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Review

Lipid-Regulated State Transitions in Inflammation, Regeneration, and Chronic Disease

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Abstract

Lipids are commonly viewed as membrane components, energy sources, or precursors of signaling molecules, yet accumulating evidence indicates a broader role in determining the functional state of cells. In this review, we present an integrative cross-domain synthesis in which lipids are discussed as important modulators of cellular functional state across inflammation, tissue regeneration, and chronic disease. We discuss how membrane lipid composition shapes receptor and ion-channel signaling, how bioactive lipid mediators govern the balance between inflammatory initiation and resolution, and how lipid metabolism regulates stem-cell quiescence, activation, and regenerative capacity. We integrate these mechanisms to show how disruption of lipid-regulated processes may bias tissues toward persistent inflammation, impaired repair, and disease progression in conditions such as rheumatic disorders, fibrosis, and neurodegeneration. Depending on context, such lipid alterations may function as causal contributors, permissive conditions, or downstream signatures of pathological state transitions. Finally, we consider how pharmacological and nutritional modulation of lipid pathways may influence cellular states, while emphasizing that the main contribution of this review is a conceptual state-transition framework that links membrane architecture, mediator balance, and lipid metabolic flux across inflammation, regeneration, and chronic disease.

Keywords: lipid-mediated signaling; cellular state transitions; membrane microdomains; phosphoinositide signaling; sphingolipid metabolism; specialized pro-resolving mediators; lipidomics; inflammation and regeneration

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1. Introduction—The Missing Perspective

Lipids have traditionally been studied as structural components of biological membranes, where they regulate membrane fluidity, curvature, and compartmental organization [1,2]. They also function as major reservoirs of metabolic energy, with fatty acids and triglycerides supporting cellular and systemic energy homeostasis [3,4]. In parallel, dietary lipids have long been investigated for their roles in nutrition, metabolic health, and cardiovascular disease risk [5]. These foundational roles have shaped much of classical lipid research and continue to define how lipids are introduced in biochemical and physiological contexts.

Over the past several decades, however, substantial evidence has demonstrated that lipids participate directly in cellular signaling processes. Membrane lipid composition influences receptor distribution and clustering, modulates ion-channel activity, and alters

intracellular signaling thresholds [6]. Enzymatically derived lipid mediators—including prostaglandins, leukotrienes, and specialized pro-resolving mediators—actively regulate inflammatory signaling cascades and immune-cell behavior [7–9]. In addition, lipid metabolic pathways have been implicated in controlling stem-cell quiescence, activation, and lineage commitment across multiple tissue systems [10,11]. Collectively, these findings indicate that lipids extend beyond passive structural or metabolic roles and contribute to the dynamic regulation of cellular responses to environmental and physiological stimuli.

Despite these advances, lipid biology is often conceptually separated from parallel developments in inflammation research, regenerative biology, and chronic disease pathology. Inflammatory studies frequently emphasize cytokine networks, immune-cell recruitment, transcriptional programs, and pattern-recognition receptor signaling as primary drivers of immune activation and resolution [12–14]. Regenerative biology and stem-cell research have focused predominantly on growth factors, niche-derived cues, and transcriptional regulators governing tissue repair and remodeling [15,16]. Chronic diseases such as rheumatoid arthritis, fibrosis, and neurodegenerative disorders are typically characterized in terms of sustained immune activation, extracellular matrix remodeling, and progressive tissue dysfunction [17,18]. Although lipid mediators and lipid metabolism are acknowledged within these domains, they are commonly discussed as modulators of discrete pathways rather than as integrative regulators of broader cellular functional states [3,19,20].

Emerging evidence suggests that lipid composition, lipid-derived mediators, and lipid metabolic flux influence transitions between distinct cellular functional states, including inflammatory activation versus resolution, quiescence versus proliferation, and regenerative repair versus fibrotic remodeling [21,22]. However, these observations are rarely synthesized into a unified framework that connects membrane organization, inflammatory balance, regenerative capacity, and disease persistence. As a result, lipid-dependent mechanisms are frequently examined in isolation, limiting appreciation of their potential role in coordinating large-scale biological transitions across tissues and disease contexts.

While numerous reviews have examined lipid mediators in inflammation, lipid metabolism in stem-cell biology, and lipid dysregulation in aging or chronic disease, these domains are typically addressed in isolation, with emphasis on discrete signaling pathways or metabolic functions. Comparatively few analyses have integrated membrane architecture, lipid mediator balance, and metabolic lipid flux into a unified conceptual axis of cellular state regulation. Moreover, connections between these lipid-dependent processes and the stabilization or failure of state transitions across inflammation, regeneration, and chronic pathology remain underdeveloped. As a result, lipid pathways are often framed as modulators of specific molecular cascades rather than as contributors to broader, cross-scale configurations of cellular responsiveness that influence whether cells resolve, repair, or persist in maladaptive states.

Prior reviews have examined many of the component themes discussed here, including immunometabolic regulation of inflammatory responses, lipid mediator class switching during resolution, membrane lipid control of receptor organization and signaling, and metabolic control of stem- and progenitor-cell behavior. However, these areas are often treated as separate areas of the literature: immunometabolism primarily emphasizes how metabolic programs regulate immune-cell function; lipid signaling reviews often focus on defined mediator pathways or membrane-associated signaling events; regeneration-focused reviews frequently emphasize growth factors, niche cues, and transcriptional control; and chronic disease reviews often discuss lipid dysregulation as a disease-associated feature or biomarker. The specific contribution of the present review is to connect these otherwise separate perspectives through the concept of lipid-regulated cellular state transitions.

In this framework, lipids are not presented simply as isolated signaling molecules, metabolic substrates, or disease-associated lipidomic changes. Rather, we propose that membrane lipid architecture, lipid mediator balance, and lipid metabolic flux can be understood as interacting regulatory layers that shape how cells enter, maintain, or exit functional states such as inflammatory activation, resolution, quiescence, proliferative repair, maladaptive remodeling, and chronic disease persistence. This distinction is important because the central question is not only whether a particular lipid pathway affects a particular molecular target, but whether lipid-dependent inputs help bias the broader cellular state toward resolution, repair, persistence, or dysfunction.

Accordingly, the novelty of this review is conceptual and integrative rather than based on the claim that the individual lipid mechanisms discussed are newly discovered. The review adds to the existing literature by organizing established and emerging lipid-related mechanisms into a cross-domain state-transition framework spanning inflammation, regeneration, aging, fibrosis, neurodegeneration, and chronic inflammatory disease. This perspective differs from conventional immunometabolism in several ways. First, immunometabolism primarily focuses on how metabolic programs shape immune-cell function, whereas the present framework extends across immune, stromal, structural, and stem/progenitor-cell compartments. Second, the framework does not focus only on intracellular metabolic programming, but integrates membrane lipid organization, mediator class balance, lipid metabolic flux, and tissue-level repair outcomes. Third, the central emphasis is not only on how lipid pathways regulate individual molecular targets, but on how lipid-dependent processes may influence the probability, stability, or reversibility of broader cellular state transitions, including inflammatory activation, resolution, quiescence, proliferative repair, maladaptive remodeling, and chronic disease persistence. It also differs from pathway-centered lipid signaling reviews by emphasizing how multiple lipid-dependent processes may converge to influence cellular responsiveness and state stability across biological contexts.

The purpose of the review is therefore not to provide exhaustive domain-specific coverage of inflammation resolution, stem-cell biology, fibrosis, neurodegeneration, or aging individually. Instead, it is to identify recurring lipid-dependent principles that become visible when these fields are considered together: lipid control of signaling thresholds, lipid mediator balance between initiation and resolution, lipid metabolic support of quiescence or activation, and lipid-associated failure of adaptive state transitions in chronic pathology. Thus, the proposed framework is new in its organization of lipid biology around cellular state transitions across inflammatory, regenerative, and chronic disease contexts, rather than around a single lipid class, immune-cell metabolic program, or disease-specific pathway.

1.1. Review Approach and Literature Scope

This article was prepared as a narrative, hypothesis-generating review rather than as a systematic review or meta-analysis. The literature was identified through iterative searches of PubMed, Google Scholar, and the reference lists of relevant primary studies and review articles. Searches were organized around the central theme of lipid-associated regulation of cellular responsiveness and state transitions, with particular attention to three recurring domains: (i) membrane lipid organization and signaling thresholds; (ii) lipid mediator balance during inflammatory initiation, resolution, and persistent inflammation; and (iii) lipid metabolic programs linked to stem-cell quiescence, activation, regeneration, aging, and chronic disease.

Because the aim of the review is conceptual integration across multiple biological fields, studies were not selected according to formal systematic-review inclusion and

exclusion criteria. Instead, priority was given to studies that met one or more of the following criteria: mechanistic relevance to lipid-dependent signaling or metabolism; direct relevance to cellular state regulation, including activation, quiescence, resolution, differentiation, survival, senescence, or maladaptive remodeling; relevance across more than one tissue or disease context; translational importance for inflammatory, regenerative, fibrotic, neurodegenerative, or rheumatologic disease; and usefulness in illustrating how lipid-dependent mechanisms may connect otherwise separate fields of the literature.

In selecting representative studies, greater emphasis was placed on mechanistic primary reports, influential experimental studies, recent reviews, and selected clinical or lipidomic studies that helped define the relationship between lipid pathways and cellular functional state. Studies were prioritized when they provided evidence for a functional role of lipid composition, lipid-derived mediators, or lipid metabolic flux rather than only documenting changes in lipid abundance. However, because the maturity of the evidence varies across fields, the manuscript distinguishes, where appropriate, between established mechanisms, context-dependent associations, and hypothesis-generating interpretations.

The disease and biological contexts included in the review were selected because they illustrate recurring lipid-associated patterns across inflammation, repair, and chronic pathology rather than because they represent an exhaustive survey of all lipid-related diseases. Rheumatoid arthritis and related inflammatory settings were included to illustrate persistent inflammatory lipid signatures and altered mediator balance. Fibrosis was included as an example of maladaptive repair. Neurodegenerative disease and aging were included because they illustrate contexts in which lipid changes are frequently observed but where causal interpretation often remains more complex. Stem- and progenitor-cell examples were included to connect lipid metabolism with quiescence, activation, regenerative competence, and age-related decline.

Accordingly, the framework advanced here should be interpreted as an integrative and hypothesis-generating synthesis rather than as a definitive evidence-weighted model. The purpose of literature selection was not to provide exhaustive coverage of each individual disease area, but to identify lipid-dependent principles that recur across biological contexts and may help explain how cells transition between inflammatory, resolving, regenerative, maladaptive, and chronically diseased states.

1.2. Defining Cellular State and Its Measurement

In this review, the term "cellular state" refers to the integrated functional condition of a cell at a given time, rather than to a single molecular marker or isolated signaling pathway. A cellular state is defined by the coordinated configuration of signaling activity, metabolic program, transcriptional and epigenetic profile, membrane organization, secretory behavior, stress responsiveness, and functional output. Examples include inflammatory activation, pro-resolving immune behavior, quiescence, proliferative activation, differentiation, senescence-like stress adaptation, myofibroblast activation, and maladaptive chronic disease-associated phenotypes.

Within this framework, a lipid-regulated cellular state does not mean that lipids alone determine cell identity or fate. Rather, it refers to a condition in which lipid-dependent mechanisms contribute to the probability, stability, or direction of a cellular response. These mechanisms may include membrane lipid composition that alters receptor clustering and signaling thresholds; phosphoinositide signaling that shapes intracellular signal propagation; bioactive lipid mediators that regulate inflammatory initiation or resolution; sphingolipid balance that influences survival, stress signaling, or apoptosis; and lipid metabolic flux that supports quiescence, activation, proliferation, or repair. Thus, lipid-regulated state transitions are understood as changes in cellular behavior in which lipid-associated mecha-

nisms interact with cytokines, growth factors, transcriptional programs, niche signals, and tissue context.

