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Review Article

Key subunits of γ-secretase complex and breast cancer progression: biological function, regulation mode and therapeutic potential

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ABSTRACT

Breast cancer (BC) is the most prevalent malignant tumor among females. The primary therapeutic options currently available include surgery, radiotherapy, chemotherapy, targeted therapy, and immunotherapy. However, the emergence of drug resistance has resulted in a gradual decline in the efficacy of these treatments. The activation of the Notch signaling pathway is closely associated with the development and progression of breast cancer. γ-secretase, a crucial hydrolase in the Notch pathway, consists of four subunits: presenilin 1 and 2 (PSEN1 and 2), presenilin enhancer 2 (PEN-2), Nicastrin (NCSTN), and anterior pharynx defective 1 (APH-1). These subunits interact to maintain the overall biological function and stability of the complex. This review utilizes the key subunits of γ-secretase as a focal point to elucidate the structure-function relationships, interactions, and their relevance to the progression of breast cancer for each complex subunit, and the preclinical studies and clinical trials were discussed, emphasizing the relationship between the key subunits of γ-secretase complex and the pathogenesis of BC. Furthermore, the challenges and prospects of γ-secretase inhibitors as potential therapies for chemoresistance in breast cancer were discussed.

1. Introduction

BC has the highest incidence rate among malignant tumors in females, accounting for 24.2 % of cases and exhibiting a trend toward affecting younger populations [1]. Currently, the field of breast cancer treatment encompasses a wide array of therapeutic strategies, including surgery, radiotherapy, chemotherapy, targeted therapy, immunotherapy, and others. Significant advancements have been made in the treatment of specific types of breast cancer. For instance, HER2-positive patients benefit from anti-HER2 therapy; BC patients with BRCA1/2 mutations show favorable outcomes with PARP inhibitors [2,3]. Furthermore, immunotherapy has led to substantial progress in breast cancer research and has become a pivotal component of treatment strategies [4]. However, breast cancer treatment continues to face numerous challenges, particularly in the context of Triple-Negative Breast Cancer (TNBC). This is largely due to the lack of effective targets and therapeutic modalities, which render current treatment options inadequate in effectively inhibiting the self-renewal and

Abbreviations: Akt, Protein kinase B; AMPK, Adenosine monophosphate-activated protein kinase; APH-1, Anterior pharynx-defective 1; APP, Amyloid precursor protein; Aβ42, Amyloid-beta 42; Bax, BcL-2-associated X protein; Bcl-2, B-cell lymphoma 2; BC, Breast cancer; Caspase, Cysteine aspartate-specific protease; CDK, Cyclin-dependent kinase; CTF, C-terminal fragment; EGF, Epidermal growth factor; EMT, Epithelial-mesenchymal transition; GSI, γ-Secretase inhibitor; GSM, γ-Secretase modulator; HER2, Human epidermal growth factor receptor 2; HIF-1α, Hypoxia-inducible factor 1-alpha; HIF-1β, Hypoxia-inducible factor 1-beta; HRE, Hypoxia response element; IL-6, Interleukin-6; MMPs, Matrix metalloproteinases; mTOR, Mechanistic target of rapamycin; NCSTN, Nicastrin; NICD, Notch intracellular domain; NTF, N-terminal fragment; PARP, Poly(ADP-ribose) polymerase; PEN-2, Presenilin enhancer 2; PI3K, Phosphoinositide 3-kinase; PSEN, Presenilin; ROS, Reactive oxygen species; TEAD, TEA domain transcription factors; TNBC, Triple-negative breast cancer; TRPS1, Trichorhinophalangeal syndrome type 1; VEGF, Vascular endothelial growth factor; Wnt/β-catenin, Wnt/beta-catenin signaling pathway; YAP, Yes-associated protein.

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multidirectional differentiation capabilities of breast cancer stem cells. Chemotherapy remains the primary treatment for TNBC; however, it is associated with significant adverse effects and a propensity to induce drug resistance [5]. Given the high prevalence of BC, the limitations of existing therapeutic options, and the considerable inter-patient heterogeneity, there is an urgent need to identify more effective and precise treatment strategies that minimize adverse effects. This is especially critical for patients with advanced or metastatic breast cancer, as the limited treatment options and unsatisfactory prognosis highlight the necessity of exploring novel therapeutic approaches.

The Notch signaling pathway plays a significant role in the pathogenesis and progression of BC. Upon binding the Notch receptor to its ligand, the receptor is cleaved by γ-secretase at the transmembrane region, resulting in the release of the Notch intracellular domain. The Notch intracellular domain then enters the nucleus, where it induces gene transcription and activates the expression of downstream target genes, thereby influencing the development of BC [6]. γ-secretase is an intramembrane protease complex comprising four core subunits: PSEN, PEN-2, NCSTN, and APH-1. These are essential hydrolases involved in the activation of Notch signaling proteins. The γ-secretase subunits interact with one another and are involved in the processes of proliferation, apoptosis, migration, invasion, and angiogenesis of BC cells. The occurrence and development of BC are closely related to the aberrant activation of the Notch signaling pathway. Abnormal activity of γ-secretase can lead to the abnormal transmission of Notch signaling, which promotes BC's progression [7–9]. Consequently, the investigation of methodologies to impede γ-secretase activity offers novel insights into the clinical management of BC and presents a promising avenue for the treatment of TNBC. γ-secretase inhibitors have been demonstrated to inhibit the activation of the Notch signaling pathway, thereby preventing or alleviating the development of BC. Furthermore, these inhibitors have been shown to regulate the migration, invasion, and apoptosis of tumor cells. Given the limited efficacy of hormonal therapies in treating TNBC and the dearth of effective targeted drugs, the study of γ-secretase inhibitors represents a promising avenue for further investigation.

The objective of this study is to elucidate the complex mechanisms by which various γ-secretase subunits contribute to the pathogenesis of BC by conducting a thorough examination of numerous preclinical studies and clinical trials. In light of these findings, we have conducted an extensive investigation into the challenges that γ-secretase inhibitors may face as potential therapeutic agents, the feasibility of alternative treatment approaches, and the prospects for future development. These studies not only provide new insights into the functional role of γ-secretase in BC but also contribute to the advancement and optimization of breast cancer therapies.

2. Structure and functions of the γ-secretase complex and key subunits

2.1. Structure of the key subunits of γ-secretase

γ-secretase is a multi-subunit complex with an aspartic intramembrane protease consisting of four types of core subunits: PSEN, PEN-2, NCSTN, and APH-1. In the human genome, two progerin homologs (PSEN1 and PSEN2) and two APH-1 genes (APH-1a and APH-1b) have been successfully identified. It is noteworthy that the APH-1a gene is able to produce two isoforms by a selective splicing mechanism [10]. Therefore, it can be deduced that there are at least six different configurations of the γ-secretase complex. In recent years, with the application of cryo-electron microscopy, high-resolution structural images of γ-secretase have been obtained. They revealed the recognition and binding mode of the γ-secretase substrate and demonstrated in detail how the active site of γ-secretase carries out the hydrolysis process of proteins. This has opened up a new research path for in-depth analysis of the mechanism of γ-secretase [11,12].

PSEN1 and PSEN2 are structurally similar and share 67 % amino acid homology, together serving as the catalytic core of the γ-secretase complex and containing nine transmembrane regions (TMs) [13]. Among them, the N-terminal fragment (NTF), consisting of TM1 to TM6, forms a horseshoe-like structure that surrounds the C-terminal fragment (CTF), consisting of TM7 to TM9. Two key catalytic aspartic acid residues located on the cytoplasmic side of TM6 and TM7, respectively, are spatially adjacent and penetrate approximately 8 angstroms (Å) into the lipid membrane. PEN-2 is a small protein containing 101 amino acid residues, possessing two predicted transmembrane domains and no signal peptide or known protein structural domains. Its hydrophobic domain 1 and loop domains are located within the water-containing chamber adjacent to the CTF of PSEN. NCSTN is a type I transmembrane glycoprotein containing 709 amino acid residues with a large N-terminal extracellular glycosylation structural domain containing multiple glycosylation sites, as well as a transmembrane region and a very short C-terminal tail. Its extracellular structural domain is divided into a large leaflet, which prevents nonessential cleavage of long substrates by the enzyme, and a small leaflet, which provides a hydrophobic fulcrum. NMR spectroscopy studies have shown that the transmembrane region of NCSTN forms an α-helix in detergent micelles, with a possible conformational change in the N-terminus, a flexible C-terminus, and a portion of the residues that interact with the membrane.APH-1 contains seven transmembrane structures, with an N-terminal and even-numbered loop (loops 2, 4, and 6) facing the lumen of the endoplasmic reticulum, while the C-terminus and odd-numbered loops (loops 1, 3, and 5) are located on the cytoplasmic side [13–20], as illustrated in Fig. 1.

