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Review

Endophilin Proteins in Membrane Dynamics, Neurodegeneration, Cancer, and Cardiovascular Disease

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Abstract

The endophilin protein family comprises a group of evolutionarily highly conserved Bin-Amphiphysin-Rvs (BAR) domain proteins that play key roles in cell membrane morphogenesis, endocytic trafficking, and organelle dynamics. The human endophilin family includes five main members, encoded by the genes *SH3GL2* (endophilin A1), *SH3GL1* (endophilin A2), *SH3GL3* (endophilin A3), *SH3GLB1* (endophilin B1), and *SH3GLB2* (endophilin B2). Notably, *SH3GLB1* gives rise to functionally distinct splice variants, including the ubiquitously expressed B1a and the neuron-enriched B1b/c, which play critical, opposing roles in conditions such as Alzheimer disease (AD). These isoforms perform distinct, often opposing functions in disease pathogenesis via specific molecular mechanisms. For instance, endophilin A1 acts as a tumor suppressor; its gene, *SH3GL2*, is frequently deleted or downregulated in cancers such as non-small cell lung cancer, and its loss promotes tumor progression by sustaining epidermal growth factor receptor (EGFR) signaling. Conversely, endophilin A2 drives cancer metastasis. In AD, endophilin A1 expression is significantly elevated, exacerbating synaptic dysfunction, while neuron-specific endophilin B1 isoforms are decreased, worsening amyloid pathology. The regulation of endophilins involves intricate networks, including post-transcriptional control by microRNAs (e.g., miR-330 targeting *SH3GL2* in glioblastoma) and post-translational modifications. This review provides a comprehensive overview of the structural characteristics and regulation of expression and activity. It delineates the molecular mechanisms by which their dysfunction contributes to disease pathogenesis, aiming to provide new insights into these multifaceted proteins in health and disease.

Keywords: endophilin; endocytosis; neurodegenerative disease; cancer; cardiovascular disease

1. Introduction

Cellular membrane dynamics are fundamental biological processes that govern essential functions such as nutrient uptake, signal transduction, cell division, and intercellular communication [1,2]. The shaping and remodeling of lipid bilayers are mediated by a sophisticated protein machinery, among which the Bin-Amphiphysin-Rvs (BAR) domain superfamily functions as a key regulator of membrane curvature [3]. Endophilin, first identified as a binding partner for the GTPase dynamin and the synaptic protein synaptojanin, is a pivotal member of this superfamily [4,5,6]. Increasing evidence has shown that endophilin is not a single protein but rather a family comprising multiple members, which can be divided into two subfamilies, the endophilin A subfamily (endophilin A1, endophilin A2 and endophilin A3) and the endophilin B subfamily (endophilin B1, also known as Bif-1, and endophilin B2) [7].

Early research on endophilin primarily focused on its central role in membrane trafficking and cellular functions, particularly as a key regulator in endocytosis. It was established as a critical modulator of both rapid synaptic vesicle endocytosis and clathrin-mediated endocytosis (CME) [5,8]. The N-terminal BAR domain facilitates membrane curvature induction by binding to phosphatidylinositol-4,5-bisphosphate (PIP2), while its dimerization forms a crescent-shaped helical bundle that drives vesicle budding. The C-terminal Src Homology domain (Src Homology 3 (SH3) domain) mediates interactions with proteins such as dynamin and synaptojanin, which are essential for vesicle fission and recycling [9,10]. For instance, endophilin deficiency in *Drosophila* models disrupts synaptic vesicle retrieval, impairing neurotransmitter release and synaptic plasticity [11,12].

As research advanced, its functional diversity expanded beyond endocytosis. Highly expressed endophilin A1 in neurons emerged as a key regulator of synaptic plasticity, while endophilin B subtypes were implicated in mitochondrial metabolism and apoptosis in HeLa cells [13,14]. Notably, members of the endophilin family have attracted attention for their roles in disease pathogenesis. For example, aberrant endophilin A1 expression was linked to Alzheimer Disease (AD) through its potential role in dys-

regulating β-amyloid (Aβ) metabolism [15]. This review provides a comprehensive overview of the structural characteristics, regulation of expression and activity, and delineates the molecular mechanisms by which their dysfunction contributes to disease pathogenesis.

2. Structural Characteristics and Membrane Dynamics of Endophilin

All endophilin proteins share a conserved domain architecture consisting of an N-terminal BAR domain and a C-terminal SH3 domain connected by a flexible linker region [9,10,16,17]. The N-terminal BAR domain forms a curved, dimeric helical bundle that acts as a fundamental module for sensing and generating membrane curvature. This domain preferentially binds to membranes containing negatively charged phospholipids through positively charged residues distributed along its concave surface [18]. The N-terminal BAR domain also incorporates an amphipathic helix (H0) at the N-terminus which inserts into the lipid bilayer to enhance membrane bending capacity and H1-insert (H1i) within the H1 helix that insert into membranes to increase membrane interactions [19]. Fluorescence microscopy of Giant Unilamellar Vesicles (GUVs) shows that the isolated H0 helix of endophilin (H0-Endo) is sufficient to induce curvature, leading to the formation of miniscule vesicles emanating from the mother GUV [20]. Also, the Quantitative studies using Surface Plasmon Resonance (SPR) have demonstrated that mutations altering the hydrophobicity of H0 (e.g., F10W) significantly increase membrane binding affinity, while truncations of H0 reduce it [21]. Notably, recent *in vivo* evidence shows H0's function requires its net positive charge, which enables it to act as a dual sensor for membrane curvature and electrostatic state, guiding synaptic vesicle recycling [22]. H0 in endophilin B subtype might be slightly longer (one or two turns) than in endophilin A subtype [7] (Fig. 1). Meanwhile, the H0 helices of endophilin B subfamily exhibit stronger membrane partitioning than the endophilin A subfamily [23].

The linker region connecting the BAR and SH3 domains is vital in determining whether endophilin promotes or inhibits receptor-mediated endocytosis. Hiroko Sugiura et al. [24] reported that endophilin A2 functions as a negative regulator of receptor-mediated endocytosis. Overexpression of endophilin A3 in COS-7 cells strongly inhibited transferrin uptake—a classic marker for clathrin-dependent endocytosis, and the variable region of endophilin A3 is responsible for its inhibitory effect [24]. It also harbors several post-translational modification sites and putative Ca^{2+} binding sites, suggesting its involvement in the post-translational regulation of endophilin activity [7,25]. In terms of molecular assembly, the linker inhibits the self-assembly capability of the N-BAR domain, thereby suppressing its propensity for phase separation, and the phase separation threshold decreases after removal of the linker [26].