Cellular states can be measured using complementary approaches rather than by a single assay. Transcriptomic methods, including bulk and single-cell RNA sequencing, can identify gene-expression programs associated with activation, resolution, differentiation, senescence, or disease-associated phenotypes. Epigenomic approaches, such as chromatin accessibility profiling and histone-modification analysis, can assess whether these states are accompanied by more stable regulatory changes. Lipidomics and metabolomics can define changes in membrane lipid composition, lipid mediator abundance, sphingolipid balance, fatty acid oxidation, and lipogenic flux. Proteomic and phosphoproteomic approaches can identify signaling pathway activation, receptor-proximal events, and downstream effector programs. Imaging and functional assays can measure receptor clustering, membrane organization, cell migration, proliferation, efferocytosis, cytokine release, extracellular matrix production, mitochondrial function, and regenerative or fibrotic behavior.

Because cellular state is multidimensional, the strongest evidence for a lipid-regulated state transition comes from studies that combine molecular profiling with functional validation. For example, evidence is stronger when a lipid perturbation changes not only lipid abundance, but also signaling thresholds, gene-expression programs, and measurable cellular behavior. Conversely, lipidomic differences observed in disease tissue without functional testing are interpreted more cautiously in this review as associations or state signatures rather than definitive evidence of causal regulation.

2. Lipid Regulation of Cellular Signaling State

2.1. Membrane Lipid Composition and Microdomain Organization

Biological membranes are not homogeneous lipid bilayers but are laterally organized structures composed of distinct lipid species that influence membrane fluidity, curvature, and protein distribution [23,24]. The concept of lipid rafts—cholesterol- and sphingolipid-enriched microdomains within the plasma membrane—has been proposed to explain the spatial compartmentalization of signaling molecules and receptors [25,26]. Although the precise biophysical nature and stability of lipid rafts remain subjects of ongoing investigation, substantial experimental evidence supports the existence of membrane microdomains that influence receptor localization and signaling efficiency [24,27].

Membrane lipid composition can affect receptor clustering and the formation of signaling platforms. For example, cholesterol depletion has been shown to disrupt microdomain organization and alter the activity of multiple receptor systems, including immune receptors and growth-factor receptors [28,29]. Similarly, changes in sphingolipid content can influence membrane order and modify the spatial assembly of signaling complexes [30]. These effects are not limited to immune cells; alterations in membrane lipid composition have been reported to influence signaling in epithelial, neural, and stem-cell populations [31].

By modulating the spatial organization of receptors and associated signaling proteins, membrane lipids contribute to signal amplification and threshold regulation. Variations in lipid composition can therefore alter the magnitude, duration, and downstream consequences of receptor activation [23,24,32]. In this way, membrane lipid organization participates in establishing the baseline signaling configuration of cells prior to inflammatory or regenerative stimuli.

2.2. Phosphoinositides and Signal Transduction

Phosphoinositides represent a functionally specialized class of membrane lipids that play central roles in signal transduction. Phosphatidylinositol 4,5-bisphosphate (PIP2) and phosphatidylinositol 3,4,5-trisphosphate (PIP3) are dynamically regulated by lipid

kinases and phosphatases and act as membrane-localized signaling intermediates [33,34]. Through direct interactions with cytoskeletal proteins, ion channels, and signaling adaptors, phosphoinositides influence receptor activity and intracellular signaling cascades [35,36].

PIP2 has been shown to regulate multiple ion channels and transporters, including voltage-gated and ligand-gated channels, by stabilizing channel conformations and modulating gating properties [37]. For example, a PIP2 substitute can mediate voltage sensor–pore coupling in KCNQ channel activation [38]. In parallel, PIP3 generated by phosphoinositide 3-kinase (PI3K) serves as a docking site for pleckstrin homology domain-containing proteins, including Akt, thereby linking membrane receptor activation to downstream pathways controlling survival, proliferation, and metabolism [36,39]. Dysregulation of PI3K–Akt signaling has been implicated in inflammatory disorders, cancer, and metabolic disease, underscoring the broader relevance of phosphoinositide signaling to cellular functional state [40,41].

Importantly, phosphoinositide levels are tightly regulated and highly localized within membrane subdomains, allowing spatial and temporal control of signaling events [36,42,43]. Perturbations in phosphoinositide metabolism can alter signaling thresholds and bias cellular responses toward activation, survival, or apoptosis depending on context [34,44,45]. Thus, phosphoinositides provide a mechanistic example of how specific lipid species modulate cellular responsiveness by shaping intracellular signaling architecture.

2.3. Sphingolipids and Ceramide in Stress Signaling

Sphingolipids constitute a structurally diverse class of membrane lipids that participate in both membrane organization and intracellular signaling. Among them, ceramide has been extensively studied as a bioactive lipid generated through sphingomyelin hydrolysis or de novo synthesis in response to cellular stressors [46,47]. Ceramide accumulation has been observed following exposure to inflammatory cytokines, oxidative stress, radiation, and metabolic perturbations [48,49], suggesting a conserved role in stress-responsive signaling pathways.

Mechanistically, ceramide can influence membrane biophysical properties by promoting the formation of ordered membrane domains, thereby facilitating receptor clustering and signal transduction events [25,50]. In addition to these membrane-level effects, ceramide has been implicated in the activation of intracellular signaling cascades associated with apoptosis, including caspase activation and mitochondrial outer membrane permeabilization [51,52]. Ceramide-dependent signaling has also been linked to stress-activated protein kinases such as JNK and p38 MAPK, which participate in inflammatory and apoptotic responses [48,53,54].

Beyond apoptosis, sphingolipid metabolites such as sphingosine-1-phosphate (S1P) exert context-dependent effects on cell survival, migration, and immune-cell trafficking [55,56]. The balance between ceramide and S1P—sometimes described as a "sphingolipid rheostat"—has been proposed to influence whether cells undergo apoptosis or maintain survival signaling [57,58]. While the rheostat model may oversimplify complex regulatory networks, substantial evidence supports the idea that shifts in sphingolipid metabolism can bias cellular stress responses and inflammatory priming [48,59].

Alterations in sphingolipid pathways have been reported in inflammatory diseases, metabolic disorders, and neurodegenerative conditions, although the precise causal relationships often remain context-dependent [49,60,61]. Collectively, these findings indicate that sphingolipids contribute to the modulation of stress signaling pathways and influence cellular responses to inflammatory and metabolic challenges.

Collectively, membrane microdomain organization, phosphoinositide-dependent amplification, and sphingolipid-mediated stress signaling illustrate how membrane lipid

architecture shapes signaling configuration, signaling thresholds, and stress responsiveness across cellular contexts (Figure 1).

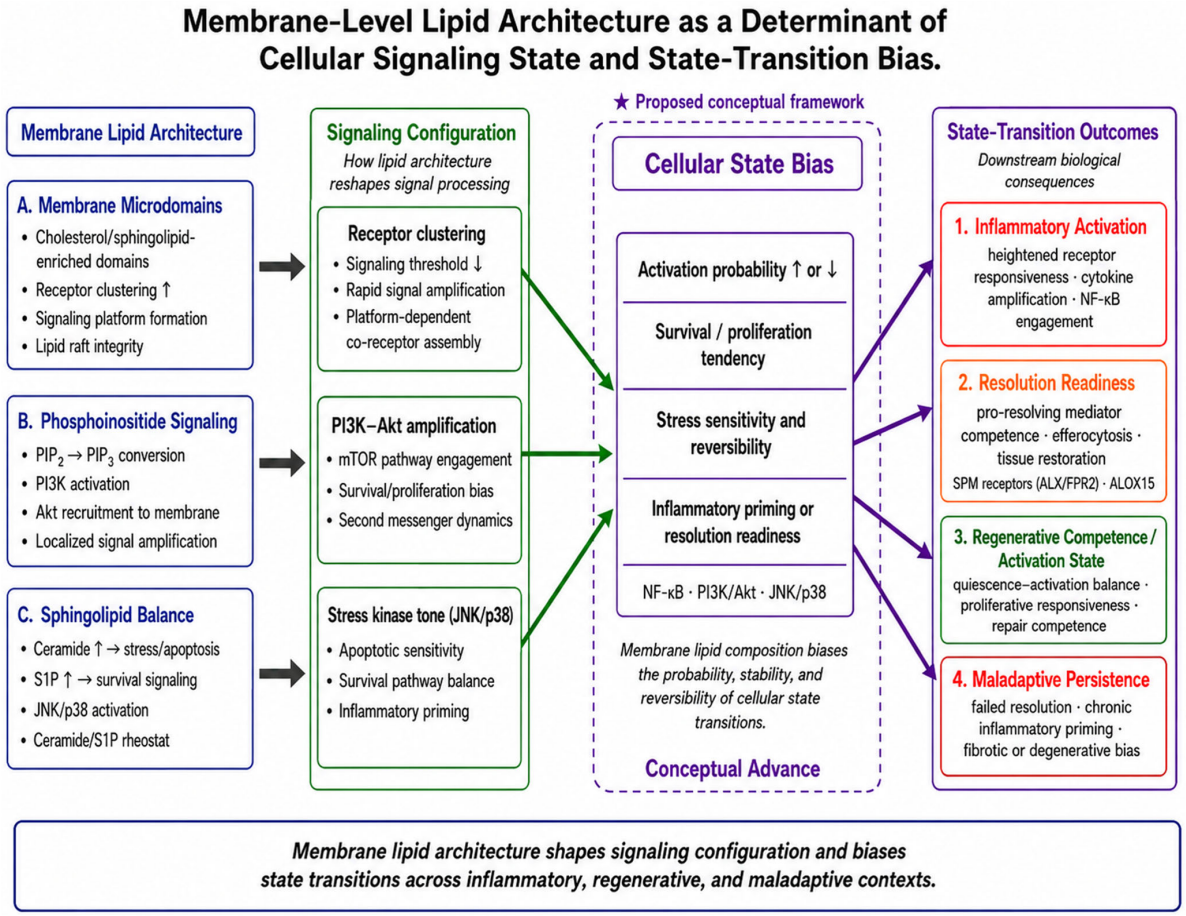


Figure 1. Membrane-level lipid architecture as a determinant of cellular signaling state and state-transition bias.

Membrane lipid architecture can influence cellular state transitions by shaping baseline signaling configuration. Membrane microdomains, phosphoinositide signaling, and sphingolipid balance regulate receptor clustering, PI3K–Akt amplification, stress kinase tone, and inflammatory priming [62–64]. In the proposed framework, these lipid-dependent inputs bias cellular state behavior by influencing activation probability, survival/proliferation tendency, stress sensitivity, reversibility, and resolution readiness. These effects may contribute to downstream outcomes including inflammatory activation, resolution readiness, regenerative competence, or maladaptive persistence.

2.4. Lipid Environment as a Baseline Determinant of Cellular Responsiveness

As defined above, cellular state is used here to describe an integrated functional configuration involving signaling activity, metabolic program, gene-regulatory profile, membrane organization, and measurable cellular behavior. As summarized in Figure 1, membrane microdomain organization, phosphoinositide signaling, and sphingolipid balance collectively influence intracellular signaling architecture and cellular responsiveness by modulating receptor clustering, PI3K–Akt signal amplification, and stress-associated kinase pathways [23,24,32,65].

Importantly, lipid composition is not static. It can be modified by metabolic state, dietary inputs, inflammatory mediators, aging, and disease-associated metabolic alterations [59,66]. Such shifts may influence whether a cell exhibits heightened sensitivity

to activation signals, maintains quiescence, engages survival pathways, or progresses toward apoptosis or dysfunction [24,65,67]. Although the precise outcomes depend on cell type and environmental context, evidence supports the view that lipid-dependent modulation of signaling thresholds contributes to variability in cellular functional states [23,24].

Accordingly, lipids may be understood not merely as structural elements or signaling intermediates, but as contributors to the baseline signaling configuration that precedes overt inflammatory or regenerative responses. By influencing receptor organization, second-messenger dynamics, and stress-adaptive pathways, the lipid environment helps establish the foundational signaling state upon which subsequent immune activation, resolution, or regenerative processes depend.

These membrane-level processes may also be interpreted as upstream contextual influences on the later domains discussed in this review. By shaping receptor clustering, signaling thresholds, phosphoinositide-dependent amplification, and stress-associated kinase activity, membrane lipid organization can influence how strongly cells respond to inflammatory stimuli, how readily they engage mediator-generating enzymatic pathways, and how signaling inputs are coupled to metabolic adaptation. These alterations in membrane organization extend beyond improving signaling efficiency; they may also influence downstream lipid metabolic programs, thereby helping align cellular metabolic requirements with inflammatory, reparative, or stress-adaptive trajectories. In this way, membrane architecture may help establish the signaling context within which inflammatory mediator balance and lipid metabolic programs later unfold, providing one mechanistic link between molecular membrane organization and broader cellular response patterns.

