Medicine Insights

Article

Advances in Studying the Role of Sphingosine Kinase 1 in Cardiovascular Disease

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Abstract: Sphingosine kinase 1 (SphK1) is a central regulator of sphingosine-1-phosphate (S1P) signaling and has been extensively implicated in cardiovascular physiology and disease. However, studies across diverse experimental models have reported apparently conflicting roles for SphK1, ranging from cardioprotective effects to the promotion of pathological remodeling. These discrepancies have complicated the interpretation of SphK1 function and hindered its translational targeting. In this review, we propose a unifying framework in which SphK1 operates as a context-dependent signaling node whose biological consequences are dictated by cell type, stress duration, and subcellular localization. We summarize current evidence showing that acute, tightly regulated activation of SphK1 in cardiomyocytes supports adaptive stress responses and cell survival, whereas sustained or dysregulated SphK1 signaling in non-myocyte populations, including fibroblasts and vascular cells, drives maladaptive processes such as fibrosis, vascular remodeling, and tissue stiffening. We further discuss the multi-layered regulatory mechanisms governing SphK1 signaling, encompassing transcriptional and post-transcriptional control, post-translational activation, and functional compartmentalization. Together, these regulatory layers determine whether elevated SphK1 expression is translated into protective or pathological S1P signaling outputs. By integrating these findings, we highlight cell-specific maladaptation as a conceptual paradigm that reconciles divergent observations in the literature. This perspective underscores the importance of spatial and temporal precision in SphK1 signaling and provides a framework for the development of more selective and cell-targeted therapeutic strategies in cardiovascular disease.

Keywords: sphingosine kinase 1; sphingosine-1-phosphate; cardiovascular disease; cell-specific signaling; lipid signaling

Published: 13 March 2026

1. Introduction

Cardiovascular diseases (CVDs) arise from complex processes involving multi-gene dysregulation and remodeling of signaling pathways. Among these, dysregulated metabolism of bioactive lipids represents a critical driver of cardiovascular pathophysiology [1-3]. Lipids not only constitute essential components of cellular membranes but also function as key signaling molecules, modulating cell cycle, apoptosis, and genomic stability [4,5]. In recent years, the sphingolipid family has attracted considerable attention in cardiovascular molecular biology due to its unique roles in microenvironmental crosstalk, metabolic reprogramming, and signal transduction [6,7].

Sphingosine kinases (SphKs), comprising two isoforms (SphK1 and SphK2), serve as rate-limiting enzymes in sphingolipid metabolism. They catalyze the phosphorylation of sphingosine to generate sphingosine-1-phosphate (S1P), thereby orchestrating the balance between cell survival and death [8,9]. Since its cloning and identification, research on

SphK1 initially focused on its pro-survival and pro-angiogenic functions. However, accumulating evidence has revealed a more complex role of SphK1 in cardiovascular pathophysiology.

Early studies indicated that moderate activation of SphK1 exerts cardioprotective effects in ischemic heart disease, reducing infarct size [10]. Subsequent research demonstrated that chronic or excessive activation of SphK1 under conditions such as chronic heart failure, hypertension, and pathological cardiac hypertrophy correlates positively with adverse ventricular remodeling, inflammatory infiltration, and fibrosis progression [11]. Interestingly, in vascular lesions, SphK1 exhibits functions distinct from those in the myocardium, where its deficiency can accelerate vascular calcification and medial stiffening [12]. This functional "duality" is closely associated with its gene structure, subcellular localization, and downstream signaling specificity.

In this review, we will discuss the structural and functional characteristics of SphK1, delineate its regulatory networks and mechanisms in cardiovascular diseases, summarize its clinical translational potential, and highlight current research limitations. This overview aims to provide a theoretical foundation for precision cardiovascular therapies targeting SphK1 (Figure 1).

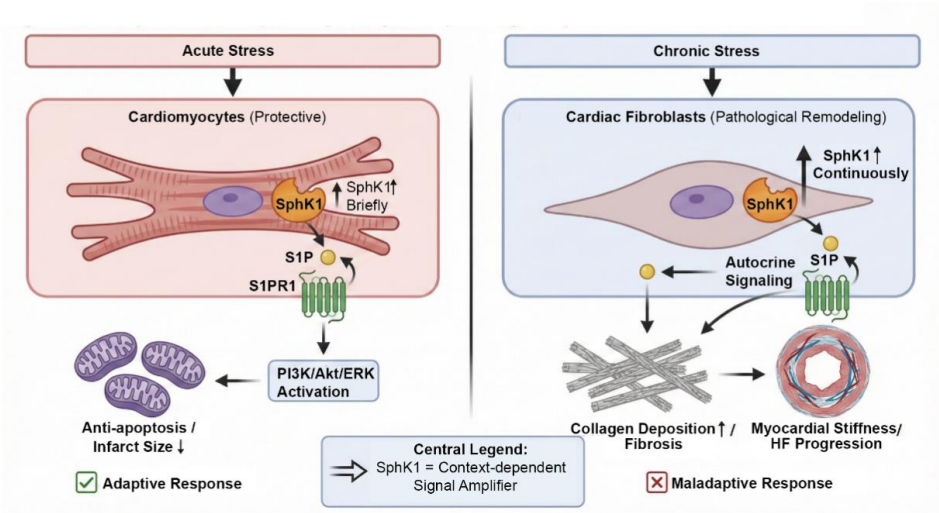

Figure 1. The functional duality of SphK1 in cardiovascular stress.