2.2. Functions of the key subunits of γ-secretase

PSEN is a core component of the γ-secretase complex and participates in the shearing of the transmembrane region of the substrate to release the secretory product through the catalytic enzymatic activity of two aspartic acid residues within its transmembrane domain. Upon assembly with other subunits (NCSTN, PEN2, APH-1), PSEN undergoes self-cleavage to form NTF and CTF that constitute the active γ-secretase. This complex is crucial in the processing of amyloid precursor protein (APP) and is responsible for cleaving the C-terminal transmembrane region of APP to generate Aβ42. In addition to γ-secretase function, PSEN is also involved in the regulation of ferritin expression, the secretion of apolipoprotein E, and its interaction with apolipoprotein E, as well as in angiotensin-converting enzyme-mediated Aβ42 to Aβ40 conversion [21–23]. PEN-2, as an essential complex subunit, is involved in assembly and activity regulation. As an essential subunit of the complex, PEN-2 is involved in the regulation of assembly and activity, and its mutation affects the interaction with PSEN, leading to decreased γ-secretase activity, abnormal Aβ production, and accumulation of accelerated cognitive decline and neurological dysfunction, and is associated with the development of familial Alzheimer's disease. PEN-2 plays a key role in neural stem cell maintenance and influences the type switch from apical progenitors to basal progenitors through the Notch signaling pathway [24,25]. NCSTN, another essential subunit, maintains complex stability and is responsible for recruiting and recognizing the substrate, and the large lobes of its extracellular region contain substrate-binding domains, which are overlaid by a specific section of the upper lobes to prevent the entry of non-specific substrates. The large lobe of the extracellular region contains the substrate-binding domain, which is covered by a specific region on the small lobe to prevent non-specific substrates from entering. When the substrate approaches, the large and small lobes move relative to each other, and the specific region moves away, exposing the binding domain for substrate recognition [26]. APH-1 is the fourth subunit of the complex and is involved in the recognition and processing of substrates. The promoter polymorphisms in the APH-1 gene have been associated with an increased risk of sporadic Alzheimer's disease, and the role of APH-1, as a part of the

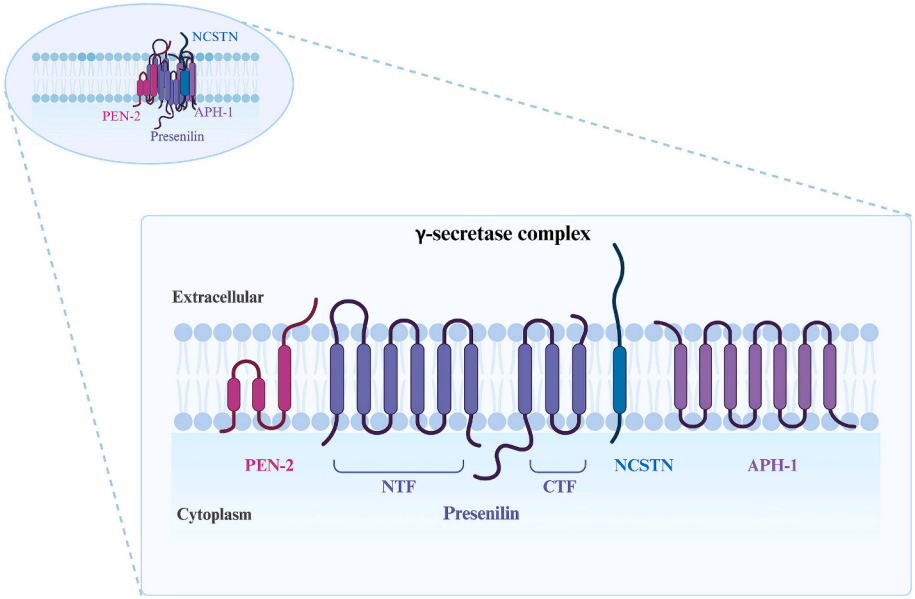


Fig. 1. The structure of the key subunits of γ-secretase. γ-secretase consists of Presenilin, PEN-2, NCSTN and APH-1. Presenilin has nine transmembrane regions (TMs), the N-terminal fragment (NTF) consisting of TM1 to TM6, and the C-terminal fragment (CTF) consisting of TM7 to TM9. PEN-2 has three transmembrane regions, NCSTN has only one transmembrane region and APH-1 has seven transmembrane regions.

γ-secretase complex, is also important for the development of related drugs [27].

2.3. Interactions between key subunits of γ-secretase

The interactions between γ-secretase subunits are dynamic and co-assembled to form large protein complexes responsible for the cleavage and hydrolysis of key transmembrane proteins. The first step in the assembly of the γ-secretase complex is the formation of a stable subcomplex by APH-1 and NCSTN, and the interactions of NCSTN with APH-1 are critical for the stability and activity of the complex. Subsequently, PSEN is added to the subcomplex to form a three-part complex. Critical interactions between TMD4 of PSEN and PEN-2, especially the YNF motif in TMD4, trigger PSEN self-cleavage to generate the NTF and CTF. The addition of PEN-2 is the final step in the assembly of the γ-secretase complex [28,29]. The whole process involves NCSTN and

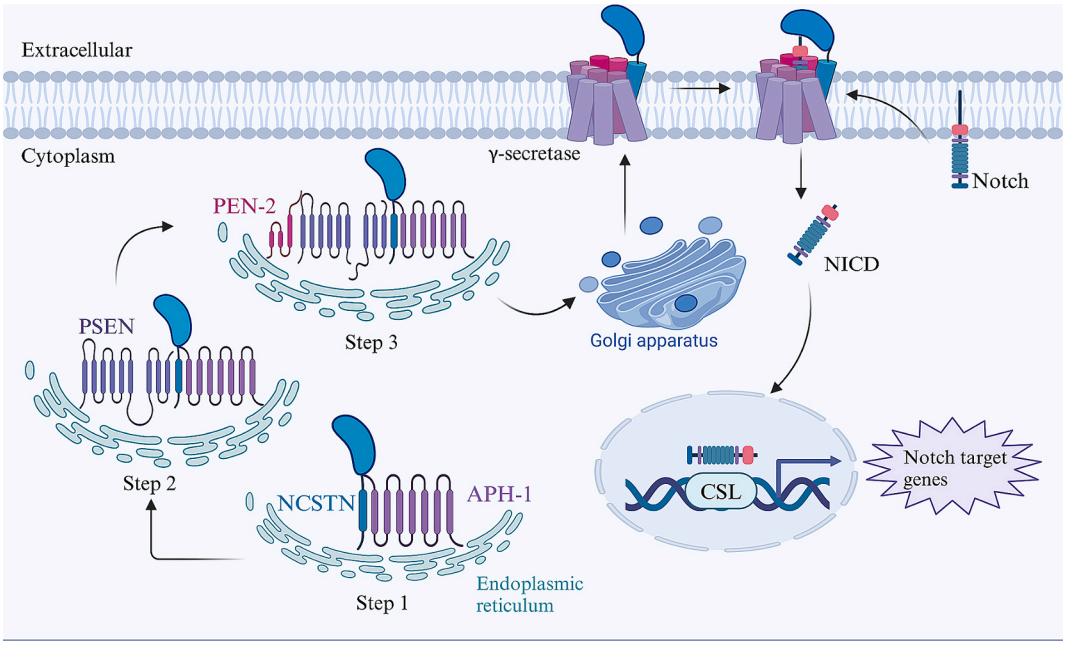


Fig. 2. The process of γ-secretase assembly, activation, and shearing of Notch. The first step of the γ-secretase assembly process is the formation of a stable subunit complex between NCSTN and Aph-1 in the endoplasmic reticulum. In the second step, PSEN is added to the NCSTN-Aph-1 complex. In the third step, the interaction of Pen-2 with PSEN triggers the self-cleavage of PSEN into the NTF and the CTF. Subsequently, the γ-secretase complex is transported to the Golgi for further maturation and stabilization to function as an active complex. Notch binds to the inactive site of PSEN and subsequently moves to the active site and uncoils, forming an ε-cleavage transition state. The extracellular domain of NCSTN covers the entrance to the active site, restricting the entry of substrates longer than 20 Å. γ-secretase performs the S3-site within the transmembrane region of Notch shear, which releases the Notch intracellular structural domain (NICD) into the cytoplasm and subsequently translocates to the nucleus, where it binds to CSL proteins and activates downstream gene expression.