The lipid-dependent processes discussed above can also be viewed in relation to broader biological states rather than only by chemical class. For clarity, Table 1 reorganizes representative lipid environments across inflammatory, resolution-associated, and regenerative contexts, highlighting how membrane organization, mediator balance, and metabolic programs align with different cellular response states.

Table 1. State-centered organization of representative lipid environments and cellular response states.

Biological State	Representative Lipid Environment/Features	Representative Molecules/Pathways	Dominant Cellular Effects	Illustrative Contexts
Inflammatory activation	Enrichment of pro-inflammatory lipid mediators; membrane signaling platforms favoring receptor clustering and rapid signal amplification; stress-associated sphingolipid signaling	Prostaglandins, leukotrienes, phosphoinositides, ceramide-associated stress signaling	Leukocyte recruitment, cytokine amplification, vascular permeability, inflammatory priming, stress signaling	Rheumatoid arthritis, asthma, acute inflammatory disorders, neuroinflammatory activation
Resolution-associated state	Shift from arachidonic acid-dominant inflammatory signaling toward pro-resolving mediator balance; restoration-oriented signaling environment	Specialized pro-resolving mediators, including resolvins, protectins, and maresins; omega-3-derived mediator pathways	Reduced neutrophil recruitment, macrophage reprogramming, efferocytosis, tissue homeostasis restoration	Resolution of acute inflammation; chronic inflammatory states with impaired resolution; atherosclerosis; rheumatologic disease contexts
Regenerative/reparative state	Lipid metabolic programs supporting quiescence, activation, proliferation, and repair; membrane remodeling linked to growth-factor responsiveness and anabolic demand	FAO-linked oxidative metabolism, de novo lipogenesis, S1P signaling, PI3K–Akt–mTOR-associated lipid signaling	Stem-cell maintenance, proliferative activation, migration, membrane biogenesis, lineage-supportive signaling, tissue repair	Stem/progenitor-cell activation, regenerative tissues, wound repair, hematopoietic and neural stem-cell contexts

These categories are intended as heuristic organizing states rather than rigid biological compartments. Individual lipid pathways may contribute to more than one state depending on cell type, tissue context, disease stage, and experimental model.

These state-oriented categories are intended as heuristic organizing groups rather than rigid or mutually exclusive biological compartments, and many lipid pathways may contribute to more than one response state depending on tissue context.

3. Lipid Mediators in the Transition Between Inflammation and Resolution

3.1. Pro-Inflammatory Lipid Mediators

Bioactive lipid mediators derived from polyunsaturated fatty acids play central roles in the initiation and amplification of inflammatory responses. Among the most extensively studied are prostaglandins and leukotrienes, which are generated from arachidonic acid through cyclooxygenase (COX) and lipoxygenase (LOX) pathways, respectively [68,69]. Arachidonic acid is released from membrane phospholipids by phospholipase A2 in response to inflammatory stimuli, providing substrate for rapid enzymatic conversion into these signaling molecules [69–71].

Prostaglandins, including PGE2 and PGD2, exert context-dependent effects on vasodilation, vascular permeability, and immune-cell activation through binding to specific G protein–coupled receptors [72,73]. PGE2, for example, has been shown to enhance local blood flow and contribute to classical inflammatory signs such as erythema and edema, while also modulating cytokine production and immune-cell differentiation [72,74]. Leukotrienes, particularly LTB4, function as potent chemoattractants, promoting neutrophil recruitment and activation at sites of tissue injury or infection [75,76]. Cysteinyl leukotrienes (LTC4, LTD4, LTE4) contribute to vascular permeability and smooth muscle contraction, further amplifying inflammatory responses [77,78].

The production of prostaglandins and leukotrienes is typically rapid and transient during acute inflammation, and their synthesis is tightly regulated by enzymatic control points such as COX-1/COX-2 and 5-LOX [68,79]. Pharmacological inhibition of COX enzymes by nonsteroidal anti-inflammatory drugs (NSAIDs) reduces prostaglandin synthesis and alleviates inflammatory symptoms, underscoring the functional importance of these lipid mediators in inflammatory activation [80,81].

While pro-inflammatory lipid mediators are essential for host defense and initiation of immune responses, sustained or excessive production has been associated with tissue damage and chronic inflammatory pathology in various disease contexts [80,82,83]. Thus, prostaglandins and leukotrienes exemplify how lipid-derived mediators can promote inflammatory activation and immune-cell recruitment, shaping the early phases of inflammatory state transitions.

3.2. Specialized Pro-Resolving Mediators

In addition to pro-inflammatory eicosanoids, inflammation is regulated by a distinct class of bioactive lipid mediators collectively termed specialized pro-resolving mediators (SPMs). These include resolvins, protectins, and maresins, which are enzymatically derived from omega-3 polyunsaturated fatty acids such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) [84,85]. SPMs are generated during the later phases of the inflammatory response and are proposed to contribute to the active orchestration of resolution rather than merely representing the passive decline of pro-inflammatory signals [21,86].

Experimental studies have shown that resolvins can reduce neutrophil infiltration, promote macrophage-mediated clearance of apoptotic cells (efferocytosis), and modulate cytokine production in various models of acute inflammation [86–88]. Protectins and maresins have been reported to influence macrophage polarization, tissue repair processes, and the restoration of barrier integrity in specific experimental contexts [89,90]. These me-

diators exert their effects through defined receptors, including G protein–coupled receptors expressed on immune and structural cells [91,92].

Importantly, resolution is now understood as an active, regulated process involving coordinated cellular and molecular events, including termination of neutrophil recruitment, promotion of apoptotic cell clearance, and restoration of tissue homeostasis [93,94]. SPMs have been implicated as contributors to these processes, although their precise roles and relative contributions in human inflammatory diseases remain an area of ongoing investigation [7,21,84]. Thus, while substantial preclinical evidence supports the role of SPMs in promoting resolution pathways, translation to clinical contexts requires careful interpretation.

3.3. Resolution Failure and Persistent Inflammation

Under physiological conditions, inflammatory initiation is followed by resolution and tissue restoration. However, disruption of this balance may contribute to persistent inflammatory states. Altered production of pro-inflammatory lipid mediators or insufficient generation of pro-resolving mediators has been reported in chronic inflammatory conditions, including rheumatoid arthritis and other rheumatologic disorders [21,95,96]. For example, elevated levels of specific eicosanoids have been detected in synovial fluid and inflamed tissues in rheumatoid arthritis, correlating with disease activity in some studies [97,98].

Conversely, alterations in SPM levels or impaired resolution signaling have been observed in certain chronic inflammatory contexts, although findings vary depending on disease stage, tissue compartment, and methodological approach [21,96,99]. These observations have led to the hypothesis that an imbalance between inflammatory and pro-resolving lipid mediators may contribute to sustained immune activation and tissue damage [21,80]. Nevertheless, causal relationships in human disease remain complex and likely involve interactions with cytokine networks, immune-cell dysregulation, and metabolic factors [95,100].

Collectively, evidence from experimental models and selected clinical studies supports the concept that lipid mediator balance influences whether inflammation resolves appropriately or progresses toward chronic pathology. While lipid mediators do not act in isolation, their regulated production and receptor-mediated signaling contribute to the trajectory of inflammatory responses and may influence the persistence or resolution of inflammatory states.

These coordinated shifts in mediator production are summarized in Figure 2, which is intended as an integrative schematic of established mediator class-switching principles and their relationship to the broader conceptual framework discussed in this review.

Lipid mediator balance can shape whether inflammatory activation progresses toward resolution or persists as a chronic inflammatory state. Arachidonic acid-derived mediators, including PGE2, PGD2, and LTB4, support inflammatory activation through neutrophil recruitment, vascular permeability, cytokine amplification, and NF-κB engagement [68,101,102]. In contrast, EPA/DHA-derived specialized pro-resolving mediators promote macrophage reprogramming, efferocytosis, neutrophil clearance, and tissue restoration. In the proposed state-transition interpretation, efficient mediator class switching supports resolution readiness, whereas impaired switching may stabilize persistent inflammatory signaling and bias the tissue environment toward maladaptive repair.

As summarized in Figure 2, inflammatory outcome is shaped not solely by the magnitude of initial pro-inflammatory signaling, but also by the efficiency of mediator class switching toward pro-resolving pathways. Impaired switching may contribute to persistent inflammatory signaling and incomplete restoration of tissue homeostasis in chronic

pathological contexts. Here, Figure 2 is used primarily as a conceptual bridge connecting established mediator biology to the broader cross-domain framework developed in the subsequent sections.

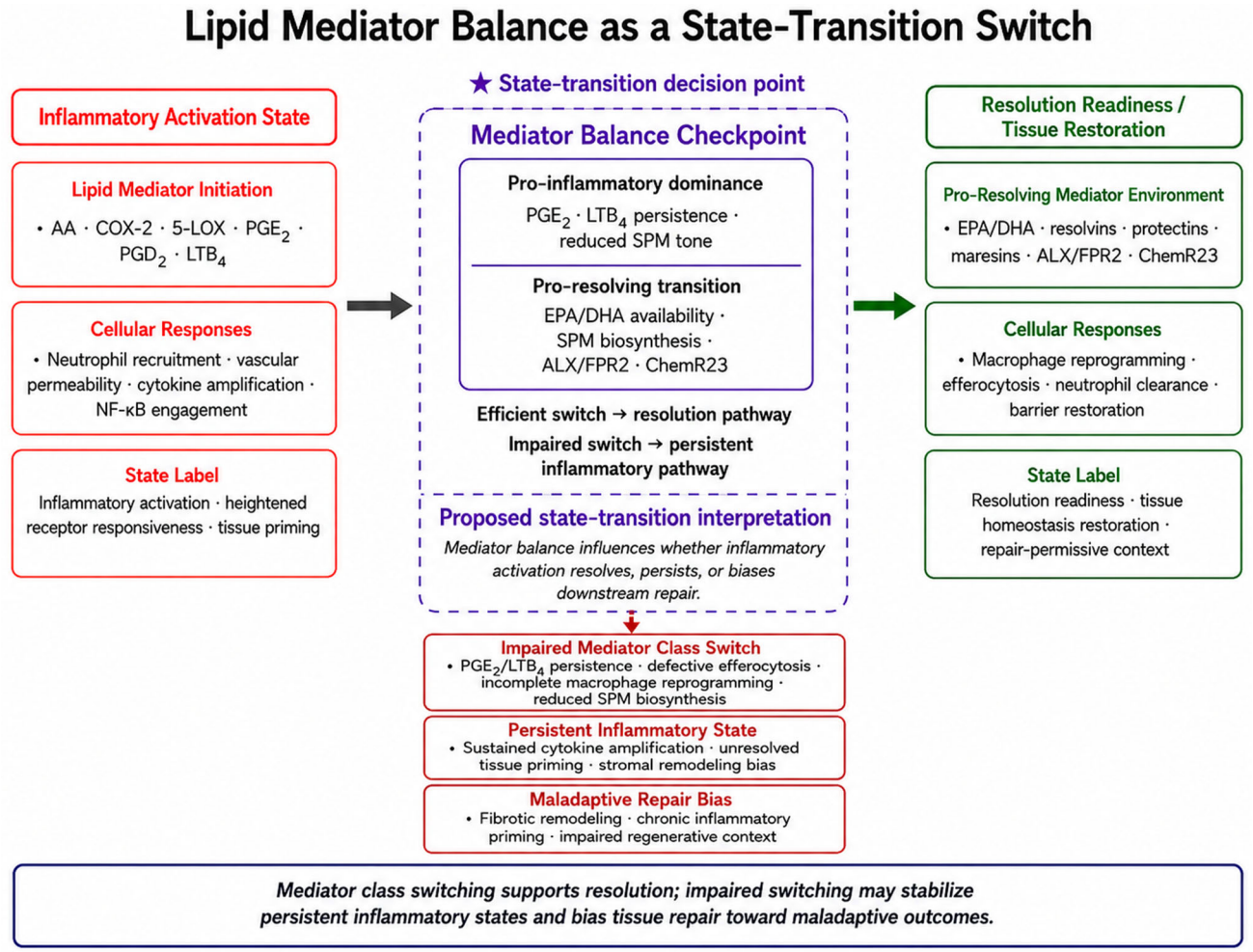


Figure 2. Lipid mediator balance as a state-transition switch.