Schematic representation of the divergent roles of SphK1 signaling dictated by stress duration and cell type. (Left Panel) Under acute stress conditions, transient activation of SphK1 in cardiomyocytes promotes survival signaling (anti-apoptosis) and reduces infarct size, representing an adaptive response. (Right Panel) Under chronic stress conditions, sustained SphK1 upregulation in cardiac fibroblasts drives autocrine S1P signaling, collagen deposition, and myocardial stiffening, contributing to maladaptive remodeling. Central Legend: The arrow emphasizes that SphK1 functions not as a static effector but as a context-dependent signal amplifier.

2. Structure and Function of SphK1

The biological functions of SphK1 are closely associated with its gene locus, sequence characteristics, and the finely orchestrated roles of its protein domains. Epigenetic modifications at the gene level determine its basal expression, whereas protein domains mediate molecular interactions that directly regulate catalytic activity and subcellular localization. Together, these features form the core basis for deciphering the mechanisms of SphK1 in cardiovascular diseases (CVDs).

2.1. Gene Structure and Expression Features

The human SphK1 gene is located on chromosome 17q25.1 and contains multiple exons, giving rise to various splice variants [13]. Post-transcriptional translation yields a lipid kinase predominantly localized in the cytoplasm. Although mutations in SphK1 are rare in CVD, abnormal fluctuations in its expression are highly prevalent, largely influenced by epigenetic modifications in the promoter region.

The SphK1 promoter is rich in CpG islands, and DNA methylation and histone acetylation represent key mechanisms regulating its transcriptional activity [14,15]. Under physiological conditions, SphK1 maintains basal expression to support normal S1P production. However, pathological stimuli, such as high-glucose or hypoxia, induce promoter hypomethylation and increased acetylation of histone H3K9, facilitating transcription factor binding (e.g., AP-1, Sp1) and leading to significant upregulation of SphK1 transcription [16,17]. This elevated expression is a critical molecular basis for myocardial hypertrophy and fibrosis. Conversely, in certain advanced heart failure or vascular calcification models, reduced expression may be observed, often associated with recruitment of specific transcriptional repressors.

Human Protein Atlas (HPA) data indicate that SphK1 is broadly expressed across multiple normal tissues, including the heart, vascular smooth muscle, and kidney [18]. Such widespread distribution supports a role for SphK1 in maintaining fundamental cardiovascular physiological processes, such as vascular tone and endothelial barrier integrity. In pathological CVD tissues, however, its spatiotemporal expression is markedly remodeled, suggesting a shift from homeostatic maintenance toward stress-driven functions.

2.2. Protein Structure and Functional Domains

SphK1 adopts a modular architecture composed of an N-terminal domain and a C-terminal domain connected by a flexible linker region. These domains cooperate to form a bilobed structure that supports both catalytic activity and regulatory signal integration.

2.2.1. Catalytic Domain and Atp-Binding Site

Structural studies demonstrate that the catalytic core of SphK1 resides within the cleft between the N- and C-terminal domains. This interdomain pocket accommodates the ATP-binding site and contains a highly conserved glycine-rich loop essential for enzymatic activity [19]. Functional regulation of this catalytic core is achieved through phosphorylation-dependent mechanisms. ERK1/2-mediated phosphorylation of SphK1 at Ser225 markedly enhances its kinase activity, and mutation of this site abolishes agonist-induced activation, indicating that phosphorylation induces an allosteric switch that promotes catalytic competence [20].

2.2.2. Calmodulin (Cam) Binding Site

A calmodulin-binding motif located within the linker region represents a distinctive regulatory feature of SphK1. This hydrophobic motif binds Ca^{2+}-activated calmodulin, enabling SphK1 to respond to intracellular calcium signals. Importantly, CaM binding has been shown to regulate the subcellular distribution of SphK1, functioning as a molecular switch that facilitates its relocalization toward membrane compartments [21].

2.2.3. Membrane Localization and CIB1 Interaction

Although SphK1 lacks a transmembrane domain, its membrane association is mediated through interactions with membrane-associated adaptor proteins. Calcium and integrin-binding protein 1 (CIB1) specifically anchors SphK1 to the inner leaflet of the plasma membrane, a localization that is critical for efficient access to its lipid substrate sphingosine [22]. This recruitment mechanism ensures spatial coupling between kinase

activation and substrate availability, thereby enabling localized S1P production and facilitating "inside-out" S1P signaling through cell-surface receptors.

3. Cell-Type-Dependent Functions of SPHK1 in Cardiovascular Remodeling

3.1. Regulating Proliferation and Apoptosis

SphK1 regulates cardiovascular cell survival and proliferative capacity in a highly cell-type-dependent manner. In cardiomyocytes, SphK1 activation is predominantly cardioprotective. Under ischemic or hypoxic stress, SphK1 is rapidly activated, resulting in increased production of sphingosine-1-phosphate (S1P). Through engagement of S1PR1, S1P activates downstream PI3K/Akt and ERK1/2 signaling pathways, upregulates anti-apoptotic proteins such as Bcl-2, and suppresses pro-apoptotic mediators including Bax and caspase-3. Collectively, these signaling events limit cardiomyocyte apoptosis and reduce infarct size in models of acute myocardial injury [10,23]. In terminally differentiated cardiomyocytes, this SphK1-mediated survival response is therefore considered largely adaptive during acute stress.