The C-terminal SH3 domain of endophilins adopts a characteristic β-barrel structure containing a hydrophobic groove that recognizes proline-rich domain (PRD) motifs in partner proteins, play a key role in mediating interactions with numerous proteins and this interaction is characterized by high and quantifiable affinity, where Surface Plasmon Resonance (SPR) studies have demonstrated that the SH3 domain of endophilin binds to the PRD of dynamin-1 with a biphasic kinetics, revealing two distinct sites: a high-affinity site (KD ~14 nM) in the N-terminus and a lower-affinity site (KD ~60 nM) in the C-terminus of the dynamin-1 PRD [27,28]. Consequently, the SH3 domain of endophilin A isoforms mediates the recruitment of dynamin, synaptojanin, and N-WASP (Neural Wiskott-Aldrich syndrome protein), which participate in distinct stages of endocytosis. Such as, dynamin is involved in vesicle fission, synaptojanin catalyzes the dephosphorylation of PIP2 to promote clathrin uncoating, and N-WASP regulates actin polymerization [29,30,31]. Meanwhile, the multivalent interactions between the SH3 domain of endophilin and lamellipodin and VASP drive the formation of liquid-like condensates, which undergo phase separation both *in vitro* and *in vivo* [32]. Additionally, the SH3 domain also mediates the direct interaction between endophilin and intersectin-1, thereby regulating exocytosis by coordinating neurosecretory vesicle priming and fusion [33]. In contrast, endophilin B1's SH3 domain interacts with distinct partners, including ultraviolet irradiation resistance-associated gene (UVRAG) and Beclin-1, to regulate autophagy and tumorigenesis [34].

An analysis of sequence identity among the human endophilin isoforms highlights both the conserved core architecture and the divergence that underlies functional specialization (Fig. 2 & Table 1). The endophilin A subfamily (A1–A3) members share high sequence identity (70.54%–66.3%), particularly within the structured BAR and SH3 domains, consistent with their overlapping roles in endocytosis and membrane dynamics. Similarly, the endophilin B subfamily (B1, B2) members share a moderate identity of 58.06% with each other. In contrast, the endophilin B subfamily shares lower identity with the endophilin A subfamily members (23.00%–25.26%), reflecting their distinct cellular functions in autophagy and apoptosis.

These structural features underpin endophilin's diverse cellular roles, including recently discovered functions in synaptic regulation. For instance, endophilin A1 facilitates organization of the GABAergic postsynaptic machinery to maintain excitation-inhibition balance, where the function requires both the membrane-binding capacity of its BAR domain and its actin polymerization-promoting activity through interaction with p140Cap. Loss of endophilin A1 weakens inhibitory synaptic transmission and causes excitatory/inhibitory imbalance, leading to increased epilepsy

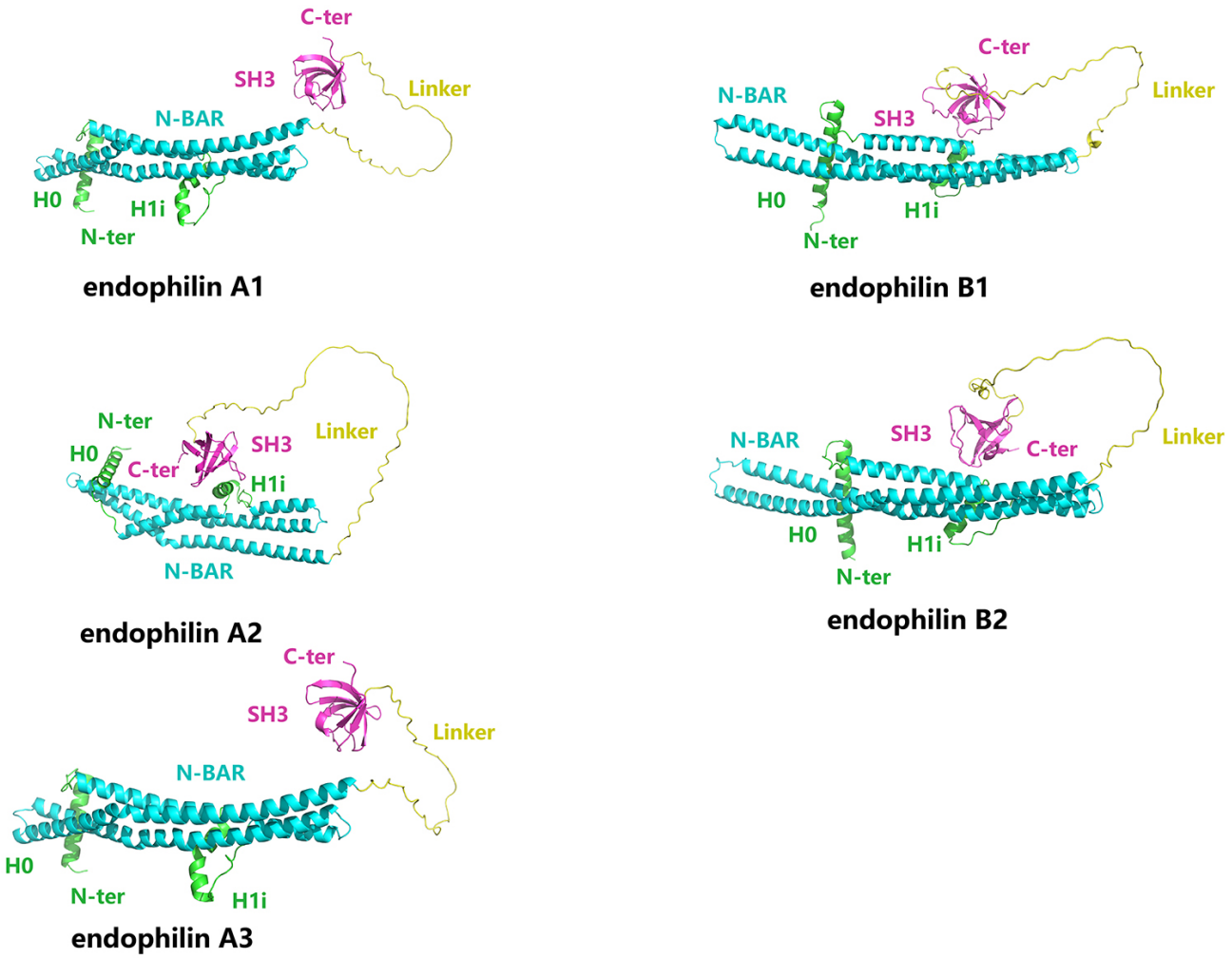

Fig. 1. Predicted domain architecture of human endophilin proteins. Structural models were generated using AlphaFold. The conserved N-terminal BAR domain (including the amphipathic helices H0 and H1i) and the C-terminal SH3 domain are predicted with high confidence, whereas the intervening linker region shows low prediction confidence. Protein sequences correspond to the following human genes (HGNC symbols): endophilin A1 (*SH3GL2*; NP_003017.1), endophilin A2 (*SH3GL1*; NP_003016.1), endophilin A3 (*SH3GL3*; Q99963.1), endophilin B1 (*SH3GLB1*; AAF73017.1), and endophilin B2 (*SH3GLB2*; Q9NR46.1). SH3, Src Homology 3; BAR, Bin-Amphiphysin-Rvs; H0, Helix 0; H1i, H1-insert; HGNC, HUGO Nomenclature Committee.