The significance of mediator balance extends beyond inflammatory cell recruitment alone. Persistent enrichment of pro-inflammatory mediators or impaired transition toward pro-resolving programs may alter the tissue environment encountered by stem, progenitor, stromal, and structural cells, thereby influencing proliferative behavior, survival, differentiation, and repair efficiency. Conversely, more effective resolution programs may create conditions more compatible with regenerative recovery. This provides a functional bridge between lipid mediator dynamics and the metabolic, transcriptional, and fate-related processes discussed in the following section.

4. Lipid Metabolism and Stem-Cell State Regulation

Because stem-cell metabolism varies across tissue type, developmental stage, niche composition, and experimental model, the lipid-associated mechanisms discussed in this section should not be interpreted as uniform across all stem-cell systems. In general, the association between cellular metabolic state and stem-cell behavior is strongly supported, particularly the coupling of quiescence, activation, proliferation, and differentiation to changes in nutrient use and biosynthetic demand [10,103,104]. However, the specific role of individual lipid pathways, including fatty acid oxidation, de novo lipogenesis, sphingolipid signaling, and lipid mediator pathways, is often context-dependent. Accordingly, this

section distinguishes between broadly supported principles, tissue- or model-specific findings, and hypothesis-generating interpretations regarding lipid control of stem-cell state transitions.

4.1. Fatty Acid Oxidation and Stem-Cell Quiescence

Stem-cell function is tightly coupled to metabolic state, and increasing evidence indicates that lipid metabolism contributes to the regulation of stem-cell quiescence and long-term maintenance. In several stem-cell systems, including hematopoietic and neural stem cells, fatty acid oxidation (FAO) has been associated with the maintenance of quiescent populations and preservation of self-renewal capacity [105,106]. FAO provides a sustained source of ATP while limiting excessive reactive oxygen species (ROS) production compared to some alternative metabolic pathways, which may support long-term stem-cell integrity [105,107].

Mechanistic studies have shown that modulation of FAO-related enzymes can influence stem-cell fate decisions. For example, perturbation of carnitine palmitoyltransferase 1 (CPT1), a key regulator of mitochondrial fatty acid entry, has been reported to alter stem-cell maintenance and differentiation in specific experimental models [105,108,109]. In hematopoietic stem cells, FAO has been linked to asymmetric division and self-renewal in certain contexts [106,110]. Similarly, neural stem-cell populations have been shown to exhibit metabolic profiles consistent with reliance on oxidative pathways, including fatty acid metabolism, during quiescent states [107,111,112].

Importantly, the contribution of FAO to quiescence appears to be context-dependent and varies across tissues and developmental stages [22,106,110]. Nonetheless, collectively available evidence supports the view that lipid catabolism contributes to the maintenance of quiescent stem-cell pools and may influence long-term tissue integrity.

4.2. Lipid Synthesis and Proliferative Activation

In contrast to quiescent states, stem-cell activation and proliferative expansion are frequently associated with increased anabolic metabolism, including de novo lipogenesis. De novo fatty acid synthesis provides essential lipid components for membrane biogenesis, organelle expansion, and production of signaling molecules during cell proliferation [113,114]. Enzymes such as fatty acid synthase (FASN) and acetyl-CoA carboxylase (ACC) have been implicated in supporting proliferative growth in multiple cell types, including progenitor and stem-cell populations [114,115].

Experimental inhibition of lipid synthesis pathways has been shown in certain systems to impair stem-cell proliferation and differentiation, suggesting that lipogenic flux contributes to regenerative expansion [114,116]. In intestinal, neural, and muscle progenitor models, increased lipid biosynthesis has been associated with activated states during tissue repair or growth [113,114]. Moreover, lipid-derived intermediates can serve as substrates for post-translational modifications and signaling molecules that further influence proliferation-related pathways [115,117,118].

While the precise metabolic configuration varies among tissues, available data indicate that transitions from quiescence to proliferation are accompanied by coordinated shifts in lipid metabolism, including enhanced lipogenesis. These metabolic changes support membrane expansion and cellular growth required for regeneration, although their regulatory hierarchy relative to transcriptional and niche-derived cues remains an area of active investigation [114,115].

4.3. Lipid Signaling in Regenerative Competence

Beyond serving as metabolic substrates, lipids function as signaling molecules that influence lineage specification, differentiation programs, and regenerative outcomes. Lipid-

derived mediators, including eicosanoids and sphingolipids, have been shown in specific experimental systems to modulate stem- and progenitor-cell proliferation and differentiation through receptor-mediated signaling pathways [119,120]. For example, prostaglandin E2 (PGE2) has been reported to enhance hematopoietic stem-cell expansion and engraftment in certain models, acting through defined receptor pathways [121,122]. Similarly, sphingosine-1-phosphate (S1P) signaling has been implicated in regulating stem-cell migration, survival, and tissue localization in multiple contexts [120,123].

In addition to classical lipid mediators, intracellular lipid signaling pathways intersect with transcriptional regulators of cell fate. Phosphoinositide signaling through PI3K–Akt–mTOR pathways can influence proliferation, survival, and differentiation decisions in stem and progenitor cells [124,125]. Moreover, lipid metabolic intermediates can contribute to epigenetic regulation by influencing acetyl-CoA availability and histone acetylation dynamics, thereby linking metabolic state to gene-expression programs relevant to differentiation [126,127].

The influence of lipid-mediated signaling on regenerative competence appears to be tissue-specific and context-dependent. In some systems, lipid signaling promotes expansion and repair, whereas in others it may contribute to premature differentiation or exhaustion when dysregulated [74,128]. Collectively, available evidence indicates that lipid signaling pathways interact with growth-factor and niche-derived cues to shape lineage decisions and tissue repair efficiency, although the relative contribution of lipid signals compared with other regulatory inputs varies across biological contexts [119,121,125]. These effects may also extend beyond immediate signaling outputs to include gene-regulatory mechanisms that help stabilize or redirect cellular state over time.

4.4. Lipid-Linked Gene-Regulatory Interfaces

Lipid-dependent regulation of cellular state is not limited to membrane signaling and metabolic substrate availability, but also intersects with gene-regulatory mechanisms that help stabilize or redirect cellular identity. One important interface is the relationship between lipid metabolism and chromatin regulation. Lipid-derived metabolites such as acetyl-CoA can influence histone acetylation, thereby linking shifts in fatty acid oxidation, lipogenesis, or citrate metabolism to transcriptional programs associated with quiescence, activation, and differentiation [127,129]. In this way, lipid metabolic state may contribute not only to immediate energetic demands, but also to longer-lived epigenetic configurations relevant to regenerative competence and cell-fate control.

A second regulatory layer involves lipid-responsive transcription factors that connect metabolic and signaling cues to nuclear responses. Members of the peroxisome proliferator-activated receptor (PPAR) family, sterol regulatory element-binding proteins (SREBPs), and related lipid-sensitive transcriptional regulators have been implicated in coordinating inflammatory tone, anabolic metabolism, and differentiation-associated gene expression across multiple tissues [130,131]. These pathways provide a mechanistic route by which lipid availability, membrane composition, and intracellular lipid flux may be translated into broader transcriptional reprogramming rather than remaining confined to short-range signaling effects.

In addition, emerging evidence suggests that lipid environments may interact with RNA-associated regulatory systems [132,133]. Extracellular vesicles enriched in distinctive lipid compositions can influence intercellular communication and may carry microRNAs and other non-coding RNAs capable of modifying inflammatory or reparative responses in recipient cells [133–136]. Although this area remains less mechanistically mature than the literature on lipid mediators or metabolic regulation, it highlights the possibility that lipid-dependent state regulation extends into post-transcriptional and intercellular gene-

regulatory processes. Taken together, these observations suggest that lipid biology intersects with chromatin regulation, transcription-factor activity, and selected RNA-mediated mechanisms, thereby linking metabolic and membrane-associated processes to more stable programs of cellular identity.

4.5. Aging, Metabolic Drift, and Declining Regeneration

Aging is associated with systemic and cellular metabolic alterations, including changes in lipid composition, lipid storage, and lipid oxidation pathways [66,137]. Age-related shifts in lipid metabolism have been reported in multiple stem-cell populations, including hematopoietic, neural, and muscle stem cells, and have been linked to functional decline in regenerative capacity [11,104]. For example, altered mitochondrial function and dysregulated fatty acid metabolism have been observed in aged stem cells, potentially contributing to increased oxidative stress and impaired self-renewal [11,104,138].

Changes in membrane lipid composition during aging may also influence receptor signaling and inflammatory sensitivity, potentially biasing cells toward pro-inflammatory states or altered differentiation trajectories [66,139]. In certain contexts, accumulation of specific lipid species—such as ceramides or oxidized lipids—has been associated with cellular dysfunction and reduced regenerative efficiency [140,141]. However, causal relationships between lipid alterations and regenerative decline remain complex and are likely influenced by systemic factors, inflammatory environment, and niche-derived signals [66,137].

Emerging studies suggest that metabolic reprogramming strategies, including modulation of lipid oxidation or synthesis pathways, can partially restore stem-cell function in aged models, although translational implications remain under investigation [104,138]. These findings support the concept that age-associated alterations in lipid metabolism may bias stem cells toward dysfunction and impaired repair, contributing to progressive decline in tissue regenerative potential.

Although discussed here in the context of stem- and progenitor-cell biology, these lipid metabolic programs are also relevant to chronic disease progression at the tissue level. Impaired transitions between quiescence, activation, and regenerative competence may interact with persistent inflammatory signaling, altered membrane responsiveness, and abnormal stromal remodeling to bias tissues away from effective repair. Thus, the metabolic state of regenerative cell populations can be viewed as one intermediate layer linking membrane-associated signaling context and mediator balance to longer-term disease outcomes.

The coordinated transitions between quiescent, activated, and aged stem-cell states—and their associated lipid metabolic configurations—are summarized in Figure 3, which highlights FAO-associated quiescence, lipogenesis-associated activation, and aging-associated metabolic drift.

Lipid metabolic configuration can influence transitions between quiescent, activated, reparative, and dysfunctional stem/progenitor-cell states. FAO-associated programs, including CPT1 and PPARδ/PGC-1α-related lipid oxidation, are shown as context-dependent features linked to quiescence, self-renewal, maintenance, and controlled ROS tone. In contrast, lipogenesis-associated programs involving FASN, ACC, SREBP, and PI3K–Akt–mTOR signaling support membrane biogenesis, proliferative responsiveness, regenerative expansion, and repair competence. With repeated stress, aging, or lipid imbalance, altered ceramide/S1P balance, oxidized lipids, impaired lipid handling, and mitochondrial stress may bias cells toward metabolic drift, exhaustion, and regenerative decline. In the proposed state-transition interpretation, lipid metabolic programs influence the probability, stability, and reversibility of transitions between quiescence, activation, repair, exhaustion, and aging-associated dysfunction.

