromised structure of lipid rafts [103]. In addition to amyloid-beta (Aβ), lipid rafts may contribute to the aggregation and misfolding of tau protein in AD. These cellular microenvironments host Aβ dimers, prion protein (PrPc), and Aβ dimer/PrPc complexes and exhibit increased levels of various molecules with Aβ dimer accumulation [104]. Consequently, lipid rafts play important roles in the production and clearance of Aβ peptides, and their alterations influence the processing of amyloid precursor protein (APP) and Aβ generation [105]. The traditional paradigm linking AD to the accumulation of amyloid plaques in the brain [106] is being reevaluated in light of emerging evidence. Notably, the Osaka mutation (E693Δ), which is strongly associated with familial AD [107], does not lead to amyloid plaque formation. Instead, this mutation accelerates the formation of synaptotoxic amyloid beta (Aβ) oligomers, which are implicated in AD pathology without the presence of amyloid plaques [108]. Current research suggests that small Aβ oligomers, particularly those that form amyloid pores, are the primary pathogenic agents in AD. These oligomers are capable of inducing a significant influx of Ca^{2+} ions, triggering a neurotoxic cascade that is characteristic of the disease. Lipid rafts play a pivotal role in the formation of these toxic oligomers. Aβ peptides first bind to gangliosides in the cell membrane, which facilitates their insertion into the lipid bilayer. This interaction, in conjunction with cholesterol, promotes the oligomerization of Aβ into amyloid pores [109]. The resulting dysregulation of calcium homeostasis initiates a series of pathological events, including oxidative stress, tau hyperphosphorylation, and neuronal dysfunction, all of which contribute to the neurodegenerative process observed in AD. Moreover, a previous study [110] revealed that voltage-dependent anion channel 1 (VDAC1) is associated with APP and Aβ within lipid rafts in neurons and that Aβ exposure-induced VDAC1 dephosphorylation is correlated with cell death, indicating that Aβ influences the phosphorylation of VDAC1 in neuronal lipid rafts and suggesting that lipid rafts play crucial roles in the development and progression of AD.

Lipid rafts: a nexus in Alzheimer's disease and diabetes pathology

AD and T2DM share a common scenario of protein misfolding and aggregation, involving tau and amylin, respectively. Recent multiscale molecular dynamics simulations have clarified the crucial interactions between hetero-oligomers, potent neurotoxic agents, and lipid raft membranes in regulating cellular signaling. The hetero-oligomers showed increased affinity for ganglioside M1 (GM1) in cholesterol- and sphingolipid-enriched raft domains, which was mediated by hydrophobic and hydrophilic interactions. These results emphasize the common role of lipid rafts in the pathology of AD and T2DM [111, 112].

Lipid rafts contribute to Parkinson's disease

PD is a neurodegenerative disorder characterized by the progressive loss of dopaminergic neurons in the substantia nigra region of the brain. Increasing evidence suggests the involvement of lipid rafts in its pathogenesis. α-Synuclein, a key player in PD, forms Lewy body aggregates in the PD-affected brain. Recent studies have revealed a potential interaction between lipid rafts and α-synuclein, suggesting their contribution to α-synuclein aggregation and toxicity [113].

Lipid raft dynamics in neonatal hypoxic-ischemic encephalopathy: implications for therapeutic interventions

Addressing hypoxic-ischemic encephalopathy (HIE) in neonatal care poses significant challenges, with current treatments primarily relying on hypothermia. The neonatal cerebellum is particularly vulnerable to HIE, which disrupts lipid raft dynamics and alters membrane protein distribution, impacting cellular signaling and development. Therefore, a recent study [114] proposed lipid rafts as potential targets for future interventions to mitigate the effects of HIE in neonates.

Alterations in lipid rafts in the ALS spinal cord

In sporadic ALS, lipid rafts from affected spinal cords exhibit significant changes in composition. Recent investigations revealed increased levels of n-6 LCPUFAs and n-7/n-9 monounsaturates, along with a lower saturated-to-unsaturated fat ratio. ALS lipid rafts also exhibit increased cholesteryl esters and unusual phospholipids with a reduction in sulfated sphingolipids. These alterations indicate that lipid rafts are destabilized in ALS [101].

Lipid rafts and psychiatric disorders

Lipid rafts, influenced by long-chain polyunsaturated fatty acids (LC-PUFAs), constitute vital nanoscale cellular domains, orchestrating the function of membrane-bound proteins involved in cell–cell signaling, including monoaminergic receptors and transporters. The physicochemical characteristics of LC-PUFAs, which regulate membrane viscosity and organization, profoundly affect the functionality of lipid rafts and further mediate the regulation of signaling pathways crucial for brain function and psychiatric well-being [115]. Given their crucial roles in cell signaling and membrane dynamics, disruptions or alterations in lipid rafts have been implicated in various psychiatric disorders, including depression. Treatment of depression often requires several weeks for therapeutic effects. In depressed individuals, the G protein Gαs, which increases cAMP, is localized in lipid rafts. Chronic antidepressant treatment removes Gαs from lipid rafts, which is correlated with delayed therapeutic onset. Unlike studies on inactive drugs, in vitro studies on C6 glioma cells have demonstrated the accumulation of various antidepressants within lipid rafts. This accumulation facilitates the translocation of Gαs to the nonraft membrane fraction, where it activates the cAMP signaling cascade crucial for antidepressant effects [116].