Table 1. Sequence identity matrix of human endophilin isoforms.

Isoform	NCBI references	Endophilin A1	Endophilin A2	Endophilin A3	Endophilin B1	Endophilin B2
Endophilin A1	NP_003017.1	100%	70.54%	68.08%	24.53%	23.71%
Endophilin A2	NP_003016.1	70.54%	100%	66.30%	25.26%	23.00%
Endophilin A3	Q99963.1	68.08%	66.30%	100%	24.73%	23.26%
Endophilin B1	AAF73017.1	24.53%	25.26%	24.73%	100%	58.06%
Endophilin B2	Q9NR46.1	23.71%	23.00%	23.26%	58.06%	100%

NCBI, National Center for Biotechnology Information.

susceptibility [35]. Endophilin A1 also critically regulates synaptic vesicle endocytosis through a high-affinity, Ca^{2+}-independent interaction between its BAR domain and the C2B domain of synaptotagmin-11 (Syt11). This interaction ensures the precision of protein retrieval during sustained neurotransmission [36]. Expanding its functional repertoire, endophilin A2 regulates mechanical sensitivity in sensory neurons by forming a triple complex with kinesin Kinesin Family Member 5B (KIF5B) and the mechanosensitive ion channel Piezo2, where endophilin A2 binds to Piezo2 via its C-terminal SH3 domain and binds to KIF5B via its N-terminal BAR domain. This adaptor function facilitates the forward membrane trafficking of Piezo2, thereby controlling touch sensation and mechanical allo-

Fig. 2. Multiple sequence alignment of human endophilin proteins. Sequence alignment of the five human endophilin proteins (endophilin-A1, -A2, -A3, -B1, and -B2). The alignment highlights the conserved regions corresponding to key functional domains. Residue numbers for the full-length proteins are indicated on the left and right sides. The alignment visualizes the higher degree of sequence conservation within the A (A1–A3) and B (B1, B2) subfamilies, respectively.

dynia in pathological pain [37]. Intriguingly, endophilin-mediated endocytic pathways can be co-opted by exogenous agents: cationic peptides such as ZIP induce AMPA receptor endocytosis via macropinocytosis and endophilin A2-dependent pathways, revealing a novel synaptic mechanism through which peptides erase memories without altering basal synaptic function [38].

3. Regulation of Expression and Activity

The transcriptional regulation of the endophilin protein family is a multi-layered and precisely coordinated process that governs the differential expression of its subtypes across specific cell types, developmental stages, and physiological or pathological conditions. For instance, endophilin A1 is predominantly expressed in neurons and testes, whereas endophilin A3 is selectively enriched in the striatum of the brain [7,39]. This specific regulation is particularly refined during development. In cochlear hair

cells, quantitative fluorescent *in situ* hybridization combined with immunohistochemistry demonstrated that premature inner hair cells (IHCs) have higher mRNA levels of endophilin A1 compared to outer hair cells (OHCs), with this difference becoming more pronounced upon maturation [40]. Additionally, endophilin A2 mRNA levels have been found to be significantly elevated in patients with systemic lupus erythematosus (SLE) relative to healthy controls [41]. Epigenetic regulators also play a role. Kis (Kismet, a chromatin-remodeling factor in *Drosophila*; its human ortholog is CHD7, Chromodomain Helicase DNA binding protein 7) functions as an epigenetic regulator that influences gene expression by binding to active transcription sites and promoting transcriptional activation and elongation [42]. Chromatin immunoprecipitation quantitative PCR (ChIP-qPCR) experiments demonstrated significant enrichment of Kis binding at the promoter region of endophilin B in the *Drosophila* central nervous system (CNS). This binding correlates with altered transcript levels, as endophilin B mRNA is reduced in Kis mutants compared to controls [43].

At the post-transcriptional level, non-coding RNAs fine-tune endophilin mRNA stability and translation. For example, in the oriental fruit fly Bactrocera dorsalis, miR-311-3p targets endophilin B1 mRNA, with its downregulation during sexual maturation correlating with increased endophilin expression and ovarian development. Manipulation of miR-311-3p levels affects endophilin B1 expression and reproductive capacity, demonstrating a microRNA-mediated layer of post-transcriptional control in insect reproductive tissues [44]. Similarly, a long non-coding RNA (lncR26319) regulates endophilin A expression post-transcriptionally through competitive binding to miR-2834, influencing vitellogenin endocytosis and oogenesis in the silkworm Bombyx mori [45]. The Fig. 3 (Ref. [46]) demonstrates the regulatory mechanisms of microRNAs (miRNAs) and long non-coding RNAs (LncRNAs) on endophilin and their roles in diseases [46,47,48,49,50,51].

4. Post-Translational Modifications

Endophilin function is dynamically modulated by an array of post-translational modifications (PTMs), including phosphorylation, acetylation, and ubiquitylation, which alter their membrane affinity, protein-protein interactions, and stability. For instance, 17β-estradiol (E2) induces tyrosine phosphorylation of endophilin A2, which correlates with altered membrane estrogen receptor (mERα) expression and downstream signaling in endothelial cells. Knockdown of endophilin A2 enhances E2-induced vasodilation by promoting Akt (Protein Kinase B), ERK1/2 (Extracellular Signal-Regulate Kinase1/2), and eNOS (endothelial Nitric Oxide Synthase) activation, indicating that phosphorylation-dependent regulation of endophilin A2 can influence vascular function and potentially cardiovascular health [52]. Similarly, phosphorylation also regulates endophilin's interaction with other endocytic proteins. Dynamin 1xA, a splice variant critical for ultrafast endocytosis, binds endophilin A1 through a site in its long C-terminal tail whose affinity is modulated by the phosphorylation state of two serine residues unique to this variant. Phosphorylation-dependent binding controls the localization of dynamin 1xA to endocytic zones and the progression of vesicle fission, highlighting how phosphorylation fine-tunes endophilin's role in synaptic vesicle recycling [53]. The interaction between endophilin A1 and dynamin 1xA also has been shown to be crucial for ultrafast endocytosis at synaptic terminals [54]. In the context of synaptic vesicle endocytosis, the interaction between endophilin A1 and amphiphysin-1 (Amph1) is regulated by the phosphorylation status of Amph1 at serine 293 within its proline-rich domain. Dephosphorylation of this residue enhances the Amph1-endophilin interaction, which is essential for efficient synaptic vesicle regeneration, underscoring the importance of phosphorylation in controlling protein-protein interactions critical for neuronal function [55]. Moreover, phosphorylation of endophilin by kinases such as Dual-Specificity Tyrosine-(Y)-Phosphorylation Regulated Kinase 1 (DYRK1) has been shown to regulate endocytosis during developmental processes, such as extracellular lumen expansion in the ascidian notochord. DYRK1 phosphorylates endophilin at serine 263, which is essential for proper endocytic activity and tubular organogenesis, demonstrating that phosphorylation controls endophilin's role beyond neuronal contexts [56].