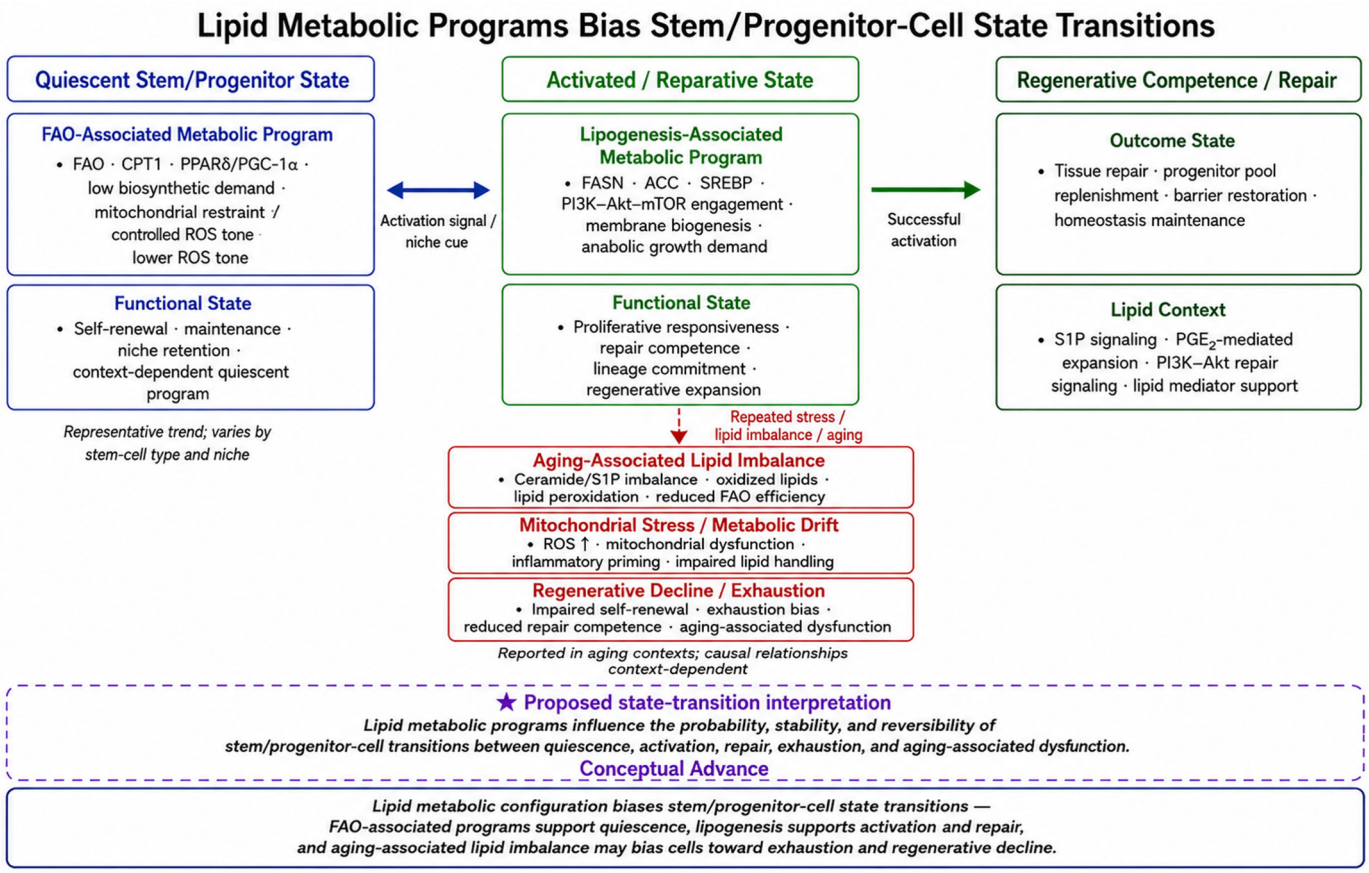


Figure 3. Lipid metabolic programs bias stem/progenitor-cell state transitions.

As shown in Figure 3, shifts in lipid metabolism are associated with distinct stem-cell states, with oxidative lipid utilization linked to quiescence, anabolic lipogenesis linked to proliferative activation, and age-associated lipid imbalance linked to oxidative stress and regenerative decline.

Overall, the strongest cross-system principle emerging from the stem-cell literature is that transitions between quiescence, activation, proliferation, and regenerative competence are accompanied by coordinated metabolic remodeling, including changes in lipid use, lipid synthesis, and membrane biogenesis. However, the direction and functional importance of specific lipid pathways are not identical across stem-cell compartments. FAO-associated quiescence has relatively strong support in selected systems such as hematopoietic and neural stem-cell models, but it should not be generalized as a universal requirement for all quiescent stem cells. Lipogenesis-associated proliferative activation is supported by the general biosynthetic requirement for membrane production during cell growth, although the dependence on specific enzymes such as FASN or ACC varies by tissue and experimental context. Lipid mediators such as PGE2 and S1P have defined roles in particular stem/progenitor-cell models, but their effects on expansion, migration, differentiation, or exhaustion are highly context-dependent [10,11,103]. Finally, links among aging, lipid imbalance, oxidative stress, and regenerative decline are supported by accumulating experimental and lipidomic evidence, but causal relationships remain incompletely resolved and should be interpreted as emerging rather than definitive across all tissues.

5. Lipid Dysregulation in Chronic Disease Contexts

The following disease contexts are presented as representative examples rather than exhaustive case studies. They were selected to illustrate how lipid-associated mechanisms

may recur across distinct pathological settings while also revealing important differences in evidentiary strength, causal inference, and tissue specificity.

To maintain this distinction across disease contexts, the following sections separate three levels of interpretation. First, "established mechanisms" refer to lipid-dependent processes supported by mechanistic experimental evidence, such as lipid mediator control of inflammatory signaling, membrane lipid effects on receptor organization, or defined sphingolipid and phosphoinositide signaling pathways. Second, "associations or state signatures" refer to lipidomic or metabolic changes observed in disease tissues or patient samples without sufficient evidence to establish causality. Third, "hypothesis-generating interpretations" refer to proposed integrative links in which lipid alterations may contribute to state persistence, maladaptive repair, neuroinflammatory progression, or age-related regenerative decline, but where the directionality and causal hierarchy remain incompletely defined. This distinction is especially important in aging, fibrosis, and neurodegeneration, where lipid changes may act as contributors, amplifiers, permissive conditions, or downstream consequences depending on biological context.

5.1. Rheumatoid Arthritis and Persistent Inflammatory Lipid Signatures

Rheumatoid arthritis (RA) is characterized by chronic synovial inflammation, immune-cell infiltration, and progressive joint destruction. Numerous studies have reported altered lipid mediator profiles in synovial fluid, plasma, and inflamed tissues of patients with RA [97,98]. Elevated levels of pro-inflammatory eicosanoids, including prostaglandins and leukotrienes, have been detected in active disease and have been associated with inflammatory activity in some cohorts [98,142]. These lipid mediators can promote leukocyte recruitment, vascular permeability, and cytokine production, thereby contributing to sustained inflammatory signaling within the joint microenvironment [75,143].

In addition to classical eicosanoids, alterations in lipidomic signatures—including changes in phospholipids, sphingolipids, and oxidized lipid species—have been observed in RA and may reflect ongoing immune activation and metabolic remodeling [97,144,145]. Certain sphingolipid species, including ceramides, have been associated with inflammatory markers and disease severity in specific studies, although findings vary across patient populations [146,147].

Conversely, reduced levels or impaired biosynthesis of specialized pro-resolving mediators have been reported in some chronic inflammatory settings, raising the possibility that insufficient resolution signaling contributes to disease persistence [98,148]. However, the extent to which altered SPM pathways are causal drivers versus secondary consequences of chronic inflammation remains under investigation [97,148].

Taken together, available evidence supports the concept that persistent inflammatory lipid signatures are present in RA and may reflect, reinforce, or in some settings contribute to sustained immune activation, but they are best interpreted as one component of a broader inflammatory network rather than as independent determinants of disease persistence. Nevertheless, chronic disease pathogenesis involves complex interactions among cytokines, immune-cell subsets, genetic predisposition, and environmental factors, with lipid dysregulation representing one component of a broader inflammatory network [97,144,148].

However, much of the available literature remains correlative, and the relative importance of lipid pathways compared with cytokine-driven, stromal, and immune-cell-intrinsic mechanisms remains incompletely resolved in human RA.

5.2. Neuroinflammation and Degenerative Progression

Neurodegenerative disorders and chronic neuroinflammatory conditions are associated with alterations in lipid metabolism and membrane composition within the central

nervous system. The brain is highly enriched in complex lipids, including sphingolipids, phospholipids, and cholesterol, which contribute to synaptic function and membrane organization [6,149]. Disruptions in lipid homeostasis have been reported in conditions such as Alzheimer's disease, Parkinson's disease, and multiple sclerosis, although patterns vary depending on disease stage and tissue compartment [150,151].

Altered sphingolipid metabolism, including increased ceramide levels, has been observed in certain neurodegenerative contexts and has been linked to apoptotic signaling, mitochondrial dysfunction, and inflammatory activation in experimental models [46,152]. Changes in membrane lipid composition may also influence receptor clustering and microglial activation, potentially modifying neuroinflammatory cascades [153,154]. In addition, lipid mediators derived from arachidonic acid have been implicated in central nervous system inflammatory signaling, including modulation of glial responses [155,156].

Importantly, while lipid alterations are consistently observed in neurodegenerative disease, the directionality of these changes—whether they initiate pathology, amplify existing inflammation, or arise secondary to neuronal injury—remains an area of active research [19,150,157]. In neurodegenerative settings, altered lipid signaling and membrane organization may interact with inflammatory pathways, but in many contexts these changes likely represent both amplifiers and consequences of ongoing tissue injury rather than primary initiating causes [158,159].

A major limitation in this area is that lipid alterations are often measured after substantial tissue injury is already present, making it difficult to distinguish initiating mechanisms from secondary consequences of neurodegeneration.

5.3. Fibrosis and Maladaptive Repair

Fibrosis represents a pathological remodeling process characterized by excessive extracellular matrix deposition, persistent activation of fibroblasts or myofibroblasts, and impaired restoration of normal tissue architecture. Lipid signaling pathways have been implicated in modulating fibrotic responses in multiple organs, including lung, liver, kidney, and heart [160,161]. For example, eicosanoids derived from arachidonic acid can influence fibroblast proliferation, cytokine production, and extracellular matrix synthesis in certain experimental systems [162,163].

Sphingolipid metabolites, including ceramide and S1P, have also been associated with fibrotic signaling pathways. S1P signaling through defined receptors has been reported to promote fibroblast activation and tissue remodeling in selected models, whereas ceramide accumulation has been linked to stress signaling and cellular injury that may precede fibrotic progression [164,165]. In addition, alterations in membrane lipid composition can influence transforming growth factor–β (TGF-β) receptor signaling and other pro-fibrotic pathways, potentially modifying the magnitude or persistence of remodeling responses [166,167].

A useful way to integrate these observations is to consider fibrosis as a setting in which membrane organization, lipid mediator balance, and metabolic lipid programs may reinforce one another over time. In injured tissue, altered membrane lipid composition may influence the sensitivity of fibroblasts and stromal cells to TGF-β and other inflammatory or pro-remodeling cues [168,169]. At the same time, persistent enrichment of pro-inflammatory and pro-fibrotic lipid mediators may help sustain cytokine production, immune-cell recruitment, and myofibroblast activation [169,170]. In parallel, metabolic shifts that support anabolic demand and stress adaptation may favor continued extracellular matrix production rather than restoration of normal tissue architecture [171]. Together, these interacting processes may create a pathological feedback loop in which inflammatory

signaling, lipid dysregulation, and maladaptive repair reinforce one another and contribute to chronic fibrotic persistence [172,173].

It is important to note that fibrosis arises from complex interactions among inflammatory signaling, mechanical stress, metabolic dysregulation, and cellular injury. Lipid-associated signaling shifts do not act in isolation and may, depending on context, function as contributory regulators, permissive remodeling conditions, or secondary signatures of fibrotic progression rather than as autonomous drivers of maladaptive repair [161,174,175]. In fibrotic disease, lipid-associated signaling changes may bias repair toward maladaptive remodeling in selected contexts, but they are best interpreted as part of a broader network of stromal, inflammatory, and metabolic processes.

Mechanistic evidence supports lipid involvement in selected pathways, but the extent to which lipid dysregulation acts as a primary organizer of maladaptive repair rather than as one component of a broader remodeling network remains uncertain.

5.4. Aging Tissues and Regenerative Failure

Aging is accompanied by systemic alterations in lipid metabolism, including changes in circulating lipid profiles, membrane lipid composition, and intracellular lipid handling [66,176,177]. These alterations occur alongside increased low-grade inflammation, often termed "inflammaging," and reduced regenerative capacity across multiple tissues [178,179]. Emerging evidence suggests that age-associated lipid imbalances may interact with inflammatory and metabolic pathways to influence cellular functional states in stem and progenitor populations [180,181].

Accumulation of specific lipid species, such as ceramides and oxidized lipids, has been reported in aged tissues and has been associated with mitochondrial dysfunction, increased oxidative stress, and impaired cellular resilience in experimental models [182,183]. Changes in membrane lipid composition may also alter receptor sensitivity and inflammatory signaling thresholds, potentially reinforcing pro-inflammatory or stress-adaptive states in aging cells [184,185]. However, causal links between specific lipid alterations and regenerative decline remain incompletely defined and likely vary across organ systems [66,176,180].