In contrast, the same pro-survival and pro-proliferative signaling becomes maladaptive in cardiac fibroblasts (CFs). Genetic and functional studies demonstrate that SphK1 is required for the basal proliferative capacity of adult CFs, underscoring its role in fibroblast homeostasis. It is worth noting that during acute stress, transient SphK1 activation in fibroblasts generates minimal extracellular matrix (ECM) and acts strictly within a homeostatic window. However, under chronic pathological conditions such as pressure overload, sustained activation of the SphK1/S1P axis promotes excessive fibroblast survival and expansion, thereby contributing to maladaptive cardiac remodeling [24,25]. Unlike cardiomyocytes, the intrinsic proliferative potential of CFs renders them particularly sensitive to persistent growth-promoting signals, shifting SphK1 function from physiological support toward pathological stromal accumulation.

Together, these findings illustrate a paradigm of cell-type-specific maladaptation, in which SphK1-mediated survival signaling is beneficial in cardiomyocytes but detrimental in cardiac fibroblasts, providing a cellular basis for divergent outcomes during myocardial injury and remodeling (Table 1 and Figure 2).

Table 1. Cell-type specific functions of SphK1 in cardiovascular physiology and pathology.

Cardiovascular cell type	Primary SphK1 function	Dominant biological outcome	Pathophysiological consequence	Representative evidence
Cardiomyocytes	Anti-apoptotic, pro-survival signaling	Reduced apoptosis, preserved cell viability	Adaptive response to acute injury	(26)
Cardiac fibroblasts	Support of proliferation; modulation of profibrotic signaling	Fibroblast activation and myofibroblast differentiation	Contribution to fibrotic remodeling	(27)
Vascular smooth muscle cells	Suppression of pro-osteogenic signaling	Reduced calcification and osteogenic marker expression	Protection against vascular calcification	(12)
Endothelial cells	Modulation of endothelial	Altered barrier	Vascular dysfunction and	(28)

Cardiovascular cell type	Primary SphK1 function	Dominant biological outcome	Pathophysiological consequence	Representative evidence
	barrier and signaling	integrity and inflammatory responses	inflammatory remodeling	

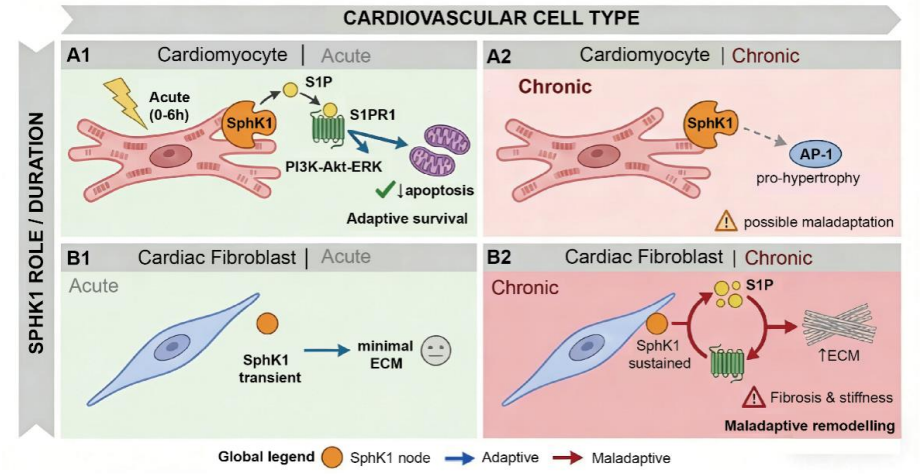

Figure 2. Paradigm of cell-specific maladaptation: Temporal and cellular divergence of SphK1 signaling.

(A) Cardiomyocytes: (A1) Acute activation (0-6 h) triggers S1P receptor 1 (S1PR1)-mediated PI3K/Akt/ERK pathways, preserving mitochondrial function and inhibiting apoptosis. (A2) Chronic activation is less defined but may contribute to AP-1-driven hypertrophic signaling. (B) Cardiac Fibroblasts: (B1) During acute stress, transient SphK1 activity is homeostatic with minimal extracellular matrix (ECM) production. (B2) Sustained chronic activation creates a feed-forward loop of S1P autocrine signaling, driving myofibroblast differentiation and pathological fibrosis. Global Legend: Green arrows indicate adaptive/beneficial outcomes; red arrows indicate maladaptive/pathological outcomes.

3.2. Modulating Phenotypic Transition

Phenotypic transition of cardiovascular cells is a key mechanism underlying structural remodeling in cardiovascular diseases. SphK1 modulates these transitions in a context-dependent manner by regulating lipid-mediated signaling that controls cellular identity and plasticity.

In vascular smooth muscle cells (VSMCs), SphK1 helps maintain the contractile phenotype. Loss or inhibition of SphK1 activity predisposes VSMCs to switch toward a synthetic phenotype, increasing susceptibility to maladaptive vascular remodeling. Mechanistically, SphK1-derived S1P restrains aberrant activation of signaling pathways associated with phenotypic switching, thereby preserving vascular wall integrity [26].

In cardiac fibroblasts, SphK1 promotes maladaptive phenotypic transitions. Profibrotic stimuli, including transforming growth factor-β (TGF-β), induce SphK1 expression and activity, enhancing S1P signaling. This promotes fibroblast activation and differentiation into myofibroblasts, with increased expression of contractile and extracellular matrix components, mediated in part through S1P receptor-dependent autocrine signaling loops [27].

Thus, SphK1 exerts divergent effects on cardiovascular phenotypic plasticity-preserving functional identity in VSMCs while driving fibrotic transformation in cardiac fibroblasts-highlighting its cell-type-specific contribution to cardiovascular pathology.