Beyond phosphorylation, ubiquitination also influences endophilin's stability and function. Parkin, an E3 ubiquitin ligase mutated in Parkinson's disease, is activated by CaMK2-mediated phosphorylation and ubiquitinates synaptojanin-1, facilitating its interaction with endophilin A1 and promoting synaptic vesicle recycling. Mutations in parkin disrupt this ubiquitination pathway, leading to defective vesicle recycling and dopaminergic neuron dysfunction, implicating ubiquitin-mediated regulation of endophilin-associated complexes in disease pathogenesis [57]. Meanwhile, HDAC2 (histone deacetylase-2) epigenetically represses the expression of the neuroprotective protein Endophilin B1b/c. This suppression promotes mitochondrial dysfunction and neuronal death, which contributes to disease progression in both AD and ischemic brain injury [58]. Key phosphorylation sites, acetylation sites, and ubiquitylation sites have been summarized in Table 2 from PhosphoSitePlus data (https://www.phosphosite.org).

5. The Role of Endophilins in Diseases

5.1 Neurological Disorders

Endophilin proteins are increasingly implicated in the pathogenesis of various neurological conditions through their roles in synaptic function, autophagy, and protein aggregation.

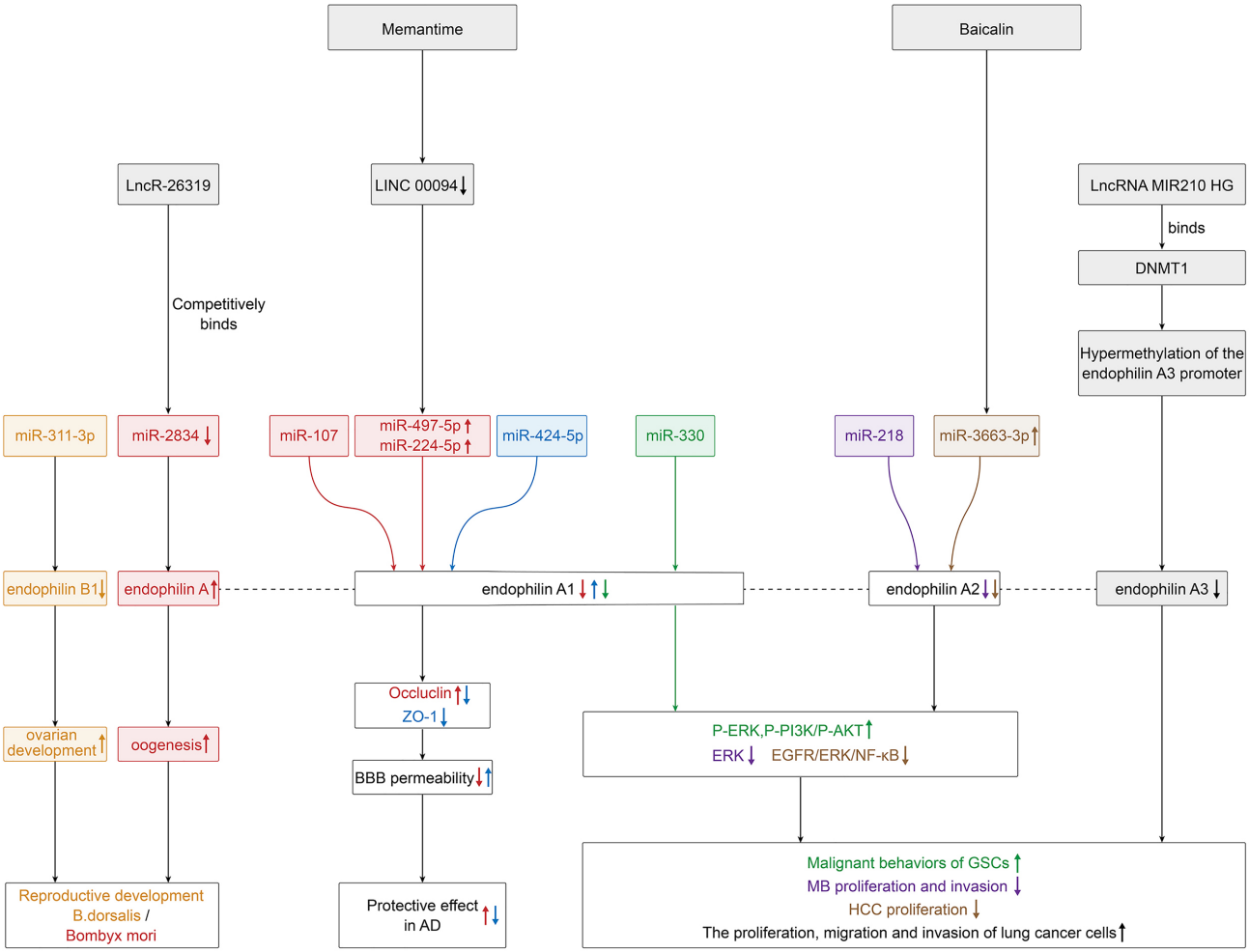

Fig. 3. Schematic diagram of non-coding RNAs regulatory network on endophilin and their implications in reproductive development and disease. MiR-311-3p directly targets endophilin B1 in Bactrocera dorsalis, and LncR-26319 competitively binds to and sequesters miR-2834, leading to the upregulation of endophilin A in Bombyx mori, respectively, thereby affecting reproductive development. Additionally, miR-107, miR-497-5p, miR-224-5p, and miR-424-5p target endophilin A1, contributing to either a protective effect or aggravation of AD. While miR-424-5p overexpression was accompanied by upregulation of endophilin A1, this suggests that some of the observed unusual positive effects of miRNA may be due to the combinatorial complexity of the system rather than due to any inherently unusual positive effect of the miRNA on its target [46]. The diagram also includes the endophilin A subtypes targeted by miR-330, miR-218, miR-3663-3p, and LncRNA MIR210 HG, which ultimately impacting cancers. Abbreviations: BBB, blood–brain barrier; DNMT1, DNA methyltransferase 1; GSCs, glioblastoma stem cells; HCC, hepatocellular carcinoma; LncRNA, long non-coding RNA; LINC, Long Intergenic Non-Coding RNA; ZO-1, Zonula Occludens-1; P-ERK, Phosphorylated Extracellular Signal-Regulated Kinase; P-PI3K, Phosphorylated Phosphoinositide 3-kinase; P-AKT, Phosphorylated Protein Kinase B; NF-κB, Nuclear Factor Kappa B. Upward arrow (↑) indicates an increase in the measured parameter, which includes upregulation of proteins, increased BBB permeability, enhanced protective effect in AD, increased cell proliferation and migration, and higher malignancy grade of GSCs. Downward arrow (↓) represents the opposite effect (decrease or reduction) for these respective parameters.