The role of lipid rafts in memory and amnesia

Amnesia, characterized by memory loss, presents significant challenges in understanding its underlying mechanisms. Recent studies have revealed the possible pivotal role of lipid rafts in memory processes. The disruption of lipid raft composition or dynamics could impair synaptic protein function and alter essential signaling pathways for memory consolidation and retrieval [117]. In vivo and in vitro experimental evidence has demonstrated that alterations in lipid rafts are associated with memory impairment. However, significant challenges remain, including elucidating the precise mechanisms by which lipid rafts influence memory and developing targeted therapeutic interventions on the basis of these insights. Lipid raft membrane dynamics are also implicated in anesthesia-induced synaptic neuronal plasticity and amnesia, where anesthetics disrupt lipid membrane bilayers. Anesthetics such as propofol destabilize lipid nanodomains at low concentrations but stabilize them at relatively high concentrations [118].

Lipid rafts as targets in pain management

The development of new analgesics presents significant challenges, prompting the exploration of alternative therapeutic strategies. Numerous ion channels and receptors involved in pain perception and signaling, including thermosensitive transient receptor potential (TRP) superfamily members (TRPV1, TRPA1, TRPM3, and TRPM8) and other receptors, such as ORs, P2X receptors, NK1Rs, TLR4, and CB1Rs, are localized within lipid rafts. Alterations in the composition and structural integrity of these rafts through sphingolipid and/or cholesterol depletion

can modulate the function of critical receptors involved in thermo and mechanosensitivity. These lipid raft disruptors affect the activity of all receptors and signaling molecules within these membrane microdomains. The recovery of neuropathic pain after the reduction in TRPV1-associated lipid raft content in dorsal root ganglion neurons [85] highlights the importance of inflammatory dynamics in retinal diseases and potential therapeutic strategies targeting the lipid raft–inflammation interplay. Nevertheless, owing to their broad effects, these compounds are considered primarily for topical application. However, modifying lipid raft integrity holds promise for future therapies targeting chronic inflammatory, neuropathic, or cancer pain, particularly by acting on peripheral mechanisms [119].

Keywords in prion pathogenesis

Prion diseases are fatal neurodegenerative disorders characterized by the misfolding of the cellular prion protein (PrPC) into its pathological isoform of prion protein (PrPSc). They are intricately linked to lipid raft dynamics. This conformational change primarily occurs within the lipid raft domains of the plasma membrane, where PrPC is known to reside and interact. Moreover, the observed increase in cholesterol levels during prion infection potentially influences this conversion process, underscoring the pivotal role of lipid rafts in prion pathogenesis [120].

Involvement in cardiovascular disease

The term cardiovascular disease (CVD) is often used to describe a range of disorders affecting the heart and blood vessels. These include conditions such as coronary artery disease, heart attacks, strokes, heart failure, arrhythmias, hypertension, and cardiac hypertrophy [121]. Lipid rafts modulate the essential cellular signaling pathways implicated in CVD pathogenesis [122, 123]. Moreover, lipid rafts serve as platforms for lipid metabolism and participate in very low-density lipoprotein (VLDL) assembly and secretion. Therapeutic strategies targeting VLDL production or enhancing VLDL metabolism via mipomers, lomitapide, and ANGPTL3 inhibitors [124] are likely to interact with these microdomains. By fine tuning lipid raft-associated proteins and enzymes, these interventions can improve the clearance of VLDL and decrease residual cardiovascular risk, offering advantages beyond the ability of low-density lipoprotein (LDL) alone to control atherosclerotic cardiovascular disease.

Atherosclerosis and inflammation

In atherosclerosis, lipid rafts are implicated in promoting inflammation, particularly in hyperhomocysteinemia-accelerated atherosclerosis. Homocysteine promotes lipid raft clustering by upregulating the enzyme acid sphingomyelinase, which facilitates the assembly of NADPH oxidase with the generation of reactive oxygen species, leading to pyroptosis. Methyl-β-cyclodextrin-induced lipid raft disruption potentially helps alleviate homocysteine-exacerbated atherosclerosis, indicating a promising strategy for targeting lipid rafts in homocysteine-related atherosclerosis [125].