APH-1 interactions, PSEN incorporation, and PEN-2 triggering PSEN self-cleavage to form the active complex, as illustrated in Fig. 2.

γ-secretase achieves recognition, binding, and hydrolysis of more than 90 substrates through subunit interactions and precise regulation of the active site. The substrates are mainly type I transmembrane proteins, such as APP and Notch receptors [28]. Initially, the substrate transmembrane domain (TMD) binds to the inactive site of PSEN. It then moves to the active site and uncoils to form an ε-cleavage transition state [30]. The extracellular domain of NCSTN covers the entrance to the active site and restricts the entry of substrates longer than 20 Å. The TMD2 of PSEN acts as a conduit for the entry of the substrate [31]. The γ-secretase first undergoes TMD *endo*-protease cleavage (ε-cleavage) to release the AICD, followed by further processing of the long Aβ peptide via carboxypeptidase-like cleavages (ζ, γ, γ'), which are performed at three-amino acid intervals, resulting in the final secretion of peptide fragments of 38–43 amino acids in length [28,32], as illustrated in Fig. 2.

The assembly and activity of the γ-secretase complex are regulated by multiple factors, including protein interactions, post-translational modifications, and conformational changes. The synergistic interaction between subunits ensures that γ-secretase can efficiently recognize and process diverse substrates, realizing its versatility in cell biology [33]. Abnormal function of any subunit may affect enzyme activity and interfere with normal cellular physiology. Therefore, the precise regulation of γ-secretase is essential for maintaining cellular homeostasis, and its complex regulatory mechanism not only reflects the depth of cell biology but also provides key targets for BC research and therapy.

3. Abnormal signaling of key subunits of γ-secretase promotes breast cancer progression

3.1. Presenilin gene mutations promote BC development

The current body of research evidence indicates that mutations in the PSEN1 gene exert a significant influence on the pathogenesis of BC. These mutations not only impact genomic stability but also facilitate the aberrant replication of DNA in heterochromatin regions within tumor cells. Firstly, variants in the PSEN gene have been linked to an elevated risk of developing breast cancer. Specific PSEN1 gene variants may enhance γ-secretase activity, which in turn exacerbates abnormalities in the Notch signaling pathway and promotes the development of BC [21,34,35]. Loss-of-function mutations in PSEN1 can result in genomic instability. Certain PSEN1 mutations, for example, lead to a significant decrease in γ-secretase activity. This affects various biological processes in the cell, including the regulation of the cell cycle and the repair of DNA damage. Ultimately, this increases genomic instability and even the risk of cellular carcinogenesis. The L435F mutation in PSEN1 leads to a near-complete loss of γ-secretase activity and exhibits severe neurodegenerative changes that may be associated with genomic instability [36,37]. Secondly, it was demonstrated that microRNA miR-27-3p could effectively inhibit the activation of the Notch signaling pathway and significantly enhance the sensitivity of TNBC cells to the anticancer drug Olaparib. This was achieved by targeting the catalytic subunit of the γ-secretase complex, PSEN1 [38–40], as illustrated in Fig. 3. This finding offers novel insights into the potential treatment of TNBC. Nevertheless, the precise mechanism by which PSEN1 modulates the Notch signaling pathway and the mechanism of this modulation in enhancing the sensitivity of TNBC to Olaparib remains to be elucidated by further comprehensive investigations.

Recent studies have demonstrated that the Trichorhinophalangeal Syndrome Protein I (TRPS1), which is associated with mutations in the PSEN1 gene, induces chromosomal copy number variations by recruiting the APC/C complex. This process regulates aberrant DNA replication in H3K9me3-modified heterochromatin regions by modulating H3K9me3, ultimately resulting in increased genomic instability and tumor cell resistance to therapy. Concurrently, TRPS1 facilitates BC cell proliferation by recruiting the corepressor complex and repressing the transcription of target genes of the Yes-associated protein/TEA domain transcription factors complex (YAP/TEAD). High expression of TRPS1 on the surface of tumor cells synergistically interacts with Programmed Death-Ligand 1 to inhibit T-cell proliferation and function, thereby promoting immune evasion from the tumor. Furthermore, the role of the

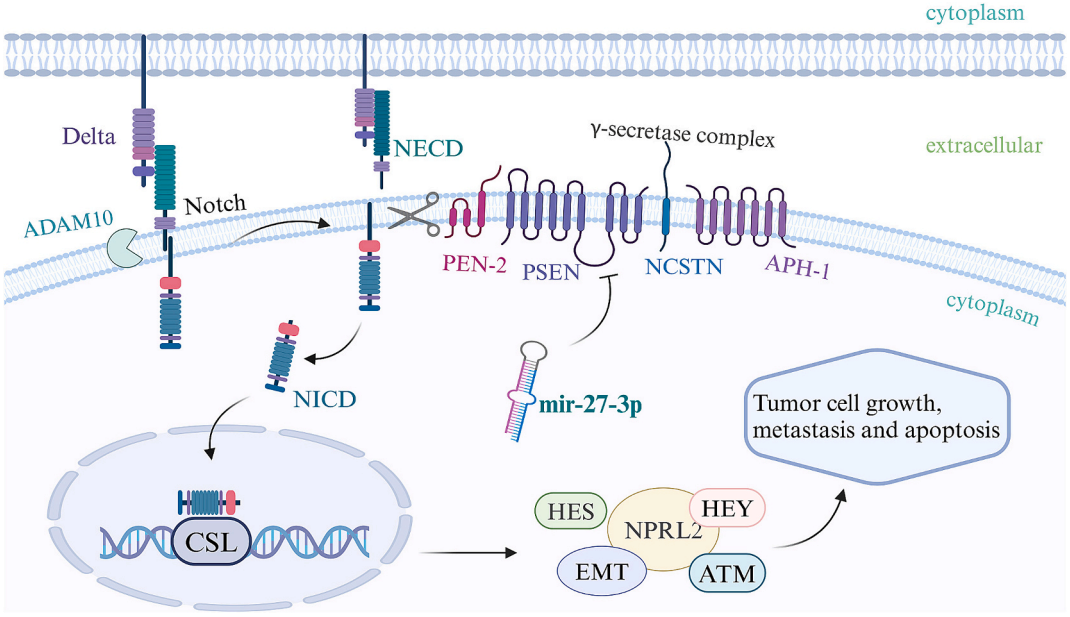


Fig. 3. miR-27-3p targets PSEN1 to inhibit TNBC progression. The microRNA, miR-27-3p, has been shown to target PSEN1, the catalytic subunit of the γ-secretase complex. This results in a decrease in PSEN1 protein levels, an inhibition of γ-secretase activity, a reduction in NICD production, an inhibition of the activation of the Notch signaling pathway, and an effect on the expression of the HES and HEY family genes downstream of Notch that are related to cellular differentiation, proliferation, and apoptosis. Ultimately, this results in an inhibition of the proliferation and survival of TNBC cells. Furthermore, the results of this study indicate that the expression of miR-27-3p enhances the sensitivity of TNBC cells to anticancer drugs by inhibiting the expression of ATM and NPRL2, genes related to drug resistance downstream of the Notch signaling pathway.

TRPS1 protein in tumor development can be described in two ways. TRPS1 inhibits the invasion and metastasis of breast tumor cells by recruiting the nucleosome remodeling and deacetylase complex (NuRD), specifically targeting the TP63 enhancer, and suppressing the expression of TP63, which subsequently leads to the down-regulation of ΔNP63 expression [41–43]. This finding provides a critical molecular biological foundation for further investigations into tumorigenesis, progression, and its evolutionary mechanisms. Additionally, several studies have highlighted the essential role of genomic variant interaction networks in disease pathogenesis. For instance, the simultaneous occurrence of mutations and copy number amplifications in tumor protein 53 and Aurora Kinase A may contribute to resistance to tamoxifen treatment in BC patients by promoting centrosome amplification and inducing aneuploidy [44]. This suggests that interactions among genomic variants significantly impact the efficacy of BC treatments. Furthermore, these findings emphasize the potential for PSEN1 gene mutations to indirectly affect the therapeutic outcomes of BC by influencing genomic stability and interacting with other gene mutations. Therefore, a comprehensive examination of the mechanisms by which PSEN1 gene mutations contribute to BC is essential for developing novel therapeutic strategies and improving patient outcomes, as illustrated in Fig. 4.