5.1.1 Alzheimer Disease (AD)

Endophilin proteins play complex and opposing roles in AD pathogenesis, depending on the specific family member. Endophilin A1 expression is elevated in the brains of AD patients and mouse models [59,60]. This increased expression of endophilin A1 has been shown to directly exacerbate Aβ-induced synaptic dysfunction, the loss of key synaptic proteins such as synaptojanin and synaptophysin, and impairment of synaptic vesicle recycling [15,60]. Conversely, knocking down endophilin A1 expression can alleviate Aβ-induced synaptic dysfunction [60]. Furthermore, endophilin A1 also influenced the permeability of the blood-brain barrier (BBB) by modulating the expression and redistribution of tight junction (TJ)-associated proteins, including ZO-1 and occludin [61,62]. Notably, memantine has been found to mitigate Aβ-induced BBB injury by in-

Table 2. The phosphorylation, acetylation, and ubiquitylation sites of endophilin isoforms.

Isoform	Phosphorylation	Acetylation	Ubiquitylation
Endophilin A1	Thr-14, Ser-75, Ser-249, Ser-262	Lys-20	Lys-76, Lys-149
Endophilin A2	Ser-14, Ser-18, Ser-75, Ser-108, Ser-286, Ser-287, Ser-288, Ser-291, Ser-292, Thr-298, Ser-302, Tyr-315	Lys-20, Lys-102, Lys-122, Lys-241	Lys-20, Lys-102, Lys-122, Lys-149, Lys-189, Lys-239
Endophilin A3	Ser-14, Thr-83, Tyr-86, Tyr-168, Ser-248, Tyr-255, Ser-263, Ser-264, Ser-265	Lys-149, Lys-261, Lys-277	Lys-82
Endophilin B1	Tyr-80, Thr-145, Thr-157, Ser-190, Ser-200		Lys-9, Lys-10, Lys-29, Lys-35, Lys-48, Lys-53, Lys-58, Lys-61, Lys-82, Lys-176, Lys-355
Endophilin B2	Ser-10, Tyr-77, Thr-108, Thr-109, Thr-142, Thr-188, Thr-195, Ser-205, Ser-207, Ser-259, Thr-262, Tyr-263, Tyr-268, Thr-389, Ser-395	Lys-178, Lys-180, Lys-185	Lys-26, Lys-32, Lys-50, Lys-55, Lys-79, Lys-117, Lys-123, Lys-153, Lys-173, Lys-185, Lys-276

hibiting endophilin A1 expression via the LINC00094/miR-224-5p/miR-497-5p axis [47].

In contrast, neuron-specific splice variants of endophilin B1 (endophilin-B1b/c) exhibit a protective role, as their protein expression was decreased in the brain tissues from AD patients and in a double mutant amyloid precursor protein and presenilin 1 (APPswe/PSEN1dE9) mouse model of AD (APP/PSEN1 transgenic mice). Loss of endophilin-B1b/c exacerbates amyloid plaque load, synaptic degeneration, cognitive impairment, and early mortality [63]. The suppression of endophilin-B1b/c in AD may be mediated by upregulated histone deacetylase 2 (HDAC2) [61]. Separately, the synthetic peptide Zfra could restore memory deficits in AD transgenic mice by blocking endophilin B2 aggregation [64].

5.1.2 Parkinson's Disease (PD)

PD is a progressive neurodegenerative disorder characterized by the loss of dopaminergic neurons in the substantia nigra [65]. While the exact etiology remains incompletely understood, growing evidence implicates synaptic dysfunction and defective endocytosis in disease pathogenesis [66]. Among the key players in these processes is endophilin, with endophilin A1 emerging as a critical factor in PD-related pathways. In the LPS-induced PD model mice, endophilin A1 expression was significantly upregulated, and its knockdown improved behavioral impairments and alleviated dopaminergic neuron damage [67]. Studies have shown that endophilin A1 regulates synaptic autophagy through calcium sensing and plays a central role in maintaining neuronal health. The PD risk mutant endophilin A1 G276V has been reported to disrupt Ca^{2+}-induced synaptic autophagy [68,69]. Supporting its genetic link to PD, genome-wide association studies (GWAS) have identified the coding gene *SH3GL2* as a risk locus. Furthermore, regional brain transcriptomic analysis reveals that *SH3GL2* expression correlates with selective vulnerability across Braak stages, providing molecular insight into its role in PD progression [70]. However, the endophilin A1 p.G276V mutation may be only one of several risk factors, or it may exhibit heterogeneity across populations. Endophilin A1 may also influence PD through other variants, such as the intronic variant rs910316833 [71]. It is essential to balance this finding with meta-analysis and consider the effect sizes of associated variants. Furthermore, endophilin A subtypes functionally interact with other PD-related proteins, such as Parkin and synaptojanin 1 [72].

5.1.3 Huntington's Disease (HD)

HD is an autosomal dominant neurodegenerative disorder caused by abnormal expansion of polyglutamine (polyQ) sequences in the huntingtin protein [73]. Annie Sittler et al. [74] found that endophilin A3 binds to the proline-rich region (PRR) of huntingtin via its SH3 domain, thereby promoting the formation of insoluble polyglutamine-containing aggregates. Polyglutamine-containing aggregates can form neuronal intranuclear inclusions (NIIs). These inclusions sequester key proteins

(such as dynamin and synaptojanin) in the brains of HD patients, disrupting synaptic function and inducing apoptosis [74,75]. Simultaneously, the aggregates may alter the binding specificity of the WW domain of HYPA (also known as FBP11), thereby affecting RNA splicing or vesicular transport and exacerbating neuron-specific death [28].