Diabetic cardiomyopathy and caveolin-1

Caveolin-1 (Cav1), a key component of lipid rafts, has emerged as a crucial player in diabetic cardiomyopathy (DCM). A study on Cav1-deficient diabetic mice revealed exacerbated cardiac injury with increased NF-κB signaling activation and increased expression of hypertrophic and inflammatory fibrosis factors. Conversely, Cav1 overexpression had the opposite effect, suggesting that Cav1 plays a protective role against DCM progression and highlighting the intricate involvement of lipid rafts in cardiomyopathy [126].

The role in nicotine-induced atherosclerosis

Nicotine, a major component of cigarette smoke, contributes to the development of atherosclerosis by activating the NACHT, LRR, and PYD domains-containing protein 3 (NLRP3) inflammasome and promoting macrophage migration into atherosclerotic plaques. Mechanistically, nicotine enhances the accumulation of α1-nicotinic acetylcholine receptors within lipid rafts, leading to NLRP3 inflammasome activation in macrophages. Therefore, disruption of lipid rafts attenuates nicotine-induced proinflammatory effects, indicating the crucial role of lipid rafts in nicotine-induced atherosclerosis development [127].

Hypertension and ion channel regulation

Hypertension is a major risk factor for cardiovascular disease and involves dysregulated ion channel function. The role of lipid rafts in regulating ion channel activity related to hypertension has been recently resolved. Research on aged mice revealed distinct lipid profiles in urinary EVs collected during the inactive and active phases, which influenced the activity of the epithelial sodium channel (ENaC) in the kidney. The presence of bioactive lipids associated with lipid rafts in urinary EVs during the active phase modulated ENaC activity, indicating time-of-day-dependent regulation of blood pressure via lipid raft dynamics and interactions with EVs [128].

Caveolae as potential regulators of cerebrovascular pathology and stroke intervention

Stroke, a common cerebrovascular event with high morbidity and mortality, occurs because of interrupted cerebral blood flow, resulting in ischemic or hemorrhagic brain injury. Caveolae have emerged as pivotal players in

this context. Their protective role in stroke is achieved by preserving the blood–brain barrier through the modulation of lipid raft components, specifically by reducing caveolin-1 expression and increasing claudin-5 levels, thereby preventing increased permeability [63]. Moreover, studies on caveolin-deficient mice revealed exacerbation of ischemic injury, in contrast with the protective effects observed with caveolin peptide administration against ischemia/reperfusion injury [129].

Lipid rafts in kidney health and disease

The role of lipid rafts in podocyte function and kidney health has been elucidated. Mutations in lipid raft-associated proteins such as podocin lead to kidney diseases such as steroid-resistant nephrotic syndrome [130]. While flotillin-2 stabilizes the podocin-nephrin complex within lipid rafts, it protects against kidney injury, and this stabilization also suggests that targeting lipid raft-associated proteins could provide promising therapeutic options for chronic kidney disease [131]. Moreover, at the immune system level, alterations in lipid rafts substantially influence the activation and function of monocytes and macrophages, which are crucial components in kidney disease. Dysregulated lipid rafts can disrupt cholesterol efflux and change the behavior of these immune cells. This alteration potentially results in abnormal activation of monocytes and macrophages and contributes to the pathogenesis of kidney diseases [16]. High cholesterol levels, on the other hand, may exacerbate kidney disorders, including chronic kidney disease [132]. Therefore, lipid rafts play multifaceted roles in kidney health and disease. Their impact extends beyond lipid metabolism, affecting cellular function, immune responses, and injury protection. As we continue to unravel the complexities of lipid rafts, new therapeutic strategies may emerge to combat kidney disorders.

Lipid rafts in the gut–brain axis: a crucial link in health and disease

Surprisingly, lipid rafts are gaining recognition for their crucial role in the gut–brain axis, a bidirectional communication pathway essential for overall health. Lipid rafts integrate signals from the gastrointestinal system, such as nutrient detection, microbial byproducts, and inflammatory signals, which influence the overall neuronal and hormonal circuits regulating cognitive functions and behaviors [16]. In the gastrointestinal tract, lipid rafts organize various receptors, transporters, and signaling entities essential for nutrient uptake, intestinal motility, and immune responses [133]. These nanoscale cellular domains facilitate interactions between the gut microbiota and host cells, affecting the synthesis of neurotransmitters, which are crucial for brain function. The modulation of synaptic activity and neuroinflammatory processes within the brain [65] underscore their broad influence on both gut and brain health. Moreover, disruption of their normal function is commonly linked to a range of gastrointestinal and neurological disorders, suggesting a potential connection to conditions such as AD [133].

The role of lipid rafts in infectious diseases

Lipid rafts critically participate in the pathogenesis of infectious diseases. Pathogens exploit them to facilitate entry, replication, and egress from host cells, making lipid rafts key players in infection mechanisms [134].