In aging tissues, lipid alterations may accompany, reinforce, or in some contexts contribute to regenerative decline, but they are intertwined with systemic metabolic change, inflammatory tone, niche disruption, and accumulated cellular damage. These effects likely occur in conjunction with genomic instability, epigenetic drift, and niche alterations rather than through lipid mechanisms alone [186–188]. Accordingly, available data support the view that lipid dysregulation may interact with other age-related processes across organ systems, without implying that it independently determines age-associated loss of repair capacity.

Across these chronic disease contexts, lipid alterations should not be interpreted as occupying a single causal category. In some settings, specific lipid pathways may contribute directly to signaling processes that influence inflammatory persistence, fibroblast activation, stem-cell dysfunction, or impaired resolution. In other settings, altered lipid composition may function more as a permissive metabolic or membrane environment that biases cellular responsiveness without independently determining outcome. In still other cases, lipidomic changes may primarily reflect downstream consequences of inflammation, tissue injury, oxidative stress, or metabolic remodeling that are already underway. Distinguishing among causal contributors, permissive conditions, and downstream signatures remains essential for interpreting lipid-associated disease states and for avoiding overstatement of mechanistic inference across heterogeneous biological systems.

The disease contexts discussed above illustrate how distinct alterations in lipid composition and mediator balance may be associated with persistent maladaptive cellular and tissue responses across chronic conditions. For clarity, representative lipid-associated patterns across selected chronic diseases are summarized in Table 2, highlighting altered lipid features, associated cellular states, levels of evidence, and potential therapeutic implications.

Table 2. Disease-context examples, evidence strength, and translational maturity of lipid-associated state changes.

Disease Context	Main Lipid-Associated Features	State-Transition Interpretation	Evidence Status	Translational Implication/Therapeutic Maturity
Rheumatoid arthritis	Elevated prostaglandins and leukotrienes; altered phospholipid and sphingolipid profiles; reduced or altered specialized pro-resolving mediator signatures in selected studies	Lipid mediator imbalance may reinforce persistent inflammatory activation and incomplete resolution	Human lipidomic and mediator-profile associations supported by preclinical mechanistic models; causal hierarchy remains incompletely defined	NSAIDs have established symptomatic utility; SPM augmentation and lipidomic-guided stratification remain investigational
Neurodegenerative disorders	Altered sphingolipid metabolism, including increased ceramide in selected contexts; membrane lipid remodeling; dysregulated arachidonic acid-derived inflammatory mediators	Lipid alterations may amplify neuroinflammatory activation, neuronal stress signaling, or degenerative progression, but may also reflect downstream injury	Clinical lipidomic associations and experimental models; directionality remains uncertain and context-dependent	S1P modulators are clinically relevant in selected immune-mediated CNS disease contexts; broader sphingolipid-targeted or metabolic approaches remain experimental
Fibrosis	Altered eicosanoid balance; increased S1P signaling in selected models; membrane lipid effects on TGF-β-associated signaling	Lipid-associated mechanisms may bias adaptive repair toward persistent fibroblast activation and extracellular matrix accumulation	Stronger preclinical support than human causal evidence; organ-specific differences remain important	Anti-fibrotic lipid-signaling strategies remain investigational; clinical translation requires organ- and stage-specific validation
Aging tissues	Accumulation of selected ceramides or oxidized lipids; altered membrane composition; systemic and tissue lipidomic drift	Lipid changes may interact with inflammaging, stem/progenitor-cell dysfunction, mitochondrial stress, and impaired repair	Human lipidomic profiling plus experimental aging models; causal relationships remain emerging rather than definitive	Dietary lipid modulation and metabolic reprogramming approaches remain context-dependent; lipid-targeted rejuvenation strategies are investigational

Evidence status is summarized qualitatively to distinguish established clinical use, human lipidomic or biomarker associations, preclinical mechanistic support, and hypothesis-generating interpretation. Therapeutic maturity refers to the specific disease context listed and should not be generalized across all lipid-targeted interventions.

Together, these observations are integrated in Figure 4, which is presented as a hypothesis-generating conceptual framework summarizing how membrane lipid organization, mediator balance, and metabolic lipid programs may be interpreted together across inflammation, regeneration, aging, and chronic disease.

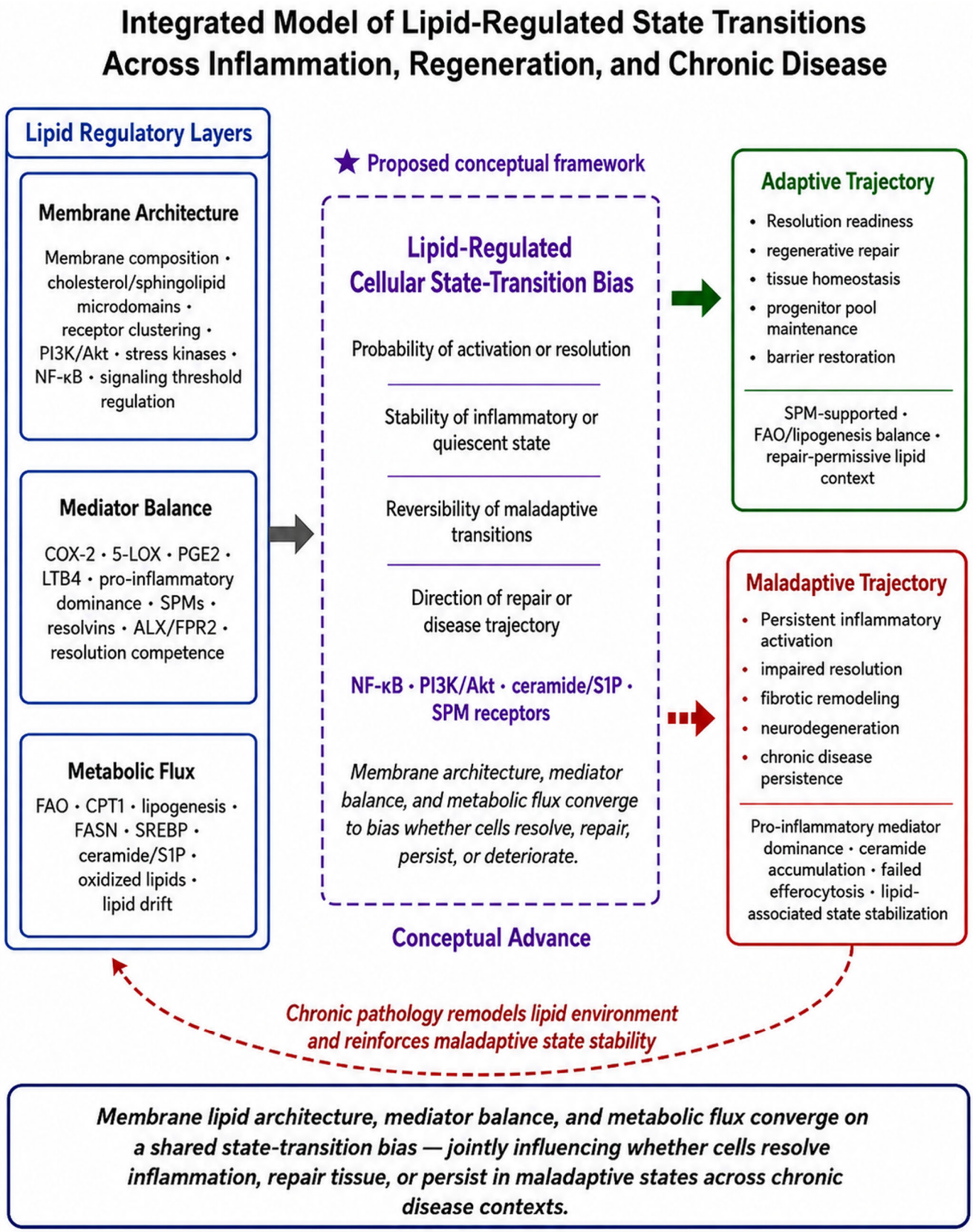


Figure 4. Integrated model of lipid-regulated state transitions across inflammation, regeneration, and chronic disease.

This figure summarizes the proposed framework in which membrane lipid architecture, lipid mediator balance, and lipid metabolic flux converge to bias cellular state transitions. These lipid regulatory layers may influence activation probability, state stabil-

ity, reversibility, and trajectory direction through pathways including NF-κB, PI3K/Akt, ceramide/S1P balance, and SPM receptor signaling. Adaptive lipid-regulated trajectories support resolution, regenerative repair, and tissue homeostasis, whereas maladaptive trajectories may promote persistent inflammation, impaired resolution, fibrotic remodeling, neurodegeneration, and chronic disease persistence. The feedback loop indicates that chronic pathology can further remodel the lipid environment and reinforce maladaptive state stability.

As summarized in Figure 4, this conceptual framework is intended as a hypothesis-generating synthesis of the reviewed literature, highlighting how chronic pathology may remodel the lipid environment and potentially reinforce maladaptive cellular states without implying a uniform causal hierarchy across disease contexts.

Interpretation in aging contexts is further complicated by the overlap of lipid alterations with systemic metabolic change, inflammaging, niche deterioration, and cumulative cellular damage, which limits straightforward mechanistic attribution.

6. Pharmacological Modulation of Lipid Pathways as State-Reprogramming Therapy

The therapeutic examples discussed in this section are not presented merely as isolated pharmacologic categories, but as interventions that intersect with the three recurring regulatory layers emphasized throughout this review: membrane signaling organization, lipid mediator balance, and lipid metabolic or reparative state. Framed in this way, lipid-targeted therapies can be compared not only by their molecular targets, but also by the level at which they may alter cellular responsiveness, inflammatory trajectory, or regenerative competence.

6.1. NSAIDs and Eicosanoid Modulation

NSAIDs are among the most widely used agents for the treatment of inflammatory pain and autoimmune conditions. Their primary mechanism of action involves inhibition of cyclooxygenase (COX) enzymes, thereby reducing the synthesis of prostaglandins derived from arachidonic acid [189,190]. By limiting prostaglandin production, NSAIDs attenuate vasodilation, vascular permeability, and inflammatory pain signaling [191,192].

Beyond symptomatic relief, COX inhibition alters the balance of lipid mediators generated during inflammatory responses. Reduced prostaglandin synthesis can modify cytokine production, immune-cell recruitment, and local inflammatory signaling networks [74,189,193]. In certain contexts, selective COX-2 inhibition has been shown to influence the inflammatory microenvironment beyond analgesic effects, although the broader immunological consequences vary depending on dose, timing, and disease context [189,193,194].

It is important to note that NSAIDs primarily suppress pro-inflammatory eicosanoid pathways rather than directly enhancing pro-resolving mechanisms. In some experimental settings, altered substrate availability following COX inhibition may shift lipid mediator production toward alternative pathways, but such effects are context-dependent and incompletely characterized in human disease [195,196]. Thus, NSAIDs exemplify pharmacological modulation of lipid pathways that can influence inflammatory state dynamics, while primarily functioning as inhibitors of specific pro-inflammatory mediators.

Within the framework proposed here, NSAIDs can therefore be interpreted as interventions acting primarily at the level of lipid mediator balance, reducing one arm of inflammatory amplification without necessarily restoring membrane-level signaling context or regenerative metabolic programs. Clinical benefit is well established for symptom control in inflammatory disease, but these effects do not by themselves demon-

strate selective restoration of tissue-level lipid-state transitions as conceptualized in the present framework.

6.2. Omega-3 Fatty Acids and Resolution Enhancement

Dietary omega-3 polyunsaturated fatty acids, including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), serve as substrates for the biosynthesis of specialized pro-resolving mediators (SPMs), such as resolvins, protectins, and maresins [84,197]. Beyond inflammation-resolution biology, omega-3 fatty acids—particularly DHA—are critical structural components of neuronal membranes and contribute to neurodevelopmental membrane assembly and synaptic signaling capacity during fetal and early-life brain development [198]. This developmental dependence illustrates how lipid substrate availability can shape long-term cellular state trajectories by constraining membrane composition and downstream signaling responsiveness. Supplementation with omega-3 fatty acids has been investigated in inflammatory and cardiovascular conditions, with variable clinical outcomes depending on dose, formulation, and patient population [199,200].