5.2 Endophilins in Cancer

Recent studies have consistently demonstrated that endophilin A1 functions as a tumor suppressor gene across multiple cancer types. Although endophilin A1 is highly expressed in normal tissues, including the brain and bladder urothelium, its expression is frequently diminished in tumors due to genetic deletion, promoter hypermethylation, or transcriptional downregulation, resulting in markedly reduced levels in glioblastoma, non-small cell lung cancer, head and neck squamous cell carcinoma, and urothelial cancer [76,77,78]. The tumor-suppressive activity of endophilin A1 is primarily mediated through its regulation of receptor tyrosine kinase trafficking (EGFR): by facilitating EGFR endocytosis and subsequent degradation, endophilin A1 effectively attenuates downstream pro-survival and proliferative signaling pathways, including ERK and STAT3 [76,77,78,79]. In addition, endophilin A1 directly regulates apoptosis and influences the immune microenvironment. For instance, loss of endophilin A1 leads to upregulation of the immune checkpoint molecule CD155, thereby contributing to tumor immune evasion [77,80].

Initial clinical investigations show an association between low endophilin A1 expression and poor clinical outcomes in specific cancers. However these findings require validation in larger, multi-center cohorts. As summarized in Table 3 (Ref. [81,82,83]), patients with low endophilin A1 expression exhibit a significantly reduced survival rate in lung adenocarcinoma [81]. Similarly, reduced *SH3GL2* expression, genetic inactivation (e.g., deletion, methylation) and the G allele of SNP (Single Nucleotide Polymorphism) rs1049430 which is linked to lower endophilin A1 expression, are associated with poor prognosis in Head and Neck Squamous Cell Carcinoma (HNSCC) [82]. Extending to breast cancer, the elevated endophilin A2 expression is associated with poor prognosis, shorter Distant Metastasis-Free Survival (DMFS), Overall Survival (OS), and Relapse-Free Survival (RFS), especially in TNBC and $HER2^+$ subtypes. Upregulate endophilin A1 correlates with improved survival outcomes. While endophilin A3 shows complex effects: increased expression of endophilin A3 links to worse DMFS but better RFS [83].

Endophilin A2 is ubiquitously expressed in multiple tissues. It drives tumor progression, metastasis, and therapy resistance across a broad spectrum of cancers by facilitating the internalization of key receptors, such as EGFR, HER2, and MT1-MMP [8,83,84]. In colorectal cancer, endophilin A2 drives multidrug resistance by upregulating the MDR1/P-glycoprotein efflux pump via the EGFR/ERK/AP-1 pathway [85]. In $HER2^+$ breast cancer, it modulates the internalization of targeted therapies like trastuzumab, influencing treatment efficacy [86]. In preliminary studies, autoantibodies against endophilin A2 have been identified as potential biomarkers for early breast cancer detection. However, their clinical utility requires further validation in larger, independent cohorts [87]. Endophilin A2 also activates a network of critical signaling pathways, including EGFR/ERK/Akt/NF-κB, and FAK (Focal Adhesion Kinase)/p130Cas, to fuel cancer cell proliferation, survival, cycle progression (e.g., via cyclin D1 regulation), invadopodia formation, extracellular matrix degradation, and epithelial-mesenchymal transition (EMT) [49,50,88,89]. Its function can be tissue-specific. For example, it exhibits nuclear localization and can fuse with the *MLL* gene to drive leukemia in hematopoietic cells [90]. In diffuse large B-cell lymphoma, it promotes survival by inhibiting ferroptosis [91].

Endophilin A3 exhibits context-dependent roles in tumor progression, demonstrating tissue-specific oncogenic or tumor-suppressive functions. In colon cancer, endophilin A3 competitively binds to TIAM1 in the presence of membrane phospholipids, thereby modulating the balance between cell migration and proliferation [92]. It is highly expressed in multiple myeloma stem cells ($CD138^-$ cells), where it regulates cell migration and invasion via the FAK/PI3K signaling pathway. Phosphorylation of FAK and PI3K enhances downstream effectors such as Src, RhoA, and ROCK, facilitating cytoskeletal remodeling and metastatic dissemination [93]. In contrast, endophilin A3 exhibits tumor-suppressive properties in lung cancer and glioblastoma. It interacts with STAT3 to inhibit its nuclear translocation, thereby suppressing the transcription of stemness-related genes (e.g., Nanog and OCT4). Concurrently, it upregulates p21 (CDKN1A), inducing G0/G1 cell cycle arrest and impairing cancer stem cell self-renewal [51,94,95]. Meantime, Kaplan-Meier survival analysis and TCGA data set show that low *SH3GL3* (SH3 domain GRB2-like 3) expression correlates with poor prognosis in lung cancer and glioblastoma, respectively [94,95]. Epigenetic regulation further underscores its clinical relevance: the lncRNA MIR210HG recruits DNA methyltransferase 1 (DNMT1) to methylate the *SH3GL3* promoter, thereby silencing *SH3GL3* expression and promoting lung cancer progression [51].

In the majority of tumor types, including pancreatic ductal adenocarcinoma, colon cancer, gastric carcinoma, and invasive urinary bladder and gallbladder cancers, the expression of endophilin B1 is downregulated, contributing to tumor initiation and progression by impairing apoptosis and autophagy-mediated cell death. Its low expression is often associated with a poor prognosis [96,97,98,99]. Moreover, endophilin B1 deficiency promotes chromosomal instability, upregulates the expression of anti-apoptotic proteins such as MCL1 and BCL2L1, and drives Myc-

Table 3. Summary of survival data from cited studies on endophilin a subtypes.

Cancer type	Key finding related to prognosis	Statistical significance	Main statistical method	Study (Citation)
Lung adenocarcinoma	High endophilin A1 expression correlates with better survival.	$p < 0.05$	KM Plot.	Zengjian Tian et al. [81]
HNSCC	The G allele of SNP rs1049430 (linked to lower endophilin A1expression) is associated with significantly worse overall survival.	$p = 0.0001$	KM Plot and Multivariate Cox analysis.	Guru Prasad Maiti et al. [82]
Breast cancer	High expression of endophilin A2 is associated with poorer prognosis, including worse DMFS, OS, and RFS.	Log-rank $p < 0.05$, HR >1	KM Plot, log-rank test, HR.	Vikrant Mehta et al. [83]
Breast cancer	High expression of endophilin A1 correlates with improved prognosis, showing better DMFS, OS, and RFS compared to low expression groups.	Log-rank $p < 0.05$, HR <1	KM Plot, log-rank test, HR.	Vikrant Mehta et al. [83]
Breast cancer	The expression of endophilin A3 shows complex prognostic associations: high levels trend toward worse DMFS (HR = 1.15, $p = 0.068$) but significantly better RFS (HR = 0.78, $p = 2.1 \times 10^{-6}$).	Mixed significance: strong for RFS, borderline for DMFS	KM Plot, log-rank test, HR.	Vikrant Mehta et al. [83]