Mechanisms of viral hijacking, immune modulation, and therapeutic implications

Lipid rafts are essential for viral replication by clustering pathogen recognition receptors and regulating autophagy, which can either promote or inhibit viral replication. Disrupting lipid rafts may offer antiviral potential and serve as a therapeutic target for viral infections [135]. Moreover, their structural organization increases the vulnerability of cells to pathogen invasion. Interestingly, viruses exploit lipid rafts at various stages of their life cycle, including attachment, internalization, membrane fusion, genome replication, assembly, and release, making them indispensable in the pathogenesis of infectious diseases [77, 134]. Viruses utilize specific receptors on the host cell surface, often concentrated within lipid rafts, to facilitate attachment and entry. For example, HIV and influenza viruses utilize lipid rafts for membrane fusion and entry into host cells [136]. Similarly, flaviviruses interact with lipid raft-associated receptors such as CD4 and coreceptor molecules to initiate viral entry [137, 138]. The highly lethal zoonotic Ebola virus can activate cellular signaling pathways through lipid rafts to facilitate entry and replication [139]. Moreover, lipid rafts provide favorable environments for the replication of certain viruses. By localizing viral replication complexes to lipid raft domains, viruses can increase their replication efficiency. For example, the hepatitis C virus (HCV) is known to assemble in lipid rafts, impacting the lipid envelope of newly formed viral particles and potentially influencing infectivity [140]. Some enveloped viruses take advantage of lipid rafts to assemble and bud from the host cell membrane. The lipid composition of viruses significantly influences the properties of their envelope, which is crucial for infection. Notably, owing to their electrostatic surface potential, lipid rafts concentrate viral particles at the host cell membrane, facilitating attachment and fusion, as observed in coronaviruses such as SARS-CoV-2, where gangliosides mediate binding and cholesterol supports fusion, optimizing viral entry and evolution [141]. Similar mechanisms have been described in other viruses, where lipid raft interactions are essential