3.2. PEN-2 activates AMPK signaling to promote/inhibit BC progression

Abnormal activation of the Notch signaling pathway is a critical factor in the development of BC. The association between the PEN-2 subunit and BC is primarily evidenced by the fact that PEN-2 is involved in maintaining γ-secretase activity, which directly influences the activation of Notch signaling. Additionally, the AMP-activated Protein Kinase (AMPK) signaling pathway plays a pivotal role in the pathogenesis of breast cancer. Research has demonstrated that metformin activates AMPK by targeting the PEN-2 subunit [45], as illustrated in Fig. 5. Activation of AMPK has been associated with the suppression of BC cells, leading to a reduction in BC cell proliferation and the promotion of apoptosis through the inhibition of the mammalian target of the rapamycin signaling pathway. Conversely, decreased AMPK activity has been linked to increased invasion and metastasis of BC cells [46]. AMPK activators stimulate oxidative phosphorylation in TNBC cells while reducing glycolysis, thereby inhibiting tumorigenesis, progression, and metastasis [47]. Furthermore, exosomes derived from highly metastatic breast cancer cells have been shown to inhibit tumor angiogenesis by activating the AMPK signaling pathway and reducing the expression of vascular endothelial growth factor. This inhibition ultimately affects BC growth and metastasis [48]. The activation of AMPK has also been demonstrated to suppress the migration of breast cancer cells and the process of epithelial-mesenchymal transition [49]. The functional mechanism of the PEN-2 subunit in breast cancer therapy may involve multiple dimensions, including the regulation of the Notch signaling pathway through the γ-secretase complex and the activation of AMPK as a target for drugs such as metformin, which in turn influence the metabolism and survival of BC cells.

3.3. The protein expression of NCSTN regulates the development of BC in both directions

There is a strong correlation between the activation of the Notch signaling pathway, the transcriptional regulation of Notch downstream target genes, and the function of the γ-secretase complex in the development and progression of BC. The γ-secretase complex, which includes the Notch receptor and its ligands, plays a pivotal role in regulating BC cell proliferation, apoptosis, invasion, metastasis, relapse, and resistance. NCSTN has two distinct effects on tumor cells, NCSTN induces EMT by activating Notch and PI3K/Akt signaling pathways, enhances tumor cell migration and invasion, promotes tumor cell growth, and inhibits apoptosis [50], as illustrated in Fig. 6. In breast cancer cells, NCSTN activates the Notch signaling pathway by enhancing γ-secretase activity, leading to the upregulation of the expression of downstream target genes such as HES1, HEY1, MYC and P21, and promoting the proliferation and survival of breast cancer cells. In addition, NCSTN maintains tumor stem cell properties by affecting the Notch signaling pathway, thereby influencing breast cancer recurrence and drug resistance. In some cases, when the expression level of NCSTN is reduced or its function is inhibited, it suppresses the activation of the Notch signaling pathway, thereby inhibiting tumor cell proliferation and

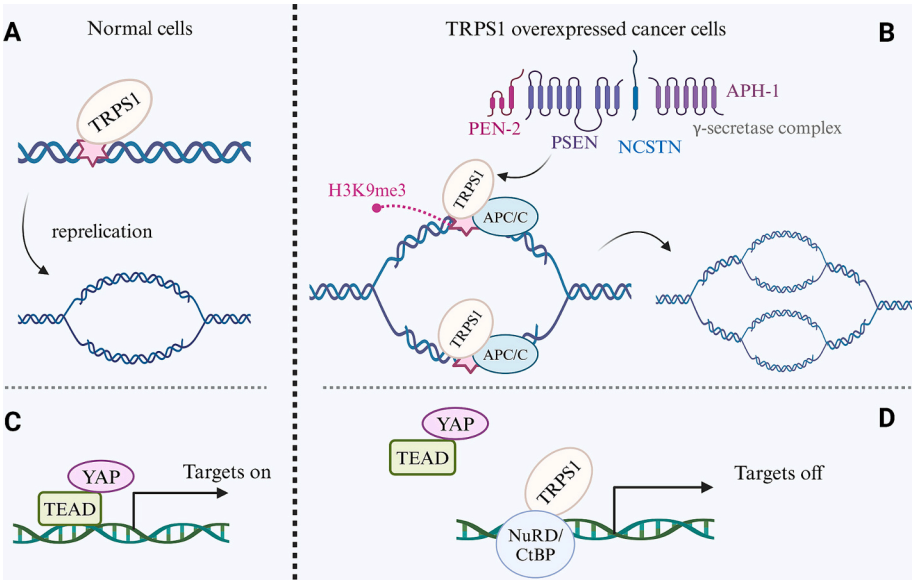


Fig. 4. PSEN1 gene mutation-associated TRPS1 protein leads to genomic instability and increased promotion of BC cell growth. A. In the typical nucleus, TRPS1 binds to replication initiation factors and plays a crucial role in regulating DNA replication. B. In cells exhibiting elevated TRPS1 expression, the TRPS1 protein oversees aberrant DNA replication in H3K9me3-modified heterochromatin regions by recruiting the APC/C complex, which ultimately leads to increased genomic instability. C. In the normal nucleus, the YAP/TEAD complex binds to the promoter regions of target genes, thereby activating the transcription of YAP/TEAD target genes. D. In cells with high TRPS1 expression, TRPS1 promotes BC cell growth by recruiting nucleosome remodeling and deacetylase/C-terminal binding protein complex (NuRD/CtBP) to the regulatory regions of YAP/TEAD target genes, thereby repressing the transcription of YAP/TEAD target genes.

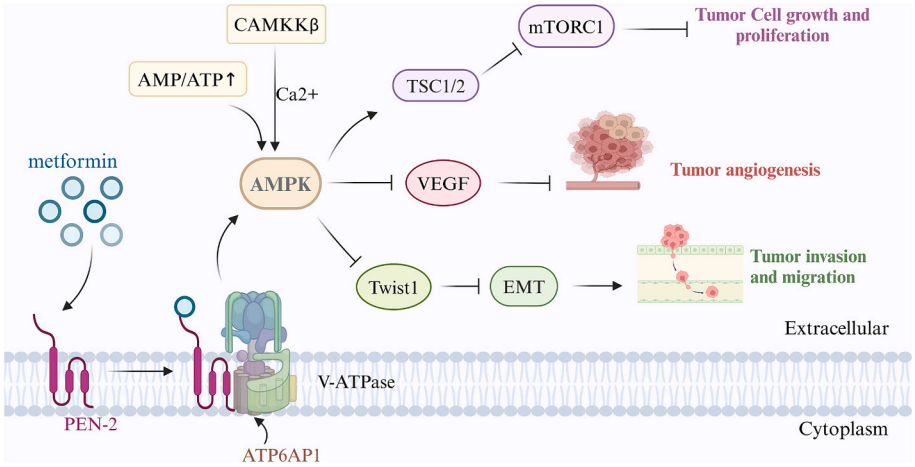


Fig. 5. Metformin targets PEN-2 to activate AMPK to inhibit BC progression. Once inside the cell, metformin binds to the PEN-2 protein. PEN-2 then interacts with the auxiliary factor ATP6AP1 of the Vacuolar-type ATPase (V-ATPase), which inhibits V-ATPase activity. This results in changes to the acidic environment within the lysosome, which activates the AMPK signaling pathway. Increased intracellular AMP or ADP levels, as well as elevated intracellular Ca^{2+} levels, can also activate AMPK directly by activating calmodulin-dependent protein kinase kinase β (CAMKKβ). Once activated, AMPK can phosphorylate and activate the tuberous sclerosis complex 1/2 (TSC1/2), thereby inhibiting the activity of mTORC1 and BC proliferation. AMPK activation also reduces the expression of vascular endothelial growth factor (VEGF), thereby inhibiting tumor angiogenesis. Furthermore, AMPK activation inhibits Twist-related protein 1 (Twist1), suppressing the EMT process in BC and preventing BC cell proliferation while promoting apoptosis.