K-M Plot, Kaplan-Meier survival analysis; HR, Hazard Ratio; HNSCC, Head and Neck Squamous Cell Carcinoma; DMFS, Distant Metastasis-Free Survival; OS, Overall Survival; RFS, Relapse-Free Survival.

dependent lymphomagenesis [100]. In contrast, in cutaneous Merkel cell carcinoma and hepatocellular carcinoma, the upregulation of endophilin B1 may promote tumor survival and progression, potentially due to its role in modulating Bax activity, and elevated endophilin B1 expression may be associated with poor prognosis [101,102]. These biological functions are closely linked to its interaction with key regulatory proteins such as Bax, Beclin-1, Cdc42 and EGFR, as well as their downstream signaling pathways [103,104,105]. Pharmacological agents such as fluoxetine have been demonstrated to restore endophilin B1 expression in triple negative breast cancer, thereby inducing autophagic cell death in MDA- MB- 231 [106]. Notably, Katja Stifter et al. [107] reported that using the mutant epitope Db/Sp244-252/R251H from the mouse endogenous antigen endophilin B2 can effectively induce specific $CD8^+$ T cell responses. This discovery provides new insights into the design of novel vaccines against tumors, particularly in the field of personalized cancer immunotherapy [107].

5.3 Endophilins in Cardiovascular Disease

Endophilin A2 plays multifaceted roles in atherosclerosis, vascular disease, and cardiac pathophysiology, with both pathological and protective functions. In atherosclerosis (AS), endophilin A2 is essential for macrophage-derived foam cell formation by interacting with scavenger receptors CD36 and SR-A, promoting the uptake of oxidized LDL and activating the ASK1–JNK/p38 signaling pathway, creating a lipid-accumulating positive feedback loop [108]. It also enhances inflammation, as evidenced by its correlation with pro-inflammatory markers in adipose tissue and its role in upregulating cytokines such as IL-6 and MCP-1 [109]. In vascular disease, endophilin A2 contributes to vascular dysfunction by inducing ubiquitination and autophagic degradation of TMEM16A chloride channels in hypertensive models, thereby disrupting vascular homeostasis [110]. It also interacts with ClC-3 chloride channels via its SH3 domain, promoting their membrane trafficking and enhancing volume-regulated chloride currents, which facilitate vascular smooth muscle proliferation and remodeling under hypertension [111,112]. In cardiac pathophysiology, endophilin A2 exerts protective effects. It suppresses pathological cardiac hypertrophy by enhancing autophagy [113], reduces oxidative stress-induced apoptosis through Bif-1/Beclin-1-mediated autophagosome formation [114], and attenuates endoplasmic reticulum (ER) stress and calcium-mediated injury during myocardial infarction by inhibiting the ERO1α/IP3R pathway [115].

Endophilin B1 has been implicated in a dual role in cardiovascular physiology and pathology. At the same