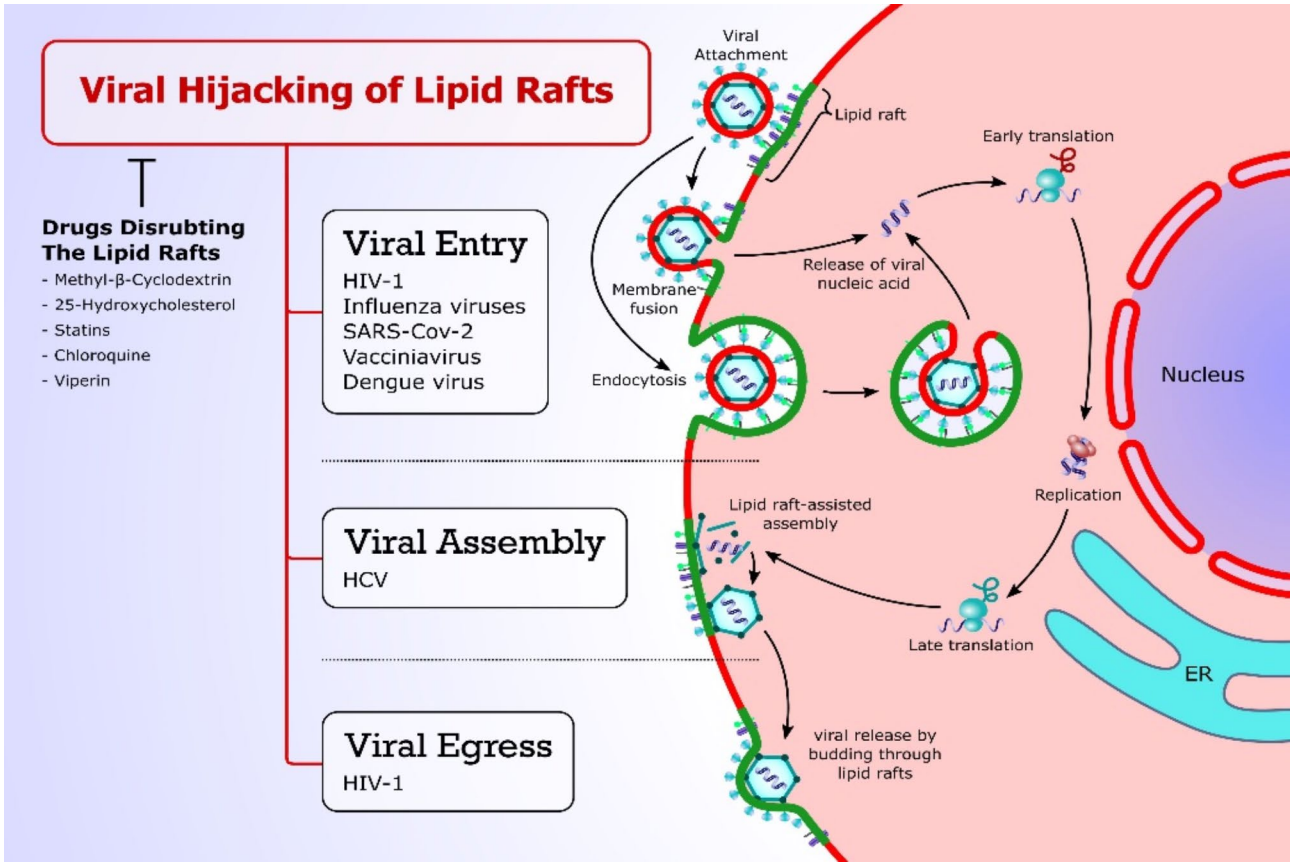

Fig. 4 Viral hijacking of lipid rafts. During viral infection, most viruses utilize lipid rafts where receptors are concentrated in various stages of their replication. Lipid rafts enriched with receptors facilitate the attachment and entry of the virus either by membrane fusion or endocytosis. Additionally, lipid rafts play important roles in the assembly of some viruses, e.g., HCV. Finally, lipid rafts facilitate viral egress by budding some viruses, e.g., HIV-1. On the other hand, drugs that actively disrupt the lipid raft structure play a significant role in reducing viral infectivity

for viral attachment [142]. Understanding these interactions has driven the development of potential antiviral strategies targeting lipid rafts, including statins, methyl-β-cyclodextrin, viperin, 25-hydroxycholesterol, and antimalarial drugs, all of which show promising efficacy in vitro and in vivo [163].

Lipid rafts also play essential roles in immune responses and inflammation during viral infection (Fig. 4). In chronic inflammation, alterations in lipid raft composition may influence immune cell signaling and the production of proinflammatory molecules. For example, HCV uses autophagy to bolster its replication, and lipid rafts are a determinant of this process. On the other hand, cholesterol disruption during HCV-induced autophagosome formation significantly impairs viral RNA replication [140]. HCV viroporin p7 acts as a lipid raft adhesion factor essential for stabilizing HCV particles, in addition to its role as an ion channel for pH equilibration. This dual role of p7 suggests new targets for anti-HCV compound development [143]. With respect to animal health, bovine parainfluenza virus type 3 (BPIV3) infection is a significant concern because of its potential to cause severe respiratory disease in cattle, resulting in substantial economic losses in the livestock industry. However, the inhibition of BPIV3 infection was observed following the disruption of cellular lipid rafts by methyl-β-cyclodextrin, confirming the importance of these rafts for viral entry. Furthermore, reducing lipid rafts within the viral envelope led to decreased viral yield, highlighting the critical role of cholesterol-rich lipid rafts in facilitating BPIV3 infection. These findings further confirm the importance of lipid rafts in viral infections in the animal field, demonstrating their potential as targets for therapeutic interventions [144].

Lipid rafts in bacterial infections: mechanisms of pathogenicity, host cell manipulation, and therapeutic implications

Multidrug-resistant bacteria present a critical public health threat, with a significant global safety challenge. Disruption of the gut flora remotely contributes to the obesity epidemic [145], NAFLD, chronic infections and inflammation [134, 146, 147]. They exploit lipid rafts for entry, survival, and proliferation within host cells.

Therefore, rafts serve as scaffolds for the assembly of signaling complexes and the concentration of receptors that bacteria hijack to control host cell performance. For example, some bacteria can use lipid transfer proteins, disrupting lipid trafficking at membrane contact sites [148]. Some other bacteria, such as *Helicobacter pylori* and *Listeria monocytogenes*, utilize lipid rafts to invade host cells and escape immune responses, manipulating raft-associated signaling pathways for their survival and replication [149, 150]. Lipid rafts linked with bacterial pathogenicity are advanced by their ability to act as scaffolds for bacterial signal transduction and cellular endocytosis, making them potential targets for therapeutic interventions. For example, a recent report clearly revealed the involvement of lipid rafts in the pathogenicity of *Clostridium innocuum*, an anaerobic bacterium associated with inflammatory bowel disease. This study revealed that rafts facilitate *C. innocuum*-induced activation of NF-κB, leading to inflammation and cell death. Moreover, reducing cholesterol with simvastatin significantly reduces *C. innocuum*-induced cell death, further demonstrating that the pathogenicity of *C. innocuum* is dependent on lipid rafts [65]. *Neisseria meningitidis* is another pathogen responsible for meningitis that relies mainly on lipid rafts for host cell invasion. It utilizes plasma membrane sphingolipids, particularly globotriaosylceramide and the raft-associated monosialotetrahexosylganglioside GM1, for invasion. Superresolution microscopy further revealed the accumulation and coating of meningococci with GM1 upon cellular uptake. However, the inhibition of GM1 binding sites markedly reduced bacterial invasion efficiency. Additionally, inducing cell cycle arrest in the G1 phase through serum starvation increased the abundance of GM1 in the plasma membrane, thereby increasing bacterial invasion efficiency [151].