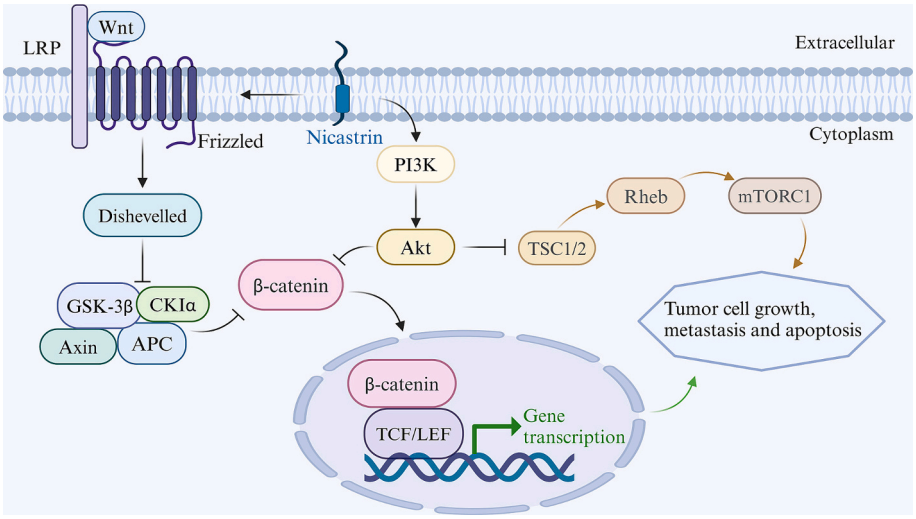


Fig. 6. NCSTN overexpression activates PI3K/Akt and Wnt/β-catenin signaling pathways to regulate tumor cell proliferation and metastasis. The overexpression of NCSTN has been shown to enhance AKT phosphorylation, which subsequently activates the mammalian target of the rapamycin signaling pathway, promoting cell proliferation and survival. Furthermore, the activation of AKT inhibits the degradation of β-catenin, leading to its excessive accumulation in the cytoplasm and subsequent translocation to the nucleus. Within the nucleus, β-catenin binds to TCF/LEF transcription factors and activates the target genes of the Wnt/β-catenin signaling pathway, thereby promoting tumor cell growth and inhibiting the apoptosis of tumor cells.

inducing apoptosis. The dual effects of NCSTN on tumor cells are mainly dependent on its functional status in the γ-secretase complex and need to be analyzed in relation to the specific cell type and tumor environment [51–53].

The potential of NCSTN in tumor immunotherapy is currently under investigation. For instance, the precise function of NCSTN in chimeric antigen receptor macrophage therapy, an innovative approach to tumor immunotherapy, remains unclear. Nevertheless, it is hypothesized that NCSTN may influence the tumor microenvironment and immune response [54]. Furthermore, NCSTN has been shown to regulate tumor cell proliferation and metastasis by modulating the Wnt/β-catenin signaling pathway, as illustrated in Fig. 6. In certain instances, the expression and activity of NCSTN are regulated by the Wnt/β-catenin signaling pathway, which establishes a positive feedback loop that promotes tumor development [55]. In summary, the expression levels of NCSTN subunits in tumor cells serve as crucial biomarkers that influence tumor progression through various mechanisms, including cell proliferation, apoptosis, and the maintenance of stem cell properties. Modulating NCSTN activity through pharmacological interventions may provide promising new avenues for the treatment of BC. However, the precise implementation and efficacy of these interventions require further validation through clinical studies.

3.4. *APH-1 regulates a key protein network to influence BC growth*

The association between the APH-1 subunit and BC is primarily evident in its influence on the activity of the γ-secretase complex and the Notch signaling pathway. First, as a crucial subunit of the γ-secretase complex, APH-1 is involved in the proteolytic processing of numerous substrates that play essential roles in cell proliferation and

differentiation [51]. In the context of BC, APH-1 impacts the proliferation cycle of tumor cells by regulating the expression of cell cycle-related proteins, including cyclin-dependent kinases and cyclins. This regulation, in turn, affects the rate of tumor growth. Additionally, APH-1 indirectly influences tumor cell proliferation and invasion by modulating the activation of the Notch signaling pathway. Furthermore, APH-1 affects tumor cell invasion and migration, regulating the dissemination of tumor foci by influencing the activity of matrix metalloproteinases [56]. Furthermore, APH-1 hinders the blood supply and nutritional support of tumors while obstructing distal metastasis of tumor foci by inhibiting the expression of vascular growth factors and promoting the expression of vascular growth inhibitory factors. Additionally, APH-1 influences the apoptotic process of tumor cells by regulating the expression or activity of apoptosis-related proteins (e.g., Bcl-2, Bax, Caspases) [57], as illustrated in Fig. 7. In light of these findings, APH-1 emerges as a crucial regulator of tumor cell growth, metastasis, and apoptosis, with the potential to serve as a promising therapeutic target in BC [18,58].

The transcription of APH-1A, an isoform of APH-1, may be regulated by hypoxia-inducible factor-1α (HIF-1α), a key transcription factor under hypoxic conditions. HIF-1α binds to hypoxia-responsive elements of target genes, thereby inducing transcriptional upregulation of related genes. In hypoxic conditions, the stability of HIF-1α is enhanced, enabling it to enter the nucleus and form a heterodimer with HIF-1β. This complex localizes to the hypoxia response element of the APH-1A gene, thereby promoting its transcription, as illustrated in Fig. 8. Given that BC cells are frequently situated within a hypoxic microenvironment, this may result in the activation of HIF-1α and an increased expression of APH-1A, which in turn affects the function of γ-secretase. This alteration may render BC cells more adapted to the hypoxic milieu and facilitate their growth and invasion by influencing the function of γ-secretase [59,60]. Future investigations must elucidate the mechanism of APH-1's role in tumor development and potential therapeutic strategies targeting APH-1, thereby providing novel concepts and approaches for the treatment of TNBC.

4. γ-secretase inhibitors and the possibility of BC therapy

4.1. γ-secretase inhibitors facilitate the development of emerging breast cancer treatment strategies

The current research on γ-secretase inhibitors encompasses a diverse array of areas, including inhibition strategies, drug design, gene editing technology, and clinical trials. The research is centered on the development of small-molecule γ-secretase inhibitors (GSIs) and γ-secretase modulators (GSMs). Recent research advances include the elucidation of the atomic-level cryo-electron microscopy structures of γ-secretase and GSI (RO4929097, BMS906024, MK-0752, and L-685,458) and GSM (E2012) that have entered clinical trials, clarifying the molecular mechanisms by which γ-secretase recognizes and acts on different types of inhibitors and modulators [61,62]. Additionally, the molecular mechanisms by which γ-secretase recognizes and acts on different kinds of inhibitors and regulators have been elucidated. Specifically, L-685,458 can directly coordinate two key catalytic aspartic acid residues in PSEN1, while E2012 binds to the variable site of γ-secretase and prevents the β-strand of amyloid precursor protein or Notch from binding to it, thereby interfering with the substrate recruitment process [27,62,63], as shown in Fig. 9. These structural findings provide a precise blueprint for understanding the regulatory mechanism of γ-secretase activity and establish a foundation for the development and optimization of next-generation GSIs and GSMs. These studies contribute to the design of more substrate-selective GSIs and GSMs that promote further cleavage of Aβ42 into shorter and safer peptides [12]. In addition, gene editing technology is widely used, particularly the CRISPR-Cas9 system, to knock out or modify genes related to γ-secretase activity, such as PSEN1, to study their role in disease. This may have practical application value in the treatment of diseases related to γ-secretase [64,65].

In the field of BC therapy, notable advancements have been made in the study of GSIs, particularly the development of RO4929097, a GSI for patients with advanced, metastatic, or recurrent TNBC. RO4929097 exerts its anti-fibrotic and anti-EMT protective effects by inhibiting Notch and ERK1/2 signaling pathways while exhibiting significant antitumor effects both in vivo and in vitro. In addition, RO4929097 possesses immunomodulatory effects, reducing the production of inflammatory cytokines and increasing the production of IL-6 [66]. The