Experimental studies indicate that increased availability of EPA and DHA can enhance the generation of SPMs in certain settings, potentially promoting resolution pathways including reduced neutrophil infiltration and enhanced efferocytosis [84,201]. In preclinical models, SPM administration has been associated with modulation of inflammatory signaling and improved tissue repair outcomes [202,203]. However, translation of these findings to consistent clinical benefit in chronic inflammatory diseases remains an area of active research [21,202].

Importantly, omega-3 supplementation does not uniformly increase SPM levels in all individuals, and endogenous biosynthetic capacity may vary depending on metabolic and inflammatory context [84,201,204]. This inter-individual variability supports a precision approach in which omega-3 interventions are matched to baseline lipid status, biosynthetic capacity, and disease context rather than applied uniformly [205]. Therefore, while omega-3–derived lipid mediators have demonstrated pro-resolving activity in experimental systems, their clinical efficacy as resolution-enhancing strategies requires careful evaluation. Nonetheless, these approaches illustrate how modifying lipid substrate availability may influence inflammatory state transitions through altered mediator balance.

In the present framework, omega-3 supplementation is mechanistically relevant because it may alter both substrate availability for pro-resolving mediator biosynthesis and, in selected tissues, membrane composition that shapes downstream signaling responsiveness. Although mechanistically attractive, clinical findings with omega-3 supplementation have been variable across diseases and study designs, and direct evidence that these interventions reproducibly restore pro-resolving tissue states in humans remains limited.

6.3. Statins and Membrane-Signaling Regulation

Statins are widely prescribed inhibitors of 3-hydroxy-3-methylglutaryl–coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in cholesterol biosynthesis [206]. While their primary clinical use is in the management of hypercholesterolemia and cardiovascular risk reduction, statins also influence cellular signaling processes through effects on membrane cholesterol content and isoprenoid synthesis [207,208].

Cholesterol is a critical structural component of membrane microdomains, and alterations in cholesterol availability can modify membrane order, receptor distribution, and lipid raft organization [185,209]. Experimental studies have shown that cholesterol depletion or modulation can affect immune-receptor clustering, T-cell activation, and inflammatory signaling thresholds in specific cellular systems [209,210]. Through reduction

in endogenous cholesterol synthesis, statins may indirectly alter membrane microdomain stability and receptor-associated signaling complexes [207,208].

In addition to cholesterol lowering, inhibition of the mevalonate pathway reduces production of isoprenoid intermediates required for prenylation of small GTPases such as Ras and Rho, which participate in intracellular signaling and cytoskeletal organization. These effects may contribute to the reported anti-inflammatory and immunomodulatory properties of statins in certain contexts, although clinical outcomes vary across diseases and patient populations [208,211,212]. Thus, statins provide an example of pharmacological modulation of lipid metabolism that can influence membrane organization and signaling thresholds beyond lipid-lowering effects alone.

Within the conceptual structure of this review, statins are most relevant as interventions that modify membrane-associated signaling context by altering cholesterol-dependent microdomain organization, with possible secondary consequences for inflammatory signaling thresholds and cellular responsiveness. Although statins provide clear clinical benefit in cardiovascular medicine, their relevance to the broader framework described here is best interpreted as evidence that membrane lipid composition can influence signaling organization, rather than as direct proof of controlled restoration of tissue-response states across inflammatory and regenerative contexts.

6.4. Emerging Lipid-Targeted Therapeutics

Beyond established drug classes, emerging therapeutic strategies aim to more directly modulate lipid-mediated signaling pathways. These include synthetic analogs of specialized pro-resolving mediators, inhibitors or modulators of sphingolipid metabolism, and agents targeting phosphoinositide signaling enzymes [213,214]. In preclinical models, such interventions have been reported to influence inflammatory responses, fibrotic remodeling, and metabolic dysfunction, although clinical translation remains ongoing [215,216].

Targeting sphingosine-1-phosphate signaling represents one clinically relevant example, as S1P receptor modulators are used in certain autoimmune conditions to regulate immune-cell trafficking [217,218]. Similarly, pharmacological inhibitors of specific lipid-metabolizing enzymes are being investigated for their potential to alter disease-associated metabolic and inflammatory states [215,216]. Advances in lipidomics and systems biology have also enabled more precise characterization of disease-associated lipid signatures, raising the possibility of stratified interventions based on lipid mediator profiles [97,219].

While many lipid-targeted strategies remain in development, these approaches illustrate a broader therapeutic concept: modulation of lipid pathways may shift cellular signaling environments and alter the trajectory of inflammatory or regenerative states. Importantly, lipid-targeted therapies operate within complex biological networks and should be interpreted as modulators of state dynamics rather than as singular corrective interventions [9,220].

Taken together, these examples suggest that lipid-targeted therapies can be organized mechanistically according to the level at which they intersect with the broader framework described in this review—whether through membrane signaling architecture, mediator balance, or metabolic and reparative state regulation. However, they do not support a uniform level of translational readiness across that framework. Some interventions already have established clinical utility for specific molecular targets or diseases, whereas others remain hypothesis-generating or preclinical. A major challenge for future work will be to determine when modulation of lipid pathways merely alters isolated signaling nodes and when it is sufficient to shift broader tissue-response states in clinically meaningful ways.

7. Integrative Perspective

7.1. Integrative Perspective on Lipid-Associated State Regulation

The preceding sections summarize established evidence showing that lipid-related processes influence cellular behavior at multiple levels, including membrane organization and signaling thresholds, mediator balance during inflammatory initiation and resolution, and metabolic programs associated with quiescence, activation, and regenerative decline [221–224]. Rather than treating these mechanisms as isolated topics, this review brings them together into an integrative perspective on lipid-associated state regulation. In this perspective, the lipid environment is viewed as one interacting regulatory layer that may bias signaling configuration, inflammatory balance, and regenerative competence across tissues [19–21,102,225,226]. This synthesis is intended to relate membrane architecture, lipid mediator dynamics, and lipid metabolic flux within a shared interpretive structure and hypothesis-generating conceptual framework, rather than to propose a new mechanistic doctrine or evidence-settled model.

Within this perspective, membrane composition, mediator balance, and metabolic lipid flux are considered complementary dimensions of cellular responsiveness rather than independent determinants of fate. Their functional significance is likely context-dependent and shaped by parallel cytokine, transcriptional, epigenetic, and niche-derived inputs. Accordingly, the purpose of this section is not to advance a standalone theoretical framework, but to clarify how previously recognized lipid-dependent mechanisms may be interpreted together across inflammation, regeneration, aging, and chronic disease.

Viewed in this way, the literature reviewed here also suggests a limited set of future questions concerning whether changes in membrane lipid organization, mediator balance, and metabolic state track with shifts in inflammatory persistence, regenerative competence, and tissue repair across different biological contexts.

The following worked examples illustrate how this framework can be applied to specific biological and disease contexts.

7.2. Worked Examples of Lipid-Regulated State Transitions

To illustrate how the framework can be applied in practice, three representative examples are outlined below. These examples are not intended to imply that lipid mechanisms act alone or determine cellular fate independently. Rather, they show how membrane organization, lipid mediator balance, and lipid metabolic flux may interact with cytokine signaling, transcriptional regulation, niche cues, and tissue context to influence cellular state transitions.

Example 1: Persistent inflammatory activation in rheumatoid arthritis. In rheumatoid arthritis, inflamed synovial tissue contains immune cells, stromal cells, cytokines, and lipid mediators that together sustain local inflammatory activity. Within the present framework, lipid-associated regulation can be interpreted at several connected levels. First, membrane lipid organization may influence receptor clustering and signaling thresholds in immune and stromal cells, thereby altering the sensitivity of these cells to inflammatory cues. Second, enrichment of arachidonic acid-derived prostaglandins and leukotrienes can support leukocyte recruitment, vascular permeability, pain, and inflammatory amplification. Third, insufficient or delayed transition toward specialized pro-resolving mediator activity may contribute to incomplete resolution. In this example, the cellular state transition of interest is the failure to move efficiently from inflammatory activation toward resolution and tissue restoration [96,148,227]. Importantly, this does not mean that lipid mediators are the sole cause of rheumatoid arthritis. Rather, the model suggests that lipid mediator imbalance may reinforce cytokine-driven and stromal inflammatory programs, helping stabilize a persistent inflammatory tissue state in selected contexts.

Example 2: Maladaptive repair and fibrotic remodeling. Fibrosis provides a second example in which lipid-dependent mechanisms may contribute to a pathological state transition. Following tissue injury, inflammatory mediators, mechanical stress, growth factors, and metabolic changes influence whether tissue repair resolves or progresses toward persistent myofibroblast activation and extracellular matrix deposition. Within this framework, altered membrane lipid composition may influence the responsiveness of fibroblasts or stromal cells to transforming growth factor-β and other pro-remodeling signals. In parallel, bioactive lipid mediators and sphingolipid pathways may modulate inflammatory tone, fibroblast survival, migration, and stress signaling. Metabolic lipid programs may also support the anabolic demands of extracellular matrix production. The relevant state transition is therefore not simply "lipid dysregulation causes fibrosis," but rather that lipid-associated changes may help bias the repair environment away from adaptive restoration and toward sustained remodeling [161,172,228]. This interpretation remains context-dependent because lipid pathways may act as contributors, permissive conditions, or downstream signatures depending on the organ, disease stage, and injury model.

Example 3: Aging-associated decline in regenerative competence. Aging illustrates a third application of the framework because lipid changes are often observed alongside reduced stem/progenitor-cell function, increased inflammatory tone, altered niche signaling, and impaired tissue repair. In aged tissues, changes in membrane lipid composition may alter receptor responsiveness and inflammatory sensitivity. Accumulation of selected lipid species, including ceramides or oxidized lipids in some contexts, may be associated with mitochondrial stress, oxidative injury, or reduced cellular resilience. At the same time, altered lipid metabolic programs may affect the balance between stem-cell quiescence, activation, and exhaustion. Here, the state transition of interest is the progressive drift from regenerative competence toward impaired repair or maladaptive stress adaptation [103,181,229]. However, this example should be interpreted cautiously: aging-associated lipid changes occur together with genomic instability, epigenetic drift, systemic metabolic change, inflammation, and niche disruption. Therefore, lipid dysregulation is best viewed as one interacting layer that may influence or reflect age-related state drift rather than as an independent driver of aging.

Taken together, these examples show how the proposed framework can be used to organize mechanisms across biological scales. In each case, the central question is not only whether a lipid pathway is altered, but whether lipid-dependent changes help shift the probability, stability, or reversibility of a cellular state. This approach may be useful for interpreting why some tissues resolve inflammation and repair effectively, whereas others remain locked in inflammatory, fibrotic, neurodegenerative, or age-associated dysfunctional states.

7.3. Cross-Tissue Relevance

Although the specific lipid species and signaling pathways vary among tissues, the general principle that lipid composition influences cellular responsiveness appears broadly conserved. In immune cells, lipid rafts and phosphoinositides regulate antigen receptor signaling and inflammatory mediator production [230,231]. In neural tissues, alterations in membrane lipids and sphingolipid metabolism have been linked to synaptic signaling and neuroinflammatory activation [19,232,233]. In connective and epithelial tissues, lipid mediators and metabolic programs influence fibroblast activation, barrier integrity, and regenerative processes [234,235].

These observations suggest that lipid-dependent modulation of signaling thresholds is not restricted to a single organ system but represents a common feature of cellular

regulation. However, the magnitude and direction of lipid effects are highly context-dependent and influenced by developmental stage, metabolic status, and environmental cues [66,236]. Therefore, although similar lipid-associated principles can be recognized across multiple tissues, their specific mechanistic manifestations differ across immune, neural, connective, and epithelial contexts.