Lipid rafts and environmental toxicants: a cellular perspective

The role of lipid rafts in compartmentalizing cellular processes is pivotal, particularly in mediating cellular responses to environmental stressors. According to Marques-da-Silva and Lagoa [73], lipid raft-like domains help organize proteins involved in key signaling pathways that regulate redox balance, calcium homeostasis, immune responses, and hormonal activity. Furthermore, a recent study [152] elucidated the interaction of lipid rafts with Rab GTPases at the late endosomal checkpoint, which is essential for plasma membrane recycling and protein sorting. These findings emphasize the essential function of lipid rafts in maintaining cellular integrity under toxicant-induced stress. The International Union for Conservation of Nature's May 2024 update on 'Plastic Pollution' provides a concerning overview, highlighting how plastic pollution is strongly linked to climate change and adversely impacts ecosystems across land, freshwater, and marine environments. Microplastics, defined as plastic particles less than 5 mm in size, are pervasive in various environments and within organisms, raising concerns about their ecological impact [153]. The dynamic nature of lipid rafts, enriched with cholesterol and specific lipids, plays a crucial role in membrane organization and cellular signaling, making them essential in this context [73]. Research on microplastics and lipid rafts is limited, but potential interactions exist. Ingested via water, food, or air, microplastics can cross the gastrointestinal barrier into the bloodstream, where they interact with cell membranes. They may disrupt lipid raft integrity by competing for lipophilic molecules like cholesterol and sphingolipids, depleting essential components. While direct evidence is scarce, their impact on cellular uptake, membrane structure, and lipid composition warrants further study.

Clinical implications and future directions

Lipid rafts play key roles in cellular signaling, trafficking, and immune response, making them potential therapeutic targets for diseases like cancer, neurodegenerative disorders, and cardiovascular conditions [77]. Modulating their composition or function may offer novel treatment strategies. Future research should develop lipid raft-targeting drugs and validate their efficacy [154]. Additionally, transplanting functional lipid rafts into diseased cells could restore normal signaling and homeostasis, potentially reversing disease phenotypes. This approach may be particularly beneficial in conditions where lipid raft dysfunction drives disease progression, such as certain cancers and neurodegenerative disorders [77, 89].

Lipid rafts as therapeutic targets: implications in cancer and neurodegenerative, cardiovascular, and infectious diseases

Lipid rafts regulate cancer cell proliferation and survival by modulating growth factor signaling and apoptosis, making them promising therapeutic targets. Edelfosine, an ether lipid, selectively induces tumor cell apoptosis by recruiting death receptors to cholesterol-rich rafts, triggering the mitochondrial apoptotic pathway [155]. Targeting raft-associated caveolin-1 also disrupts cancer signaling, potentially reducing tumor aggressiveness [89, 156, 157].

In neurodegenerative disorders, lipid rafts influence APP processing, Aβ plaque formation in AD, and alpha-synuclein aggregation in PD [158, 159]. Their dysfunction is linked to abnormal protein aggregation and toxic signaling, while restoring raft integrity may slow disease progression [71, 160]. While in cardiovascular diseases, lipid rafts regulate endothelial function and inflammatory

responses in atherosclerosis and play roles in cardiac hypertrophy and heart failure [16, 92]. Their role in selective cholesterol efflux further suggests therapeutic potential in angiogenic and inflammatory diseases [161].

Pathogens, however, exploit lipid rafts for host cell invasion. Disrupting raft integrity blocks infections and interferes with pathogen lifecycles. Modifying lipid composition or targeting raft signaling hinders invasion and reduces inflammation, offering new therapeutic strategies. Notably, cholesterol-lowering drugs destabilize lipid rafts, preventing viral entry [134, 147, 150]. Studies on *Clostridium innocuum* and *Neisseria meningitidis* underscore the critical involvement of lipid rafts in mediating bacterial infections and highlight potential avenues for therapeutic intervention.

Lipid rafts in medicine and disease: implications for regenerative medicine, biomarkers, targeted therapies, and advanced research techniques

Lipid rafts substantially affect stem cell behavior, suggesting promising avenues in regenerative medicine. Identifying stem cell-specific lipidomes reveals how lipid profiles affect stem cell function, influencing tissue homeostasis and repair [162]. Changes in lipid homeostasis, driven by diet, aging, or disease, can alter stem cell functionality, indicating the importance of lipid balance in effective stem cell-based therapies. By dynamically harboring signaling proteins, lipid rafts act as functional rheostats that modulate stem cell fate [24]. On the other hand, the unique composition and dynamics of lipid rafts make them valuable in biomarker research for diseases like cancer and neurodegenerative disorders. Raft-associated proteins, including caveolin and flotillin, show potential as prognostic markers and therapeutic targets in cancer [93]. Moreover, understanding the role of lipid rafts in cellular processes, such as embryonic development, stem cell biology, and cancer progression, provides a basis for identifying predictive biomarkers [24]. The strategies for targeting lipid rafts include the development of antagonists that specifically target inflammatory receptors in activated homo or heterodimers within pathological lipid rafts. Selective targeting of lipid rafts disrupts disease-specific signaling while preserving normal cellular function. HDL mimetics, liver X receptor agonists, and ABCA1 overexpression enhance cholesterol efflux and modulate pathological signaling, while cyclodextrins like methyl-β-cyclodextrin deplete cholesterol, interfering with EGFR pathways. Apolipoprotein A-I binding protein further stabilizes lipid rafts while regulating their signaling [16, 77]. Nanoparticle-based drug delivery improves specificity, reducing off-target effects, while CRISPR/Cas9 offers gene-editing strategies to manipulate lipid raft-associated proteins. Ionizable lipid nanoparticles efficiently deliver CRISPR/Cas9 in cancer models, and lipid-based nanocarriers enhance drug efficacy with minimal side effects. These approaches position lipid rafts as key therapeutic targets in infection and cancer treatments [162]. Conversely, stabilization strategies maintain their integrity for proper cellular signaling [24].