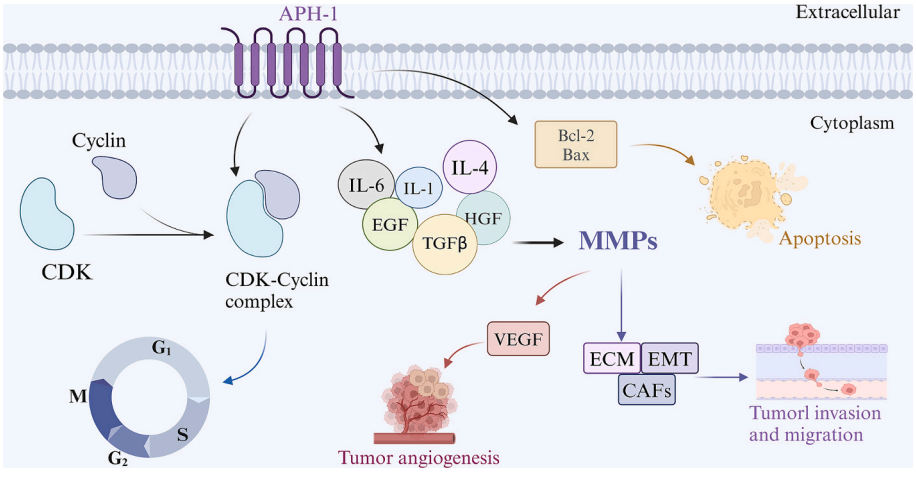


Fig. 7. APH-1 affects the cleavage of multiple substrates and thus the proliferation, differentiation, and apoptosis of tumor cells. APH-1 influences the proliferation cycle of tumor cells by regulating the expression of key molecules, such as cyclin-dependent kinase (CDK) and cyclin. It also controls the production of matrix metalloproteinases (MMPs) by affecting the activity of growth factors such as interleukin-1 (IL-1), interleukin-4 (IL-4) and interleukin-6 (IL-6), as well as transforming growth factors such as epidermal growth factor (EGF), hepatocyte growth factor (HGF) and transforming growth factor beta (TGF-β). This regulates the extracellular matrix (ECM), epithelial-mesenchymal transition (EMT), cancer-associated fibroblasts (CAFs) and vascular endothelial growth factor (VEGF), thereby influencing tumor cell invasion, migration and angiogenesis. Furthermore, APH-1 influences tumor cell apoptosis by regulating the expression or activity of the apoptosis-related proteins Bcl-2 and Bax.

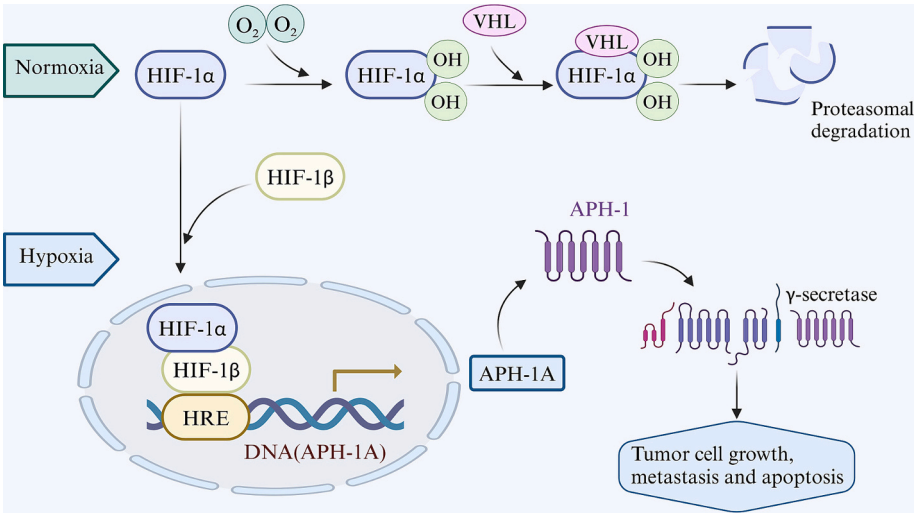


Fig. 8. Expression of APH-1A in a hypoxic environment is regulated by HIF-1α. In normoxic concentrations, HIF-1α binds to the von Hippel-Lindau protein, which results in the ubiquitination of HIF-1α and subsequent proteasomal degradation. In hypoxic conditions, the stability of HIF-1α is enhanced, enabling its entry into the nucleus, where it forms a heterodimer with HIF-1β. This complex localizes to the hypoxia response element of the APH-1A gene, promoting transcription. This process affects the function of γ-secretase, which in turn promotes the growth and invasion of breast cancer cells. γ-secretase inhibitors and the possibility of BC therapy.

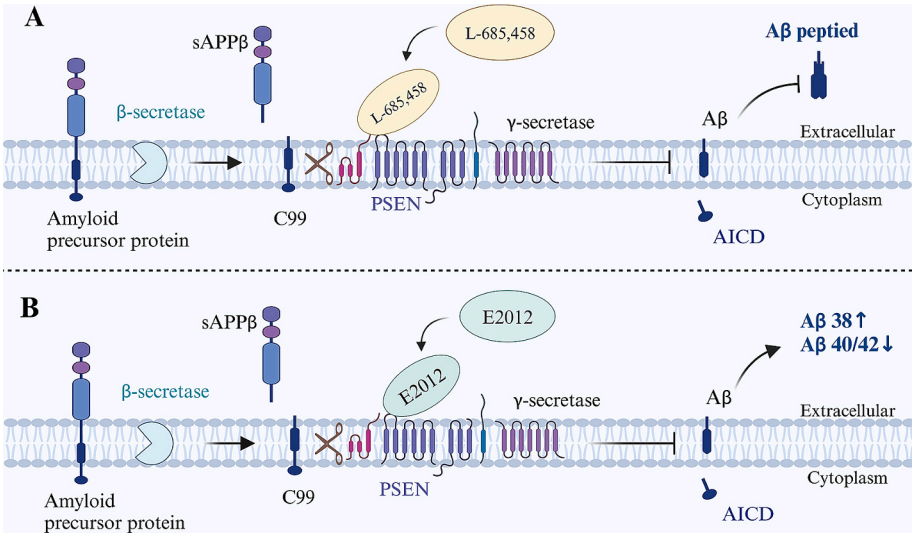


Fig. 9. Regulation of γ-secretase activity by L-685,458 and E2012 interferes with the substrate recruitment process. A. APP is initially cleaved by β-secretase into a 99-residue peptide segment, which is then subjected to a multi-step enzymatic cleavage by γ-secretase. L-685,458 functions as a γ-secretase inhibitor. A γ-secretase inhibitor, it effectively inhibits the activity of γ-secretase by occupying the active site in its PSEN, thereby mimicking the transition state of the γ-secretase catalytic process. B. E2012 binds to the variable site of γ-secretase, increasing the possibility of cleaving Aβ into shorter fragments. In the presence of E2012, the yields of Aβ40 and Aβ42 were found to be reduced, while the yield of Aβ38 was observed to be elevated.

primary objective of the study was to evaluate the antitumor efficacy of RO4929097 using the response evaluation criteria in solid tumors criteria and 6-month progression-free survival. The study also included the secondary objectives of safety and tolerability assessment of RO4929097, as well as the expression of Notch biomarkers in TNBC patients and the interaction of these biomarkers with RO4929097 responsiveness and its potential toxic response [67,68]. These studies provide a scientific basis for the use of γ-secretase inhibitors in breast cancer treatment. In a separate study, NMK-T-057 demonstrated considerable inhibition of the proliferation and colony-forming capacity of an array of breast cancer cells (including MDA-MB-231, MDAMB-468, 4T1, MCF-MC) while exhibiting minimal toxicity in non-cancerous cells (e.g., MCF-10A cells and peripheral blood mononuclear cells). The results of the fluorescence assay of γ-secretase activity demonstrated that NMK-T-057 was capable of effectively inhibiting γ-secretase activity [69,70]. Consequently, NMK-T-057 is anticipated to serve as a promising anti-breast cancer therapy. Finally, the inhibitory effect on the growth of breast tumors was investigated by the combined application of two γ-secretase inhibitors, MK-0752 and RO4929097, and IL-6. It was found that the expression level of Notch-3 was significantly increased in BC stem cells, and the combined application of the γ-secretase inhibitors and IL-6 antagonists successfully reduced the expression of IL-6 in BC stem cells and inhibited tumor growth [71,72]. We have also summarized the anticancer drugs that may target γ-secretase, as shown in Table 1. These findings provide an important theoretical basis for developing new strategies for BC treatment.

Table 1
List of γ-secretase inhibitors related to anticancer.