7.4. Integrative Relevance for Multi-Omic and Cross-Disciplinary Studies

Lipidomics, integrated with transcriptomic and proteomic profiling, has revealed disease-associated lipid signatures that correlate with inflammatory activity and metabolic state [66,237,238]. Considered together with the literature reviewed in the preceding sections, these observations suggest that membrane composition, mediator balance, and lipid metabolic state may all contribute to how cellular responses are organized across inflammation, regeneration, and chronic disease. Taken together, the literature reviewed here suggests that lipid-dependent processes intersect with membrane biology, immunology, metabolism, and regenerative biology across multiple levels of tissue organization. Rather than being viewed solely as peripheral modulators, lipid pathways can be considered alongside cytokine, transcriptional, and metabolic regulation when interpreting complex biological responses. This broader view may also be useful when interpreting variability in inflammatory persistence, regenerative competence, and therapeutic response across disease contexts [19,66,239].

8. Translational Considerations

Therapeutic modulation of lipid pathways has clear biological relevance, but the level of clinical support varies substantially across intervention types and disease contexts. Therefore, lipid-targeted interventions should not be treated as a single therapeutic category. Some interventions have established clinical utility for defined indications, such as cyclooxygenase inhibition for inflammatory pain, statins for cardiovascular risk reduction, and approved sphingosine-1-phosphate receptor modulators for selected immune-mediated diseases [240–242]. Other approaches, including omega-3-based resolution strategies, specialized pro-resolving mediator analogs, sphingolipid enzyme modulation, and lipid metabolic reprogramming, remain more heterogeneous, context-dependent, or experimental [243–245]. Accordingly, the therapeutic examples discussed below are intended to illustrate different levels of translational maturity and mechanistic relevance, rather than to imply uniform clinical efficacy across lipid-targeted strategies.

At the clinical level, lipid-targeted interventions can be grouped into different levels of translational support. The strongest human evidence exists for interventions with established clinical indications, such as cyclooxygenase inhibition by NSAIDs for inflammatory pain and symptom control, statins for lipid lowering and cardiovascular risk reduction, and approved sphingosine-1-phosphate receptor modulators for selected immune-mediated diseases. These interventions demonstrate that lipid-related pathways can be clinically actionable, but they should not be interpreted as proof that broad lipid-state reprogramming has been achieved. A second category includes interventions with plausible biological rationale and variable human evidence, such as omega-3 fatty acid supplementation, where effects may depend on dose, formulation, baseline lipid status, inflammatory context, and endogenous capacity to generate specialized pro-resolving mediators. A third category includes approaches that remain largely experimental or early translational, including specialized pro-resolving mediator analogs, inhibitors of selected sphingolipid enzymes, lipid metabolic reprogramming strategies, and lipidomics-guided precision interventions [243–245]. These approaches are mechanistically important but should be interpreted cautiously until supported by stronger human outcome data.

8.1. Lipid Biomarkers in Inflammation and Disease Contexts

Advances in analytical chemistry and mass spectrometry have enabled increasingly precise quantification of circulating and tissue-associated lipid mediators. Targeted lipidomic profiling can measure eicosanoids, specialized pro-resolving mediators, sphingolipids, phospholipids, and oxidized lipid species in biological fluids and tissues [246–248]. Altered lipid mediator profiles have been reported in inflammatory, metabolic, cardiovascular, and neurodegenerative conditions, often correlating with disease activity or progression in specific cohorts [249,250].

Circulating levels of prostaglandins, leukotrienes, and related metabolites have been associated with inflammatory burden in certain autoimmune and infectious contexts [251,252]. Similarly, shifts in sphingolipid species, including ceramides, have been linked to cardiometabolic risk and inflammatory activation in some clinical studies [253,254]. In experimental settings, changes in specialized pro-resolving mediator levels have been interpreted as indicators of resolution capacity, although their reliability as clinical biomarkers remains under active investigation [21,247].

Beyond soluble mediators, membrane lipid composition—including cholesterol content, phospholipid distribution, and sphingolipid abundance—may influence cellular signaling thresholds and inflammatory sensitivity [255,256]. While direct clinical assessment of membrane microdomain structure remains technically challenging, surrogate measures of lipid composition and lipid metabolic flux may provide indirect insights into cellular functional states [248,257].

It is important to emphasize that lipid profiles are influenced by diet, metabolic status, medication use, and systemic inflammation, complicating interpretation in heterogeneous patient populations [258–260]. Therefore, lipid biomarkers should be considered as components of integrated molecular signatures rather than as standalone diagnostic indicators. Nevertheless, accumulating data support the feasibility of using lipid mediator patterns to reflect changes in inflammatory or reparative biology in defined contexts.

8.2. Lipidomics in Translational Research

The emergence of high-resolution lipidomics has expanded the capacity to profile hundreds to thousands of lipid species within biological samples [248,259,261]. When integrated with transcriptomic, proteomic, and metabolomic datasets, lipidomic analyses can provide broader insight into metabolic and inflammatory network states [262,263]. Such integrative approaches have been applied to investigate disease subtypes, treatment response, and metabolic vulnerabilities in selected clinical settings [250,264,265].

In inflammatory and autoimmune diseases, multi-omic studies have identified lipid-associated signatures that distinguish active versus quiescent disease states in certain cohorts [97,266]. In oncology and cardiometabolic disease, lipidomic patterns have been investigated as predictors of therapeutic response or disease progression [250,265]. However, reproducibility across populations and standardization of lipidomic platforms remain ongoing challenges [259,260].

From a translational standpoint, incorporation of lipidomic data into clinical and experimental studies may help clarify how lipid-associated pathways relate to inflammation, tissue injury, and repair across different disease contexts. In selected settings, lipid mediator balance, membrane lipid composition, or metabolic flux may prove informative for understanding disease heterogeneity or treatment response, although these applications remain investigational [250,267]. At present, most lipidomic approaches still require further validation, harmonization of analytical methods, and longitudinal outcome studies before broader clinical use can be considered [250,259,260].

Despite these limitations, advances in quantitative lipid profiling may help refine understanding of how lipid composition and mediator balance relate to inflammatory activity, tissue injury, and repair in selected biological contexts. Continued translational research will be needed to determine how reliably such lipid-associated measures correspond to disease trajectory and therapeutic response.

8.3. Why Lipid-Targeted Therapies May Fail in Patients

Several factors may explain why lipid-targeted interventions that appear mechanistically promising do not always produce consistent clinical benefit. First, lipid pathways are highly redundant and interconnected. Blocking one pathway may redirect substrates toward alternative lipid mediators or compensatory metabolic routes, producing incomplete or unexpected biological effects. For example, inhibition of one eicosanoid pathway may alter mediator balance without necessarily promoting resolution or restoring tissue homeostasis [68,243].

Second, lipid signaling is strongly context-dependent. The same mediator may have different effects depending on cell type, receptor expression, disease stage, tissue compartment, and inflammatory environment. A lipid pathway that promotes repair in one context may contribute to maladaptive remodeling, immune suppression, or fibrosis in another. This makes it difficult to predict clinical benefit from pathway modulation alone.

Third, many lipid-targeted interventions affect isolated molecular nodes rather than the broader cellular state. Suppressing a pro-inflammatory mediator may reduce symptoms, but it may not restore resolution programs, regenerative competence, membrane signaling organization, or tissue-level repair [201,243]. Similarly, changing circulating lipid levels does not necessarily imply that disease-relevant tissue compartments have undergone functional state reprogramming.

Fourth, patient heterogeneity may limit therapeutic consistency. Baseline lipid status, diet, genetics, microbiome composition, metabolic disease, medication use, inflammatory burden, and disease duration may all influence lipid mediator production and response to treatment. This is particularly relevant for nutritional interventions such as omega-3 supplementation, where substrate availability does not guarantee efficient conversion into specialized pro-resolving mediators [201,243].

Fifth, tissue delivery and timing remain major barriers. Lipid mediators are often locally produced, rapidly metabolized, and tightly regulated in time and space. Systemic administration may not reproduce the concentration, timing, receptor engagement, or cellular localization required for effective resolution or repair [243]. In chronic disease, the therapeutic window may also be narrowed by established fibrosis, tissue damage, immune remodeling, or irreversible niche alteration.

Finally, clinical trials often measure broad symptomatic or disease-activity outcomes rather than direct markers of lipid-state restoration. Without integrated lipidomic, transcriptomic, proteomic, and functional readouts, it may be difficult to determine whether a therapy failed because the target was biologically irrelevant, because the intervention did not reach the relevant tissue state, or because the measured endpoint did not capture lipid-dependent remodeling [243,245]. These limitations support the need for precision approaches that combine patient stratification, tissue-relevant biomarkers, and functional validation of lipid-regulated state changes.

9. Conclusions

Lipids have long been recognized as essential structural components of biological membranes and as central participants in metabolic homeostasis. The evidence reviewed here indicates that lipid composition, lipid-derived mediators, and lipid metabolic path-

ways also contribute to the regulation of cellular signaling architecture, inflammatory balance, and regenerative capacity. Across immune, neural, connective, and epithelial tissues, alterations in membrane organization, phosphoinositide signaling, sphingolipid metabolism, and bioactive lipid mediator production are associated with changes in cellular responsiveness and tissue behavior.

Taken together, the literature reviewed here supports the view that lipids should be considered not only as structural or metabolic entities, but also as important contributors to signaling, inflammatory regulation, and regenerative biology across diverse tissues. At the same time, lipid-mediated processes do not act independently of genetic, transcriptional, cytokine-driven, or microenvironmental mechanisms, but instead interact with these influences within broader biological networks. These interactions likely extend to regulatory layers involving metabolic control of chromatin state, lipid-responsive transcriptional programs, and selected RNA-associated mechanisms that help stabilize or redirect cellular identity across changing tissue environments.

Viewed together, the literature considered in this review suggests that membrane organization, mediator balance, and metabolic lipid programs represent recurring and interacting themes across inflammation, regeneration, aging, and chronic disease.

In chronic inflammatory, fibrotic, and degenerative conditions, altered lipid composition, mediator imbalance, and metabolic disruption may contribute to disease persistence alongside other recognized drivers of pathology. Considering lipid biology together with immunology, metabolism, and regenerative biology may therefore help refine mechanistic interpretation across these disease contexts.

Because this review was designed as a narrative cross-domain synthesis, it is not intended to provide a systematic ranking of evidence across all biological systems discussed. Rather, its purpose is to identify recurring mechanistic themes linking membrane lipid organization, mediator balance, and metabolic state across inflammation, regeneration, and chronic disease. Further experimental and longitudinal studies will be needed to clarify how these relationships operate across specific tissues and pathological conditions.

10. Limitations and Open Questions

The present review should be interpreted as an integrative conceptual synthesis rather than as a unified mechanistic account. Although substantial evidence supports roles for membrane lipid organization, mediator balance, and metabolic lipid flux in shaping cellular signaling and functional outcomes, the relative contribution of these processes varies across tissues, developmental stages, and disease contexts. In many chronic conditions, lipid alterations may represent both drivers and consequences of pathological processes, complicating causal inference. Distinguishing whether a given lipid alteration functions primarily as a mechanistic regulator, a permissive condition, or a downstream disease signature will require context-specific perturbation studies rather than inference from association alone. In addition, because this review was developed as a narrative cross-domain synthesis rather than a systematic review, literature selection was necessarily interpretive and guided by conceptual relevance, with some domains supported by stronger mechanistic evidence than others. This broad comparative scope supports cross-domain synthesis, but it also limits the depth with which any single disease domain can be evaluated relative to a more narrowly focused review.

Moreover, much of the mechanistic evidence linking lipid composition to shifts in cellular functional configuration derives from experimental and preclinical systems. Human data, while increasingly supported by lipidomic profiling studies, remain heterogeneous and influenced by diet, medication exposure, metabolic status, and comorbid conditions.

Further standardization of lipidomic methodologies and longitudinal analyses will be important for clarifying predictive and mechanistic relationships.

Future studies may help clarify whether coordinated changes in membrane lipid organization, mediator balance, and metabolic state precede or accompany shifts in inflammatory persistence, repair efficiency, and regenerative decline across specific tissue contexts. Such work will likely benefit from longitudinal and perturbation-based approaches that relate lipid-associated changes to broader cellular and tissue-response patterns.

Taken together, these limitations underscore that the present review is best viewed as an interpretive cross-domain synthesis of observations spanning inflammation, tissue regeneration, aging, and chronic disease, rather than as a unified mechanistic model. More broadly, the literature discussed here supports the view that lipid-dependent processes interact with signaling, inflammatory, and metabolic pathways across diverse tissue contexts, without suggesting that they function as singular determinants of tissue fate.

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