Advanced techniques such as mass spectrometry, proteomics, lipidomics, and high-resolution imaging provide insights into lipid raft composition and dynamics in disease [24, 71]. However, their analysis requires combined approaches, as individual techniques face limitations. Computational biology aids data interpretation, while clinical correlation studies validate biomarker relevance.

Detergent-resistant membranes (DRMs) isolate lipid rafts, and fluorescence microscopy reveals their distribution and dynamics. Mass spectrometry identifies raft-associated proteins, elucidating signaling network [79]. Moreover, superresolution and cryo-electron microscopy enable nanoscale visualization of lipid rafts, revolutionizing structural analysis [163]. The Lipid Microscopy and Analysis Platform (Lipid-MAP) integrates microscopy, nanochemistry, and machine learning to visualize lipid interactions at nanoscale resolution, revealing lipid contributions to cellular processes [164]. Additionally, imaging mass spectrometry is a cutting-edge, noninvasive technique used to elucidate the expression patterns of lipid rafts, although it is typically not performed in real time or in vivo. Together, these technologies significantly advance the study of cell membrane dynamics and lipid behavior, although they are not typically conducted in real time or in vivo [165].

Unresolved aspects and therapeutic potential of engineered lipid rafts

Although substantial progress has been made in understanding the biological roles of lipid rafts, it is important to recognize that most of these findings are derived from cell culture and animal models. The translation of this knowledge into clinical applications remains a significant challenge, necessitating further studies on human tissues to bridge this gap. Moreover, basic questions regarding the exact composition, size, dynamics, and stability of lipid rafts remain largely unresolved [166]. Their physiological roles in cellular processes and their implications in various diseases, such as cancer and neurodegenerative disorders, are still under active investigation [167]. Emerging technologies, including high-resolution imaging and mass spectrometry, offer new perspectives on these complex nanoscale membrane domains, revealing previously inaccessible structural and functional attributes. Interestingly, recent studies have proposed the potential of engineered lipid raft transplantation as a novel therapeutic strategy, particularly for diseases with limited therapeutic success [168]. Unlike traditional liposomal therapies, which often face challenges in terms of

cellular uptake and functional integration, engineered lipid rafts potentially restore disrupted cellular activities more effectively. However, realizing the therapeutic potential of lipid raft transplantation relies on overcoming several key obstacles. Ensuring the stability and integration of transplanted rafts in host cell membranes, mitigating immune responses to minimize rejection, and developing targeted delivery systems for precise cellular application are essential steps in advancing this approach. By overcoming these obstacles, lipid raft-based interventions might be able to prove their full therapeutic potential, providing hope for diseases that are difficult to treat. This strategy represents a shift toward the development of focused, potent treatments for complicated illnesses by utilizing lipid raft biology.

Conclusion

This review comprehensively addresses the importance of lipid rafts, highlighting their indispensable roles in cellular processes and significant implications for health and disease. Lipid rafts are essential for maintaining cellular homeostasis because they regulate key functions, such as signaling, energy metabolism, immune responses, and autophagy. Dysregulation of these genes has been implicated in a wide range of pathological conditions, including neurodegenerative diseases, cardiovascular disorders, MS, cancer, and infections. This work further explains how their interplay with cellular organelles such as the ER and mitochondria influences processes such as apoptosis, contributing to disease progression.

Recent advances have underscored the potential of lipid rafts as therapeutic targets, offering new avenues for the treatment of complex diseases. Emerging strategies focusing on lipid raft stabilization, prevention of protein aggregation, and restoration of membrane function show promise in addressing conditions that have remained difficult to treat. Moreover, cutting-edge technologies, including advanced imaging methods, provide new insights into lipid raft dynamics, facilitating the development of novel therapeutic interventions.

Specific research avenues include the exploration of lipid raft-associated proteins and lipids in neurodegenerative diseases, cardiovascular disorders, and cancer, utilizing high-resolution imaging and omics technologies to map their interactions and functions. Clinical importance lies in their potential to serve as biomarkers for early disease detection and as targets for therapeutic interventions aimed at stabilizing or modulating raft-associated pathways. Further studies should focus on understanding the molecular mechanisms underlying lipid raft formation and function, as well as their role in disease pathology.