3.3. Regulating Oxidative Stress and Ferroptosis

Oxidative stress is a common pathological driver of cardiomyocyte injury and vascular dysfunction across a broad spectrum of cardiovascular diseases. As a central enzyme in sphingolipid metabolism, SphK1 indirectly shapes redox homeostasis by controlling the balance between pro-apoptotic sphingolipids (such as ceramide and sphingosine) and the bioactive lipid mediator sphingosine-1-phosphate (S1P). In experimental cardiomyocyte systems, reactive oxygen species (ROS) generation is associated with inhibition of SphK1 activity, increased pro-apoptotic sphingolipids, and reduced S1P, whereas enforced SphK1 expression protects against ROS-induced apoptosis, highlighting a role for the sphingolipid rheostat in modulating oxidative damage and cell survival [28,29].

In cardiomyocytes subjected to hypoxia/reoxygenation injury, activation of S1P receptor-mediated signaling attenuates ROS accumulation and mitochondrial dysfunction and reduces markers of ferroptosis and lipid peroxidation. These protective effects involve downstream activation of antioxidant defense pathways, including increased expression of Slc7a11, GPX4, and MnSOD, which are key regulators of cellular redox balance and lipid peroxide metabolism, indicating that S1P produced downstream of SphK1 can mitigate both oxidative stress and ferroptotic cell death pathways in cardiac injury models [30].

The influence of SphK1 on ferroptosis in cardiovascular tissues therefore appears to be indirect and context-dependent. Rather than directly regulating iron handling, SphK1 impacts cellular susceptibility to ferroptotic injury by modulating intracellular sphingolipid composition and downstream receptor signaling. Accumulation of ceramide and sphingosine species under conditions of reduced SphK1 activity promotes oxidative stress and membrane instability, whereas enhanced S1P production favors cell survival under oxidative conditions. In this regard, SphK1 functions as a metabolic rheostat that modulates the threshold for oxidative and lipid-peroxidative cell death. However, similar to its role in cell survival and proliferation, sustained activation of SphK1 signaling may also support maladaptive remodeling in non-myocyte compartments. Thus, the net impact of SphK1 on oxidative stress and ferroptosis reflects a balance between acute cytoprotection and long-term structural consequences.

4. Regulatory Mechanisms of SphK1 Expression

4.1. Transcriptional Regulation: A "Priming" and "Driving" Model

The expression of SphK1 is regulated by a hierarchical transcriptional program in which epigenetic mechanisms establish a permissive chromatin landscape ("priming"), while stress-responsive transcription factors provide stimulus-dependent transcriptional activation ("driving"). This two-step regulatory logic helps reconcile how SphK1 can be broadly inducible across cardiovascular pathologies yet exert divergent, cell type-specific functional consequences, as discussed in Section 3 (Figure 3).

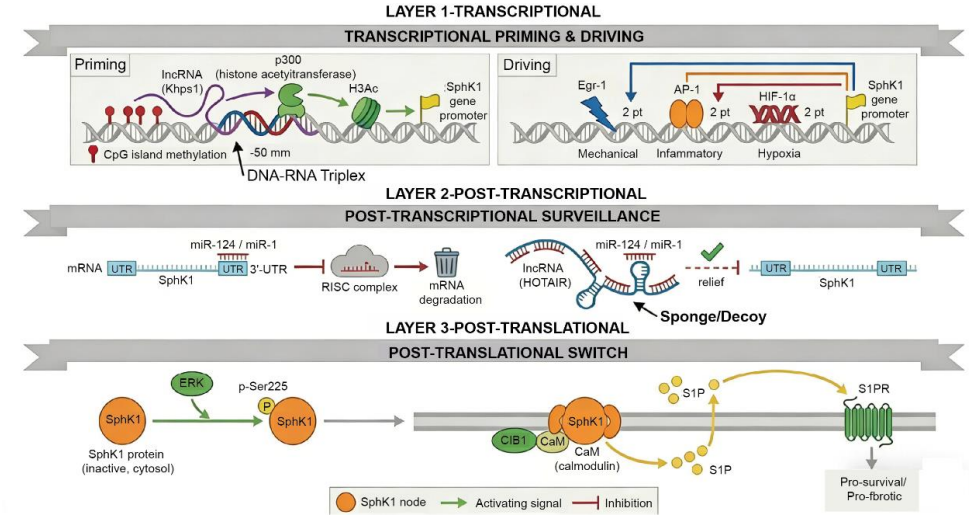

Figure 3. Hierarchical regulatory architecture of SphK1 expression and activation.

The regulation of SphK1 operates across three distinct layers:

Layer 1 (Transcriptional): Illustrates the "Priming and Driving" model. Basal repression is relieved by lncRNA Khps1 forming a DNA-RNA triplex that recruits p300 for histone acetylation (Priming). Subsequently, stress-specific transcription factors (Egr-1, AP-1, HIF-1α) drive robust expression (Driving).

Layer 2 (Post-transcriptional): MicroRNAs (e.g., miR-124, miR-1) act as surveillance mechanisms to degrade SphK1 mRNA. lncRNAs such as HOTAIR can function as ceRNA sponges to sequester these miRNAs, derepressing SphK1.

Layer 3 (Post-translational): The inactive cytosolic protein requires phosphorylation at Ser225 (by ERK1/2) and recruitment by CIB1/CaM to translocate to the plasma membrane, enabling efficient S1P production.