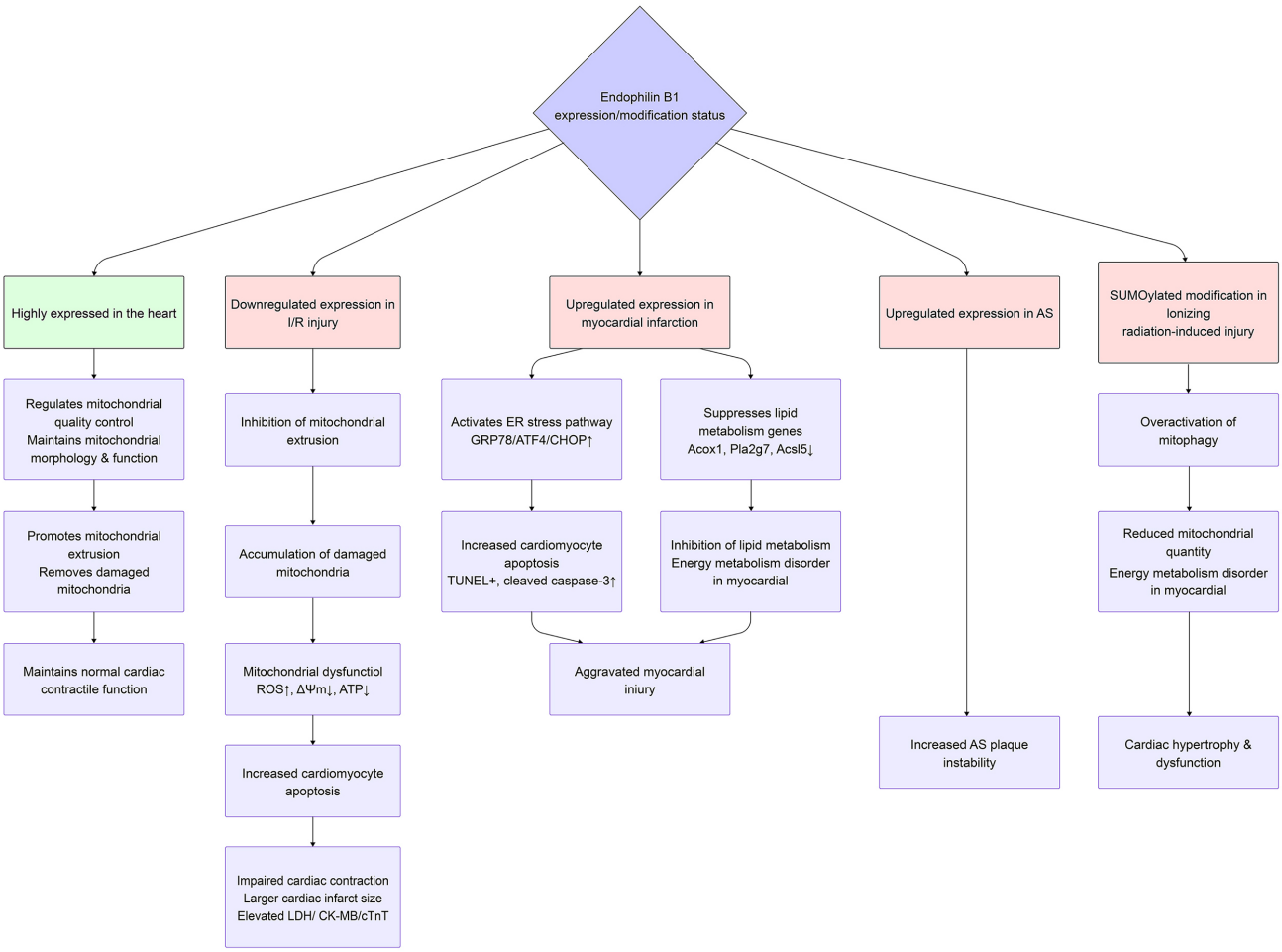

Fig. 4. Roles of endophilin B1 in cardiovascular disease. Endophilin B1 expression is upregulated in normal myocardial tissue, promoting mitochondrial extrusion and removing damaged mitochondria, thereby supporting normal cardiac contractile performance. At the same time, endophilin B1 was decreased in myocardial ischemia and reperfusion injury (I/R), leading to mitochondrial dysfunction, apoptosis, and impaired cardiac contraction. Endophilin B1 expression was increased after myocardial infarction, where the endoplasmic reticulum (ER) stress pathway was activated, and lipid metabolism genes were suppressed, synergistically contributing to aggravated myocardial injury. SUMO2-mediated SUMOylation of endophilin B1 promotes hypertrophic cardiomyopathy by overactivated mitophagy in ionizing radiation-induced cardiac injury. Endophilin B1 also affects AS plaque stability. ROS, Reactive Oxygen Species; LDH, Lactate Dehydrogenase; CK-MB, Creatine Kinase-Myocardial Band; GRP78, Glucose-Regulated Protein 78; ATF4, Activating Transcription Factor 4; CHOP, C/EBP Homologous Protein; TUNEL, Terminal deoxynucleotidyl transferase dUTP Nick-End Labeling; AS, atherosclerosis.

time, evidence remains preliminary and context-dependent (Fig. 4). For instance, it promotes mitophagy and mitocytosis, processes essential for clearing damaged mitochondria [116]. In hypertrophic cardiomyopathy, ionizing radiation upregulates endophilin B1, exacerbating cardiac hypertrophy via SUMO2-mediated SUMOylation [117]. Conversely, in myocardial infarction, inhibiting endophilin B1 attenuates adverse remodeling, improves cardiac function, and reduces ER stress and apoptosis [118]. Interestingly, recent cryo-EM studies reveal that endophilin B1 adopts distinct conformations upon membrane binding, with its amphipathic helices (H0 and H1i) inserting into cardiolipin-rich mitochondrial membranes to induce permeabilization. This activity facilitates Bax-mediated apoptosis, linking it directly to mitochondrial dysfunction and cardiovascular injury [119]. The endophilin B1 protein was also upregulated in unstable AS plaques, but its associated circRNA, hsacirc_000411, was downregulated, and its effects on AS remain unknown [120]. Future studies integrating single-cell RNA sequencing (scRNA-seq) data from atherosclerosis atlases will help elucidate cell-type-specific roles of endophilin B1 and refine its therapeutic targeting in distinct cardiovascular pathologies.

5.4 Other Diseases

Endophilin proteins have been implicated in a broad spectrum of diseases beyond their well-established roles in neurodegeneration, cancer, and cardiovascular disease, with emerging evidence supporting their involvement in additional conditions. For example, endophilin A2 also influences both B-cell and T-cell responses. In B cells, deficiency in endophilin A2 impairs germinal center responses, antibody affinity maturation, and high-affinity IgG production, as evidenced in mouse models and in human cases with *SH3GL1* mutations, leading to panhypogammaglobulinemia and reduced memory B cells [121,122]. Also, mutations or deficiencies in *SH3GL1*, the gene encoding endophilin A2, confer protection against autoimmune arthritis by modulating T cell effector functions and altering the activation threshold of autoreactive T cells in rodents [123].

6. Discussion

The endophilin protein family, as evolutionarily conserved regulators of membrane dynamics, plays a complex and critical role in the pathogenesis and progression of various diseases. For instance, endophilin A1 affects synaptic function in dopaminergic neurons by regulating synaptic vesicle endocytosis and recycling in PD [57,124]. Specific risk variants in *SH3GL2* can also disrupt calcium sensing, thereby impairing neuronal activity-induced synaptic autophagy, which provides a new perspective for understanding early synaptic dysfunction in PD [68,69]. In the field of oncology, different isoforms of the endophilin protein family exhibit distinct clinical significance. It is noteworthy that the functions of endophilin proteins extend beyond classical endocytic pathways. Fast Endophilin-Mediated Endocytosis (FEME), as a regulated clathrin-independent endocytic pathway, is rapidly triggered upon stimulation by specific receptor ligands, potentially offering novel interventional strategies for the treatment of cancer and neurodegenerative diseases [125]. These findings broaden our understanding of the functional diversity of endophilin proteins and underscore the complex interconnections between membrane trafficking, the cytoskeleton, and disease.

7. Conclusions and Future Perspective

The endophilin family functions as a key regulator at the interface of membrane biology and cellular signaling, making their roles crucial for understanding cell function and disease mechanisms. Understanding their intricate roles opens up new and exciting avenues for therapeutic intervention across a broad spectrum of human diseases. This review has synthesized diverse findings that collectively highlight endophilin's role in fundamental cellular processes and in the pathogenesis of multiple diseases. Dysfunction of specific endophilin isoforms underlies the pathogenesis of a wide array of diseases. Such as in the nervous system, disrupted endophilin A function is a common pathway in neurodegenerative diseases like PD and AD, leading to synaptic failure. In oncology, endophilin proteins act as tumor suppressor or drive cancer progression depends on the context. Their roles in cardiac desensitization and metabolic regulation further expand their disease relevance.

Future research should clarify the precise molecular pathways through which endophilin exerts its diverse functions. To this end, the application of cutting-edge technologies will be critical. For example, deep learning-based structural prediction tools like AlphaFold-Multimer can be leveraged to model the atomic details of endophilin BAR domain complexes with key partners like dynamin, providing unprecedented insights into the mechanics of membrane remodeling. Spatial proteomics approaches could map the precise localization and molecular neighbors of endophilin isoforms (e.g., endophilin A1) within pathological structures such as AD, directly linking subcellular context to dysfunction. Furthermore, systematic functional genomics using CRISPR interference (CRISPRi) screens across diverse cancer models can uncover the context-specific dependencies on endophilin genes or their regulators, identifying novel therapeutic vulnerabilities. Additionally, *in vivo* models that recapitulate human disease contexts are essential to validate the therapeutic potential of targeting endophilin.

Author Contributions

XYL and SXF conducted the primary literature search and data acquisition, performed the initial analysis and interpretation of the collected information, drafted the original manuscript. XDP participated in the literature search and data collection. HMP and WWS contributed to the interpretation of data. SL conceived and designed the review and contributed significantly to the writing of key sections, critically reviewed, edited, and revised the entire manuscript for depth, clarity, and coherence. All authors have read and agreed to the published version of the manuscript. All authors contributed to editorial changes in the manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflicts of Interest

The authors declare no conflicts of interest.

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