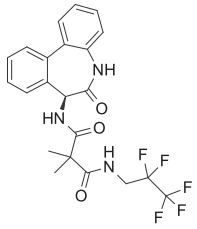
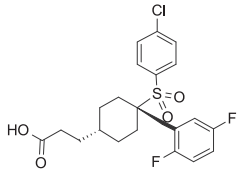
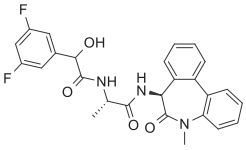
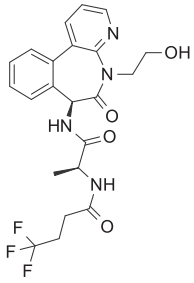
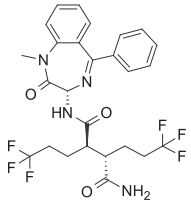
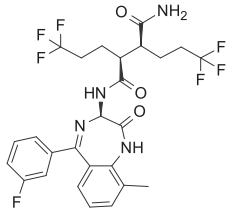
Agents	Chemical structure	Cancer	Study stage	Ref.
RO4929097 (RG-4733)		Metastatic colorectal cancer	Phase II	[73]
		Pancreatic ductal adenocarcinoma	Phase II	[74]
		Metastatic melanoma	Phase II	[75]
		Epithelial ovarian cancer	Phase II	[76]
		Recurrent/progressive Glioblastoma	Phase II	[68]
		Advanced solid tumors	Phase Ib	[77]
		Glioma	Phase I	[78]
		Recurrent malignant glioma	Phase I	[79]
		Breast cancer	Phase Ib	[80]
		Advanced sarcoma	Phase Ib	[67]
		Oral cancer	Phase II	[81]
		Lung adenocarcinoma	Phase II	[82]
		Multiple myeloma	Phase II	[83]
		Prostate cancer	Phase II	[84]
MK-0752		Pancreatic ductal adenocarcinoma	Phase I	[85]
		Advanced solid tumors	Phase I	[86]
		Ovarian cancer	Phase I	[87]
		Colorectal cancer	Phase I	[88]
		Breast cancer	Phase I	[89]
		Lung adenocarcinoma	Phase I	[90]
		Glioma	Phase I	[91]
		Melanoma	Phase I	[92]
		Head and neck squamous cell carcinoma	Phase I	[93]
		Uterine leiomyosarcoma	Phase I	[94]
LY411575		Triple-negative breast cancer	Preclinical studies	[71]
		Liver cancer	Preclinical studies	[95]
		Oral cancer	Preclinical studies	[81]
		Lung adenocarcinoma	Preclinical studies	[96]
Crenigacestat (LY3039478)		Adenoid cystic carcinoma	Phase I	[97]
		Advanced or metastatic cancer	Phase I	[98]
		Advanced or metastatic solid tumors	Phase Ib	[99]
		Advanced solid tumors	Phase I	[100]
		T-cell acute lymphoblastic leukemia	Phase I	[101]
		Intrahepatic cholangiocarcinoma	Phase II	[102]
		Multiple myeloma	Phase I	[103]
		Soft tissue sarcoma	Phase II	[104]
		Head and neck squamous cell carcinoma	Phase II	[105]
		Osteosarcoma	Phase II	[106]
		Gastric cancer	Phase II	[107]
BMS-906024 (AL101)		Triple-negative breast cancer	Phase II	[108]
		Adenoid cystic carcinoma	Phase Ib	[109]
		Non-small-Cell Lung Cancer	Preclinical studies	[110]
		Lung adenocarcinoma	Preclinical studies	[111]
		Acute lymphoblastic leukemia	Preclinical studies	[112]
BMS-986115 (AL102)		Advanced solid malignancies	Phase I	[113]

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Table 1 (*continued*)

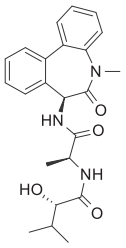
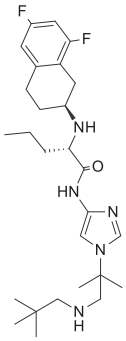
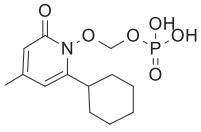
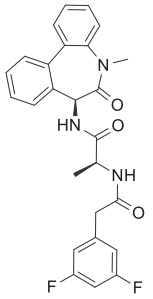
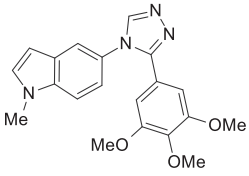
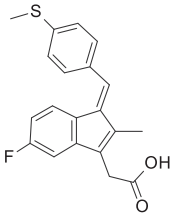
Agents	Chemical structure	Cancer	Study stage	Ref.
LY900009		Advanced cancer	Phase I	[114]
		Ovarian cancer	Phase I	[114]
Nirogacestat (PF-03084014)		Desmoid tumor	Phase III	[115]
		T-cell acute lymphoblastic leukemia	Phase I	[116]
		Advanced solid malignancies	Phase I	[117]
		Chronic lymphocytic leukemia	Phase I	[118]
		Liver cancer	Phase II	[119]
		Prostate cancer	Preclinical studies	[120]
		Triple-negative breast cancer	Phase II	[121]
		Multiple myeloma	Phase I	[122]
		Pancreas	Phase II	[123]
		Melanoma	Phase I	[124]
		Tracheal adenoid cystic carcinoma	Preclinical studies	[125]
Fosciclopirox (CPX-POM)		Urothelial cancer	Phase II	[126]
YO-01027 (Dibenzazepine)		Colorectal cancer	Preclinical studies	[127]
NMK-T-057		Breast cancer	Preclinical studies	[128]
Sulindac sulfide		Colorectal cancer	Preclinical studies	[129]
		Thyroid cancer	Preclinical studies	[130]
		Triple-negative breast cancer	Preclinical studies	[131]
		Head and neck cancer	Preclinical studies	[132]

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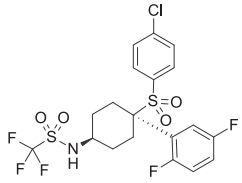
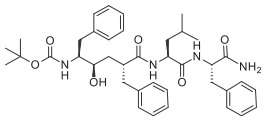
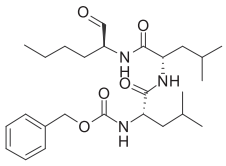
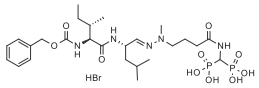
Table 1 (*continued*)

Agents	Chemical structure	Cancer	Study stage	Ref.
MRK-560		Acute lymphoblastic leukemia	Preclinical studies	[133]
L-685458		Lung cancer Breast cancer Tongue carcinoma	Preclinical studies Preclinical studies Preclinical studies	[134] [135] [136]
GSI-I (Z-LLNle-CHO)		Prostate cancer Acute lymphoblastic leukemia Breast cancer Alveolar rhabdomyosarcoma	Phase I Phase I Phase I Phase I	[137] [138] [135] [139]
BT-GSI (HY-145428)		Multiple myeloma	Preclinical studies	[140]

4.2. γ-secretase inhibitors show promise as an effective strategy for BC treatment

γ-secretase inhibitors targeting the Notch signaling pathway have shown potential efficacy in BC therapy, and γ-secretase inhibitors are expected to be a new strategy for BC treatment. With the in-depth study of the γ-secretase complex and its mechanism of interaction with small molecule drugs, an extract of *Cimicifuga dahurica* (CREE) was able to induce apoptosis by activating the endogenous apoptotic pathway, and the p38 mitogen-activated protein kinase (MAPK) signaling pathway, and inhibit the proliferation, migration, and invasion of MDA-MB-231 and MCF-7 of BC cells [141], as shown in Fig. 10. By forming a tight bond with the active site of PSEN1, a pivotal subunit of the γ-secretase complex, Cimigenoside, a monomer derived from the CREE, effectively inhibits the activity of PSEN1. This leads to a reduction in the shearing activity of the γ-secretase complex on the Notch receptor, which in turn affects the activation of the Notch pathway. This interruption in the onset and development of BC is a result of these combined effects

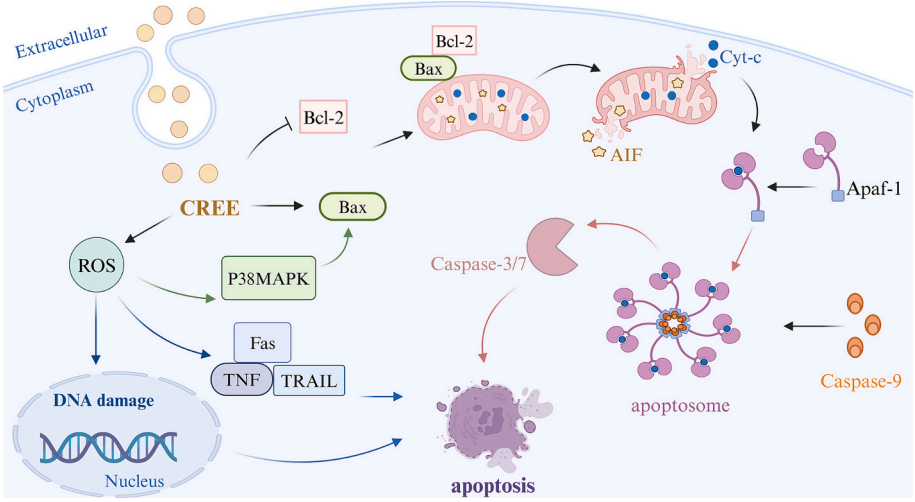


Fig. 10. CREE activates the endogenous apoptotic pathway and p38MAPK signaling pathway to inhibit BC cell proliferation, migration, and invasion. CREE was able to upregulate the expression of the pro-apoptotic protein Bax and downregulate the expression of the anti-apoptotic protein Bcl-2. These changes led to an increase in the permeability of the mitochondrial membrane and the release of cytochrome C (Cyt—C) and apoptosis-inducing factor (AIF) into the cytosol. In the presence of ATP/dATP, the released Cyt-C is able to bind to apoptosis-associated factor 1 (Apaf-1) and further bind to Caspase-9 to form an apoptosome. The activation of Caspase-9 has been demonstrated to directly cleave and activate Caspase-3/7, thereby initiating a cascade of subsequent caspases that ultimately results in the process of apoptosis. Furthermore, CREE has been demonstrated to induce apoptosis by increasing intracellular reactive oxygen species (ROS) levels, activating p38MAPK, and up-regulating the expression of the pro-apoptotic protein Bax. Furthermore, CREE has been demonstrated to promote apoptosis by increasing ROS levels and activating death receptors such as Fas, TNF, and TRAIL, whilst concomitantly inhibiting the DNA repair system.