4.1.1. Epigenetic Priming: Chromatin Accessibility and the lncRNA-p300 Axis

The SphK1 promoter region contains a CpG-rich segment whose methylation status has been linked to tissue-specific expression, with differential methylation correlating with Sphk1 expression in rodent tissues, suggesting that DNA methylation and chromatin context can constrain basal SphK1 transcriptional activity under homeostatic conditions [14]. Such epigenetic repression may be relieved by active chromatin remodeling that enhances promoter accessibility.

Mechanistic work has identified a long non-coding RNA, Khps1, as a regulator of SPHK1 transcription through locus-specific recruitment of chromatin modifiers. Khps1 is transcribed antisense to SPHK1 and forms a sequence-specific DNA-RNA triplex with a homopurine stretch upstream of the SPHK1 transcription start site, anchoring the lncRNA to the locus. This triplex serves as a molecular scaffold for the recruitment of the histone acetyltransferases p300/CBP, leading to local histone acetylation and chromatin relaxation that facilitate transcriptional activation of SPHK1 in model systems [31].

Although the Khps1-p300 axis has not yet been systematically studied in cardiovascular tissues, this mechanism illustrates how locus-specific recruitment of histone acetyltransferases by an RNA-DNA triplex can overcome basal epigenetic repression and render the SphK1 promoter transcriptionally competent in response to regulatory stimuli.

4.1.2. Transcriptional Driving: Signal Integration and Stress Responsiveness

Once a permissive chromatin state is established, the SphK1 promoter functions as an integration platform for diverse environmental and cellular stress signals. These cues include mechanical and growth factor stimulation, metabolic and inflammatory stress,

hypoxia, and organelle stress, each engaging distinct transcription factors with context-specific temporal dynamics and pathological relevance.

In the setting of vascular remodeling, mechanical stress and growth factor signaling rapidly induce the immediate early transcription factor early growth response 1 (Egr1). In human pulmonary artery smooth muscle cells (hPASMCs), platelet-derived growth factor (PDGF) stimulation markedly upregulates Egr1 expression and activates the SphK1 promoter. Chromatin immunoprecipitation assays further demonstrate direct binding of Egr1 to GC-rich elements within the SphK1 promoter, establishing a mechanistic link between PDGF/Egr1 signaling and SphK1 transcriptional activation in vascular remodeling contexts, including pulmonary arterial hypertension [32,33].

Chronic metabolic and inflammatory stress engages the activator protein-1 (AP-1) transcriptional complex. In glomerular mesangial cells exposed to hyperglycemic conditions, AP-1 components c-Jun and c-Fos are induced and occupy consensus binding motifs within the SphK1 regulatory region. Functional studies demonstrate that knockdown of c-Jun or c-Fos reduces SphK1 expression, whereas their overexpression enhances it, supporting an AP-1-dependent transcriptional program that sustains SphK1 expression under chronic metabolic stress [16,34].

By contrast, hypoxia-induced SphK1 transcription is tightly coupled to HIF-dependent transcriptional regulation. Under hypoxic conditions, stabilization of hypoxia-inducible factors, particularly HIF-1α, promotes transcriptional activation of the SphK1 gene. Promoter analyses have identified a functional hypoxia response element (HRE) upstream of the SphK1 transcription start site that is required for hypoxia responsiveness. Genetic silencing of HIF-1α markedly attenuates hypoxia-induced SphK1 expression, establishing SphK1 as a bona fide HIF-1α target gene in endothelial cells. Functionally, hypoxia-driven SphK1 upregulation enhances endothelial cell migratory capacity, suggesting a role for this axis in hypoxia-associated vascular remodeling rather than direct cytoprotective signaling [35]. Unlike the static survival response seen in cardiomyocytes, this endothelial upregulation prioritizes motility and angiogenesis to restore oxygen supply, further highlighting the cell-specific nature of SphK1-driven outputs.

Emerging evidence also implicates activating transcription factor 3 (ATF3) as an upstream regulator of SphK1 under conditions of endoplasmic reticulum (ER) stress and ischemic injury. In myocardial infarction models and oxygen-glucose deprivation experiments, ATF3 expression is concomitantly increased with SphK1 upregulation. Genetic downregulation of ATF3 reduces SphK1 expression and alleviates ER stress-associated injury, supporting the existence of a stress-responsive ATF3-SphK1 transcriptional axis in cardiac injury models [36].

Collectively, these findings position SphK1 as a convergent transcriptional target for heterogeneous stress-responsive transcription factors. Rather than operating through a single dominant regulatory mechanism, SphK1 expression is shaped by the nature of the upstream stress signal, the engaged transcription factor repertoire, and the cellular context, thereby linking diverse pathological stimuli to context-dependent vascular and cardiac remodeling processes.

4.2. Post-Transcriptional Regulation: The ncRNA Surveillance Network

Post-transcriptional regulation constitutes a critical buffering layer that fine-tunes SphK1 expression independently of transcriptional activation. This regulatory tier is primarily mediated by non-coding RNAs, particularly microRNAs (miRNAs), which bind to the 3′ untranslated region (3′-UTR) of SphK1 mRNA to modulate transcript stability and translational efficiency.

Under physiological conditions, specific miRNAs function as constitutive repressors that constrain basal SphK1 expression. In cardiomyocytes, miR-124 directly binds to the SphK1 3′-UTR, resulting in reduced SphK1 mRNA and protein levels and attenuation of downstream S1P signaling [37]. Similarly, in human pulmonary artery smooth muscle

cells, the muscle-enriched miRNA miR-1 targets the SphK1 3′-UTR, suppressing SphK1 expression and limiting S1P production, thereby restraining pathological vascular remodeling [38]. Together, these studies support a model in which miRNAs act as a post-transcriptional surveillance mechanism that maintains SphK1 activity below a pathological threshold under homeostatic conditions.