Continued exploration of their molecular mechanisms and therapeutic potential should be performed to understand and unlock new avenues for restoring cellular homeostasis and enhancing immune function in various disease contexts. Lipid rafts represent a vital area of research with vast potential to improve disease management and uncover innovative treatments.

Abbreviation

GPI	Glycosylphosphatidylinositol
TCRs	T-cell receptors
LCPUFAs	Long-chain polyunsaturated fatty acids
DHA	Docosahexaenoic acid
ER	Endoplasmic reticulum
GPCRs	G protein-coupled receptors
ECM	Extracellular matrix
HSPs	Heat shock proteins
RTKs	Receptor tyrosine kinases
ERLIN1	ER lipid raft associated 1 protein
IP3R	Inositol 1,4,5-triphosphate receptor
ALKBH5	α-ketoglutarate-dependent dioxygenase homolog 5
FGFR2	Fibroblast growth factor receptor 2
GRB2	Growth factor receptor-bound protein 2
HSPB11	Heat shock protein beta-11
HSP70	Heat shock protein 70
HSC70	Heat shock cognate protein 70
JEV	Japanese Encephalitis Virus
EV	Extracellular Vesicles
GAG	Glycosaminoglycan
BRB	Blood–Retinal Barrier
BBB	Blood–Brain Barrier
BTB	Blood–Testis Barrier
VGSC	Voltage-Gated Sodium Channels
NF-κB	Nuclear Factor Kappa B
NOD2	Nucleotide-Binding Oligomerization Domain-Containing Protein 2
FGF-2	Fibroblast Growth Factor-2
T2DM	Type 2 Diabetes Mellitus
APS	Antiphospholipid syndrome
LRP8	low-density lipoprotein receptor-related protein 8
ApoER2	Apolipoprotein E receptor 2
eNOS	endothelial nitric oxide synthase
MS	Metabolic Syndrome
UDCA-LPE	Ursodeoxycholyl lysophosphatidylethanolamide
LPCAT3	Lysophosphatidylcholine Acyltransferase 3
TLR4	Toll-Like Receptor 4
IFN-α	Interferon Alpha
EGFR	Epidermal Growth Factor Receptor
PI3K/AKT	Phosphatidylinositol 3-Kinase/AKT
ERK	Extracellular Signal-Regulated Kinase
FAS	Death receptor
DISC	Death-inducing signaling complex
FADD	FAS-associated death domain protein
CASMER	Cluster of apoptotic signaling molecule-enriched raft
IGF	Insulin-like growth factor
IGF-1R	Insulin-like growth factor 1 receptor
PI3K	Phosphoinositide 3-kinase
PIP2	Phosphatidylinositol 4,5-bisphosphate
PIP3	Phosphatidylinositol (3,4,5)-trisphosphate
Akt/PKB	Akt/protein kinase B
BAD	BCL2-associated agonist of cell death
BAX	BCL2-associated X protein
BIM	Bcl-2 interacting mediator of cell death
FKHR	Forkhead protein
MDM2	Mouse double-minute-2 homolog
XIAP	X-linked inhibitor of apoptosis protein
HER2	Human Epidermal Growth Factor Receptor 2
ALS	Amyotrophic lateral sclerosis
AD	Alzheimer's disease
PD	Parkinson's disease
PrPc	Cellular prion protein
PrPSc	Pathological isoform of prion protein

APP	Amyloid precursor protein
Aβ	Amyloid-beta
GM1	Ganglioside M1
HIE	Hypoxic-ischemic encephalopathy
TRP	Transient receptor potential
TRPV1	Transient receptor potential vanilloid 1
TRPA1	Transient receptor potential ankyrin 1
TRPM3	Transient receptor potential melastatin 3
TRPM8	Transient receptor potential melastatin 8
ORs	Opioid receptors
P2X	Purinergic ligand-gated ion channel
NK1Rs	Neurokinin 1 receptors
CB1Rs	Cannabinoid receptor 1
VDAC1	Voltage-dependent anion channel 1
Cav1	Caveolin-1
ENaC	Epithelial sodium channel
CVD	Cardiovascular disease
VLDL	Very low-density lipoprotein
LDL	Low-density lipoprotein
NLRP3	NACHT, LRR, and PYD domains-containing protein 3
cAMP	Cyclic adenosine monophosphate
HCV	Hepatitis C virus
HIV-1	Human Immunodeficiency Virus-1
NAFLD	Non-Alcoholic Fatty Liver Disease
HDL	High-Density Lipoprotein
DRMs	Detergent-Resistant Membranes
Lipid-MAP	Lipid Microscopy and Analysis Platform
ABCA1	ATP-binding cassette transporter A1

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