[142,143]. Although natural-origin active ingredients have become a prominent choice for targeted drug candidates in breast cancer treatment due to their low toxicity and high efficacy, the discovery of γ-secretase inhibitors of natural origin remains limited. The specific mechanism of action and effects of these inhibitors require further verification [144]. In the future, the discovery of additional γ-secretase inhibitors of natural origin is anticipated to be a significant focus in BC targeted therapy research.

The application strategies of γ-secretase inhibitors in BC therapy are showing diversification. Combining γ-secretase inhibitors with endocrine therapeutic agents and CDK4/6 inhibitors, among others, can significantly improve therapeutic efficacy [71,145,146]. Faced with the clinical challenge of chemotherapy resistance, γ-secretase inhibitors are seen as a possible solution aimed at overcoming or delaying the emergence of resistance by combining them with targeted drugs [7]. According to the specific conditions of patients' hormone receptor status, HER2 status, and menopausal status, selecting the appropriate combination regimen of γ-secretase inhibitors and other therapeutic means to implement individualized treatment is the key direction of current BC treatment [147]. γ-secretase inhibitors have the potential to be employed in neoadjuvant and adjuvant therapy, particularly in the treatment of tumor types that are resistant to standard therapeutic regimens or possess specific molecular signatures. Monitoring the efficacy of γ-secretase inhibitors in real-time is crucial for evaluating the therapeutic effect and adjusting the treatment regimen promptly based on the assessment results. As we gain deeper insights into the mechanisms of action and clinical efficacy of γ-secretase inhibitors, future treatment strategies will be further refined and optimized.

The application of γ-secretase inhibitors in BC therapy shows promise but still faces a series of challenges. (1) Specificity issue: γ-secretase is involved in Notch signaling and other biological processes. Therefore, it is of particular importance to develop inhibitors that are highly specific in targeting γ-secretase to avoid interference with other key pathways [27]. (2) Risk of side effects: APP is a substrate for γ-secretase, and inhibition of γ-secretase interferes with the normal processing of APP, which in turn increases the risk of developing other diseases in BC patients [148]. (3) Problem of drug resistance: As is the case with other cancer treatment drugs, the long-term use of γ-secretase inhibitors may result in the development of drug resistance in cancer cells, thereby reducing the efficacy of the treatment regimen [149]. (4) The impact of adverse drug reactions on adherence to treatment: Adherence to endocrine therapy may be compromised by adverse drug reactions affecting the skeletal, joint, muscular, gynecological, and cardiovascular systems. It is of the utmost importance to manage these adverse reactions during treatment effectively [150]. (5) Individual variability of patients: The response of different patients to γ-secretase inhibitors varies, necessitating that medical professionals conduct individualized assessments and treatments in clinical applications [151]. (6) The significance of therapeutic monitoring and assessment: Throughout treatment, it is essential to evaluate the therapeutic impact by monitoring the patient's response to γ-secretase inhibitors and modifying the therapeutic regimen following the assessment outcomes. This process necessitates the utilization of efficacious biomarkers and assessment instruments to guarantee treatment optimization [152].

5. Discussion and prospect

The function of γ-secretase in BC is complex and significant. The individual subunits have distinct roles within the enzyme complex, collectively regulating the core signaling pathways that are intimately associated with BC development. (1) PSEN, which constitute the core of γ-secretase, exist in a dimeric form. It is directly involved in the substrate cleavage process and represents a crucial link in the biological function of γ-secretase. Abnormal expression or mutation of PSEN is more common in BC. Specific PSEN gene variants may alter the function of γ-secretase, affect the normal regulation of the Notch signaling pathway, and promote the development of BC. PSEN1 gene mutation may also indirectly affect the therapeutic effect of BC by affecting the stability of the genome and the interaction with other genes [44,153]. (2) PEN-2, functioning as a co-subunit of γ-secretase, plays a role in maintaining the stability of the γ-secretase complex through interactions with PSEN and NCSTN. Additionally, it enhances the activity of γ-secretase by promoting the correct folding and localization of PSEN proteins, which in turn affects Notch signaling. Furthermore, PEN-2 serves as a target for drugs such as metformin, activating AMPK and influencing the metabolism and survival of tumor cells [154,155]. (3) NCSTN plays a pivotal role in the γ-secretase complex, which is responsible for substrate recognition and binding. This ensures that the substrate is precisely guided to the active center of γ-secretase. The expression level of NCSTN is an important biomarker, and NCSTN abnormality or functional variability may affect the efficiency of substrate cleavage and indirectly influence the developmental process of BC cells [50,53]. (4) APH-1 functions as an assisting subunit of γ-secretase, forming a stable enzyme complex through interactions with PSEN and NCSTN. APH-1 regulates tumor growth and proliferation in BC by affecting the cell cycle, signaling pathways, tumor cell migration, invasive ability, and the tumor microenvironment. Consequently, APH-1 represents a potential target for BC therapy [10].

The γ-secretase subunit has the potential to be a valuable tool in the field of breast cancer therapy. A comprehensive examination of the structure of γ-secretase and its substrate complex may elucidate the molecular mechanism by which γ-secretase accurately identifies and shears substrates, thereby providing a crucial structural foundation for developing targeted breast cancer drugs. The creation of substrate-selective inhibitors may have a beneficial impact on breast cancer therapy while circumventing the adverse effects associated with the inhibition of the Notch signaling pathway [6]. Deepening the understanding of the mechanism of action, strengths and weaknesses, and possible binding sites of γ-secretase inhibitors can help optimize drug design, enhance therapeutic efficacy, and reduce side effects [156]. Mutations in γ-secretase, especially PSEN, have been shown to be associated with the development of a variety of diseases. Therefore, drug design targeting γ-secretase subunits may provide new strategies for BC therapy. Exploring the efficacy of γ-secretase inhibitors when combined with other drugs, such as endocrine therapeutic agents, CDK4/6 inhibitors, and Poly (ADP-ribose) Polymerase inhibitors, may lead to the discovery of more effective combination therapy options [157]. The objective is to elucidate the mechanisms by which BC cells develop resistance to γ-secretase inhibitors and to investigate strategies to overcome resistance and enhance the long-term therapeutic effects of drugs. Additionally, the search is for biomarkers associated with γ-secretase activity and predictors of patient response to treatment, with the goal of developing more precise and individualized treatment plans [89].

In conclusion, the various subunits of γ-secretase function collectively to regulate signaling pathways that are intimately associated with BC progression by interacting with each other during the development of BC. While the precise mechanism of action of certain γ-secretase subunits in BC remains unclear, there is compelling evidence that aberrant γ-secretase function is associated with the malignant progression of BC and drug tolerance. Further investigation of γ-secretase and its subunits may yield novel targets and strategies for BC treatment.

CRediT authorship contribution statement

Ran Xu: Writing – original draft, Writing – review & editing. **Xin Yang:** Supervision, Writing – review & editing. **Kuo Yao:** Visualization, Investigation. **Ke-Fan Yang:** Visualization, Investigation. **Li-Zhi Hu:** Visualization, Investigation. **Xiang-Yi Zhan:** Supervision, Writing – review & editing. **Ming-Sheng Zhou:** Supervision, Writing – review & editing. **Hui Jia:** Funding acquisition, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare no competing interests.

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Data availability

No data was used for the research described in the article.

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