Dysregulation of this miRNA-mediated repression appears to represent a permissive event for pathological SphK1 upregulation rather than a primary initiating driver. Increasing evidence indicates that miRNA availability can itself be modulated by long non-coding RNAs (lncRNAs) acting as competing endogenous RNAs (ceRNAs), thereby indirectly releasing target transcripts from post-transcriptional constraint. In models of renal interstitial fibrosis, the lncRNA HOTAIR is robustly upregulated and has been shown to directly bind and sequester miR-124, as demonstrated by RNA immunoprecipitation and luciferase reporter assays [39,40]. Through this interaction, HOTAIR attenuates miR-124-mediated repression of downstream targets and promotes fibrotic remodeling.

Although this ceRNA-based regulatory mechanism has not yet been systematically validated in cardiovascular tissues, it provides a mechanistically coherent framework through which pathological conditions may erode miRNA-dependent restraint of SphK1 expression. Given the established involvement of miR-124 and miR-1 in cardiovascular inflammation and remodeling, analogous lncRNA-miRNA-SphK1 regulatory axes may operate in a context- and cell-type-dependent manner.

Collectively, post-transcriptional regulation constitutes a secondary yet essential control layer that shapes the amplitude and persistence of SphK1 induction. While transcriptional and post-transcriptional mechanisms together define the magnitude and duration of SphK1 expression, they are insufficient to fully account for the rapid and context-dependent changes in SphK1 signaling observed during cardiovascular stress. Accumulating evidence suggests that SphK1 function is further modulated at the post-translational level, where dynamic modifications, subcellular localization, and protein-protein interactions determine whether elevated SphK1 expression translates into effective S1P signaling. Thus, beyond RNA-centered regulatory layers, post-translational control emerges as a decisive checkpoint that integrates cellular stress, metabolic state, and signaling compartmentalization in SphK1-driven cardiovascular remodeling.

4.3. Post-Translational Regulation and Functional Compartmentalization of SphK1

Although transcriptional and post-transcriptional mechanisms determine SphK1 availability, they are insufficient to explain the rapid, reversible, and context-dependent nature of SphK1 signaling observed in cardiovascular stress. Accumulating evidence indicates that SphK1 activity is not constitutive but requires precise post-translational activation and subcellular redistribution to exert its signaling functions. This additional regulatory layer provides temporal precision and contextual specificity, ensuring that increased SphK1 expression is translated into appropriate sphingosine-1-phosphate (S1P) signaling outputs during cardiovascular stress.

Post-translational regulation allows SphK1 to act as a rapid-response signaling node, integrating upstream kinase cascades, membrane dynamics, and organelle stress signals. Importantly, dysregulation at this level may uncouple SphK1 expression from its physiological roles, contributing to maladaptive signaling in cardiovascular diseases.

4.3.1. Phosphorylation-Dependent Activation and Membrane Translocation of SPHK1

SphK1 protein abundance alone is insufficient to confer biological activity. Instead, its enzymatic function is tightly controlled by post-translational modifications, among which phosphorylation-dependent activation represents the most extensively characterized mechanism. Early biochemical studies established that SphK1 exists

predominantly in an inactive cytosolic form under basal conditions and requires upstream kinase signaling to acquire full catalytic competence.

Phosphorylation of SphK1 at serine 225 (Ser225) has been identified as a critical regulatory event governing both its enzymatic activation and subcellular redistribution. This modification is primarily mediated by extracellular signal-regulated kinases 1/2 (ERK1/2) in response to growth factor stimulation. Mutation of Ser225 abolishes agonist-induced SphK1 activation and prevents its translocation from the cytosol to the plasma membrane, demonstrating that Ser225 phosphorylation is necessary for stimulus-dependent SphK1 signaling [20,41].

Membrane translocation is functionally essential for SphK1 activity, as its substrate sphingosine is enriched within membrane compartments. Upon ERK-dependent phosphorylation, activated SphK1 associates with the inner leaflet of the plasma membrane, where it locally catalyzes the production of sphingosine-1-phosphate (S1P). This spatial coupling of kinase signaling and lipid substrate availability ensures rapid amplification of extracellular cues into S1P-mediated signaling outputs [42].

In cardiovascular cells, phosphorylation-driven activation of SphK1 provides temporal precision to stress responses. Acute activation facilitates short-term adaptive signaling, whereas sustained kinase activity may lead to prolonged SphK1 membrane association and excessive S1P production [43,44]. Importantly, this regulatory step does not intrinsically encode cell type specificity; rather, it serves as a permissive switch that enables SphK1 to participate in diverse signaling programs depending on the cellular and pathological context.

Collectively, phosphorylation-dependent activation and membrane targeting constitute a decisive post-translational checkpoint that converts SphK1 expression into functional lipid signaling. Dysregulation at this level may therefore uncouple SphK1 abundance from physiological control, contributing to maladaptive signaling during cardiovascular remodeling.

4.3.2. Subcellular Localization as a Determinant of SPHK1 Signaling Specificity

Beyond phosphorylation-dependent activation, the biological consequences of SphK1 signaling are critically shaped by its subcellular localization. Accumulating evidence indicates that SphK1 does not function as a freely diffusing cytosolic enzyme, but instead operates within spatially restricted, membrane-associated compartments. This spatial organization constitutes an additional regulatory layer that influences whether SphK1-derived sphingosine-1-phosphate (S1P) is coupled to receptor-dependent signaling or remains confined to intracellular sphingolipid metabolism.

Upon activation, SphK1 is recruited to the plasma membrane, where access to membrane-enriched sphingosine enables efficient S1P production. Membrane-associated SphK1 has been closely linked to inside-out S1P signaling, facilitating autocrine and paracrine activation of S1P receptors and amplification of growth factor, inflammatory, and mechanical cues, particularly in vascular and stromal cells [45,46].

In contrast, cytosolic SphK1 appears to contribute primarily to intracellular sphingolipid homeostasis without strong engagement of receptor-mediated signaling. Experimental disruption of SphK1 membrane recruitment-through mutation of key regulatory residues or interference with membrane-anchoring interactions-markedly attenuates downstream S1P receptor signaling despite preserved SphK1 protein expression, underscoring that subcellular localization rather than expression abundance is a principal determinant of signaling output [47,48].

In cardiovascular systems, localization-dependent signaling provides a mechanistic framework to interpret the divergent outcomes of SphK1 activation across cell types. In cardiomyocytes, transient membrane recruitment of SphK1 during acute stress has been associated with adaptive survival signaling [44]. By contrast, in cardiac fibroblasts and vascular cells, sustained engagement of the SphK1-S1P axis has been linked to prolonged

receptor activation and profibrotic or pro-remodeling responses [27]. Thus, spatial regulation enables SphK1 to function as a context-sensitive signaling amplifier, with subcellular localization biasing downstream biological outcomes.

Collectively, subcellular compartmentalization represents a critical post-translational checkpoint that integrates kinase activation with spatial signal routing. Together with phosphorylation-dependent activation, this regulatory layer confers temporal precision and contextual specificity to SphK1 signaling, independently of transcriptional output. Dysregulation at this level may uncouple SphK1 activity from physiological constraints, favoring sustained and cell type-specific pathological lipid signaling in cardiovascular disease.

5. Discussion and Future Prospects

Accumulating evidence indicates that sphingosine kinase 1 (SphK1) does not exert uniform effects across cardiovascular tissues. Instead, its biological consequences are strongly shaped by cellular identity, stress duration, and signaling context. Integrating the findings summarized in this review, we propose a unifying framework of cell-specific maladaptation, in which shared regulatory mechanisms governing SphK1 expression and activation give rise to divergent-and sometimes opposing-pathological outcomes depending on the responding cell type.

In cardiomyocytes, SphK1 activation is predominantly associated with acute stress conditions such as ischemia and hypoxia. Under these settings, transient induction of SphK1 enhances intracellular sphingosine-1-phosphate (S1P) signaling, supporting short-term cell survival and metabolic adaptation. This response appears largely compensatory and temporally restricted, consistent with experimental models demonstrating reduced myocardial injury following acute activation of the SphK1-S1P axis during early ischemic stress [35]. Importantly, cardiomyocyte SphK1 signaling is typically disengaged once the acute insult resolves, limiting its potential for long-term maladaptation.

In contrast, sustained SphK1 activation in non-myocyte populations is increasingly linked to pathological remodeling. In cardiac fibroblasts, chronic neurohumoral and mechanical stimuli drive persistent SphK1 upregulation, leading to prolonged downstream kinase signaling and fibroblast expansion. Unlike the transient activation observed in cardiomyocytes, this sustained SphK1 activity promotes excessive extracellular matrix deposition and contributes directly to myocardial fibrosis and ventricular stiffening. These effects appear largely cell autonomous, underscoring that SphK1 signaling in fibroblasts is not merely secondary to cardiomyocyte injury but represents an independent driver of maladaptive remodeling.

A similar pattern of divergence is evident in the vascular compartment. In vascular smooth muscle cells and endothelial cells, inflammatory, oxidative, and mechanical cues robustly induce SphK1 expression. While short-term activation may support adaptive vascular responses, prolonged SphK1 signaling enhances proliferative and migratory phenotypes, favoring neointimal formation and pathological vascular remodeling [16,32]. Thus, sustained SphK1 activation in vascular cells shifts its role from stress adaptation to disease amplification.

Importantly, these contrasting outcomes cannot be explained by differences in transcriptional regulation alone. As discussed above, post-translational activation and subcellular compartmentalization emerge as decisive checkpoints that determine whether increased SphK1 expression is translated into adaptive or maladaptive signaling. Transient, spatially restricted membrane recruitment of SphK1 supports controlled S1P signaling, whereas sustained membrane association biases signaling toward chronic receptor activation and pathological remodeling. This spatial and temporal uncoupling provides a mechanistic basis for how identical regulatory inputs may yield distinct biological consequences across cell types.

Together, these observations support a revised view of SphK1 in cardiovascular disease-not as an inherently protective or deleterious factor, but as a context-dependent signaling amplifier (figure4). The pathological relevance of SphK1 is therefore dictated not by its expression per se, but by the cellular environment in which it is activated and the duration for which signaling is sustained. Recognition of this cell-specific maladaptation framework helps reconcile prior conflicting reports and underscores the need for therapeutic strategies that selectively modulate SphK1 signaling in a cell- and context-specific manner (Figure 4).

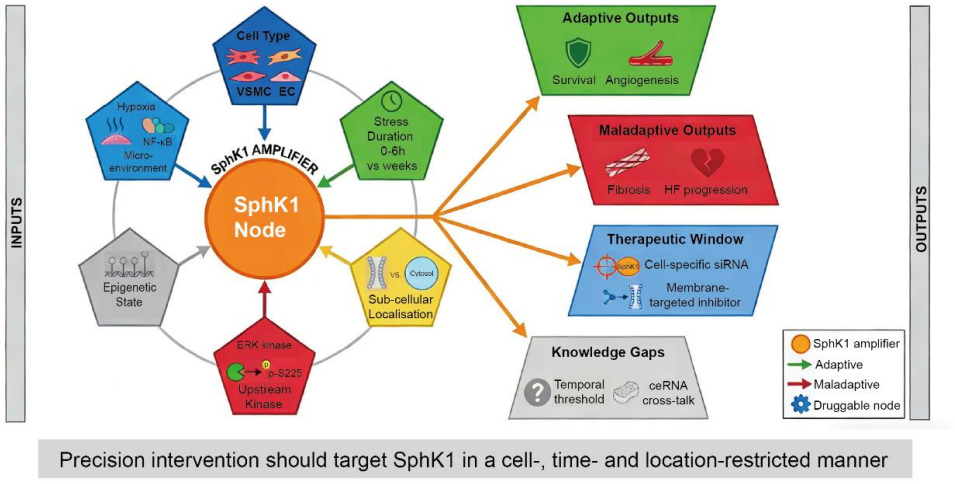

Figure 4. The "SphK1 Amplifier" model: A unifying framework for context-dependent signaling. Proposed conceptual model integrating the inputs, processing node, and outputs of SphK1 signaling.

(Inputs) Diverse stimuli (hypoxia, mechanical stress, epigenetic state) converge on the SphK1 node.

(Amplifier Node) The biological impact is filtered through spatial and temporal contexts: cell type (myocyte vs. non-myocyte), stress duration (acute vs. chronic), and subcellular localization (membrane vs. cytosol).

(Outputs) Depending on these filters, the output bifurcates into adaptive survival/angiogenesis or maladaptive fibrosis/remodeling.

(Therapeutic Window) Precision interventions should target the specific "maladaptive" arm (e.g., membrane-targeted inhibitors or cell-specific siRNA) rather than global inhibition.

Despite substantial progress in elucidating the regulatory architecture and functional roles of SphK1 in cardiovascular biology, several limitations should be acknowledged when interpreting the current literature. Importantly, these limitations do not undermine the conceptual framework proposed here, but rather reflect intrinsic constraints shared by most existing studies in this field.

First, the majority of mechanistic evidence supporting SphK1 function is derived from global or constitutive gain- and loss-of-function models, which preclude precise dissection of cell-type-specific effects. Given that SphK1 exerts divergent-and in some cases opposing-roles in cardiomyocytes versus non-myocyte populations, conclusions drawn from whole-tissue or systemic manipulations may obscure context-dependent signaling outcomes. This issue is exemplified by studies demonstrating protective roles of acute SphK1 activation in cardiomyocytes under ischemic stress [35], while parallel work in fibroblasts and vascular cells links sustained SphK1 signaling to pathological remodeling. The lack of temporally controlled and cell-restricted genetic models therefore remains a major barrier to resolving causality across disease stages.

Second, the distinction between adaptive and maladaptive SphK1 signaling is often blurred by insufficient temporal resolution. Many studies assess SphK1 expression or activity at single or late disease time points, limiting insight into dynamic transitions from early compensatory responses to chronic pathological activation. For example, hypoxia-induced HIF-1α- dependent SphK1 upregulation has been shown to promote short-term cardiomyocyte survival during ischemia [35], whereas prolonged activation in vascular smooth muscle cells driven by transcription factors such as Egr-1 and AP-1 is associated with sustained proliferative and inflammatory signaling [16,32]. Without systematic time-course analyses, it remains difficult to define the temporal threshold at which SphK1 signaling shifts from protective to maladaptive.

Third, direct assessment of subcellular SphK1 compartmentalization in vivo remains technically limited, despite strong in vitro evidence that membrane localization is a key determinant of signaling specificity. While phosphorylation-dependent membrane recruitment of SphK1 is well established in cultured cells, in vivo validation of spatially restricted S1P production and its receptor engagement remains largely indirect. As a result, the contribution of spatial mislocalization to chronic SphK1-driven pathology-particularly in fibrotic and vascular remodeling contexts-has not been fully resolved.

From a forward-looking perspective, future studies integrating cell-type-specific, temporally inducible genetic models with spatially resolved lipidomics and single-cell transcriptomic approaches will be essential to refine the cell-specific maladaptation paradigm proposed here. Such approaches will allow SphK1 signaling to be interpreted not as uniformly beneficial or detrimental, but as a dynamic, context-sensitive regulatory axis whose pathological relevance emerges from the interplay between cell identity, disease stage, and subcellular organization.

6. Conclusion

In summary, this review integrates current evidence to clarify how sphingosine kinase 1 (SphK1) functions as a context-dependent regulator of cardiovascular remodeling. Rather than exerting uniform effects, SphK1 activity is shaped by multi-layered regulatory mechanisms and translated into divergent biological outcomes depending on cell type, stress duration, and disease stage. Acute and tightly controlled SphK1 activation may support adaptive responses, whereas sustained or mislocalized signaling preferentially drives maladaptive remodeling in non-myocyte populations. This framework of cell-specific maladaptation provides a unifying explanation for previously conflicting observations across cardiovascular disease models. A deeper understanding of these regulatory hierarchies may facilitate the development of more precise therapeutic strategies targeting SphK1-S1P signaling while preserving its context-dependent protective functions.

Funding: The study was supported by the Health Talents Training Program of Pudong New Area Health Commission(2026PDWSYCBJ-02).

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