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Review

Inhibition of γ-secretase/Notch pathway as a potential therapy for reversing cancer drug resistance

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ABSTRACT

The mechanism of tumor drug resistance is complex and may involve stem cell maintenance, epithelial-mesenchymal transition, the activation of survival signaling pathways, transporter protein expression, and tumor microenvironment remodeling, all of which are linked to γ-secretase/Notch signaling. Increasing evidence has shown that the activation of the γ-secretase/Notch pathway is a key driver of cancer progression and drug resistance development and that γ-secretase inhibitors (GSIs) may be the most promising agents for reversing chemotherapy resistance of tumors by targeting the γ-secretase/Notch pathway. Here, we systematically summarize the roles in supporting γ-secretase/Notch activation-associated transformation of cancer cells into cancer stem cells, promotion of the EMT process, PI3K/Akt, MEK/ERK and NF-κB activation, enhancement of ABC transporter protein expression, and TME alteration in mediating tumor drug resistance. Subsequently, we analyze the mechanism of GSIs targeting the γ-secretase/Notch pathway to reverse tumor drug resistance and propose the outstanding advantages of GSIs in treating breast cancer drug resistance over other tumors. Finally, we emphasize that the development of GSIs for reversing tumor drug resistance is promising.

1. Introduction

Poor clinical prognosis, metastasis, and recurrence are important factors contributing to high cancer mortality, all of which are associated with oncologic chemotherapy resistance. Therefore, reducing tumor chemoresistance is the key to improving survival rates in cancer patients. Currently, mechanistic studies that involve tumor drug resistance mainly focus on those aspects: atypical activation of the Notch pathway, self-renewal and self-healing properties of cancer stem cells (CSCs), epithelial-mesenchymal transition (EMT) of cells, PI3K/Akt, MEK/ERK and NF-κB pathway activation, drug transport function of ATP-binding cassette (ABC) proteins, and the influence of tumor microenvironment (TME). Interestingly, all the above-mentioned mechanisms of tumor drug resistance are intricately linked to the γ-secretase/Notch signaling axis.

It has been suggested that tumor cells may escape from anti-tumor therapy and produce drug resistance to tumors through the following ways: Firstly, the drugs that can kill cancer cells may be less effective in killing CSCs. It has been shown that some hormones released from cancer cells may promote the transformation of cancer cells to CSCs, as a result, drug resistance of tumors has developed [1]. Next, the accelerated EMT process may enhance the metastatic and invasive capacity of cancer cells. Thirdly, the activation of the PI3K/Akt and NF-κB pathway promotes cancer cell proliferation and anti-apoptosis properties,

Abbreviations: ABC, ATP-binding cassette transporter; ALDH, aldehyde dehydrogenase; AP-1, activator protein 1; APH-1, anterior pharynx-defective; BCSCs, breast cancer stem cells; CR, complete response; CSCs, cancer stem cells; EMT, epithelial mesenchymal transition; 5-FU, 5-fluorouracil; GCCT, GSIs combined with conventional therapy; GSIs, γ-secretase inhibitors; HCC, hepatocellular carcinoma; HER2, human epidermal growth factor receptor-2; HIF, hypoxia-inducible factor; KLF4, Krüppel-like factor 4; mAbs, monoclonal antibodies; NCST, nicastrin; NECD, Notch extracellular domain; NICD, Notch intracellular domain; NSCLC, non-small cell lung cancer; PD, progressive disease; PEN-2, Presenilin enhancer; PIP_2, phosphatidylinositol-4,5-bisphosphate; PIP_3, phosphatidylinositol-3,4,5-trisphosphate; PR, partial response; PSEN, Presenilin; RR, radiographic responses; SD, stable disease; SPP, signal peptides peptidase; SPPL, signal peptide peptidase-like; T-ALL, T-cell acute lymphoblastic leukemia; TME, tumor microenvironment.

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activation of the MEK/ERK pathway can increase cancer cell growth and differentiation. Finally, ABC transporter proteins may pump drugs from the cytoplasm out of the cell, which may reduce the intracellular concentration of anti-tumor drugs. In addition, the hypoxic environment of TME, as well as the dynamic remodeling, may promote tumor drug resistance. Notably, CSCs, EMT, PI3K/Akt, MEK/ERK and NF-κB pathway activation pathways, ABC transporter proteins, and TME are all regulated by the γ-secretase/Notch signaling axis.

It has been shown that the activation of the Notch pathway plays an important role in tumor cells escaping from anti-tumor therapy and developing drug resistance. Abnormal activation of the Notch pathway can trigger the following biological responses: (1) an increased ability to enrich small numbers of drug-resistant cells in tumors which may stimulate their resistance to conventional therapeutic strategies; (2) an increased ability to enhance stem-cell-like features during tumor cell dedifferentiation; (3) an increased ability to promote EMT, which may facilitate the transformation of tumor cells into CSCs; (4) the association with the expression of ABC membrane-bound proteins and PI3K/Akt, MEK/ERK and NF-κB pathway activation; (5) In addition to affecting the tumor cells directly, Notch signaling plays a role in regulating TME through juxtacrine and paracrine signaling [2–4]. Therefore, the Notch signaling pathway is a crucial regulatory pathway for reversing tumor drug resistance, with γ-secretase being a critical hydrolase for Notch pathway activation. Consequently, γ-secretase presents itself as a potential target for reversing tumor drug resistance. This paper will summarize a series of preclinical and clinical studies to unravel the molecular mechanism of the γ-secretase/Notch signaling axis and tumor drug resistance and discuss therapeutic strategies for GSIs to overcome tumor drug resistance. This review will aid in promoting research and development of GSIs and provide novel ideas to facilitate the reversal of tumor drug resistance.

2. The activation of the Notch pathway by γ-secretase

Notch ligands, including Delta-like proteins-1, -3, -4, Jagged-1, -2, and their receptors-1, -2, -3, and -4, are transmembrane proteins [5]. The activation of the Notch pathway is initiated by cropping the Notch receptors at the S1 site by a furin-like protease in the Golgi apparatus, which generates the Notch extracellular domain (NECD) and the Notch transmembrane fragment. The NECD and Notch transmembrane fragment form a heterodimeric complex of the Notch receptors that reaches the cell membrane surface. After the ligand binds to the NECD of the Notch receptors, ADAM protease cuts the S2 site of the NECD fragment of the receptor generating two fragments: N-terminal cleavage product and C-terminal cleavage product. The N-terminal cleavage product is engulfed by the ligand-expressing cells and the remaining C-terminal fragment of the Notch receptors is cleaved by a protease called γ-secretase. This cleavage event promotes the release of the Notch intracellular domain (NICD) from the membrane into the nucleus where it binds to the CSL (CBF1, Su (H), LAG1) transcription factors and recruits the nuclear transcriptional activator protein family (MAML). This causes the switch of CSL transcription factors from transcriptional suppression to transcriptional activation, therefore, increasing the transcription of target genes (Hes, Hey) and its downstream genes expression [6–8], as depicted in Fig. 1. Therefore, the activation of the Notch pathway requires the cleavage of the C-terminal fragment of the Notch receptor by γ-secretase to release NICD, which is necessary for downstream gene expression, and the typical activation of Notch pathway demonstrates

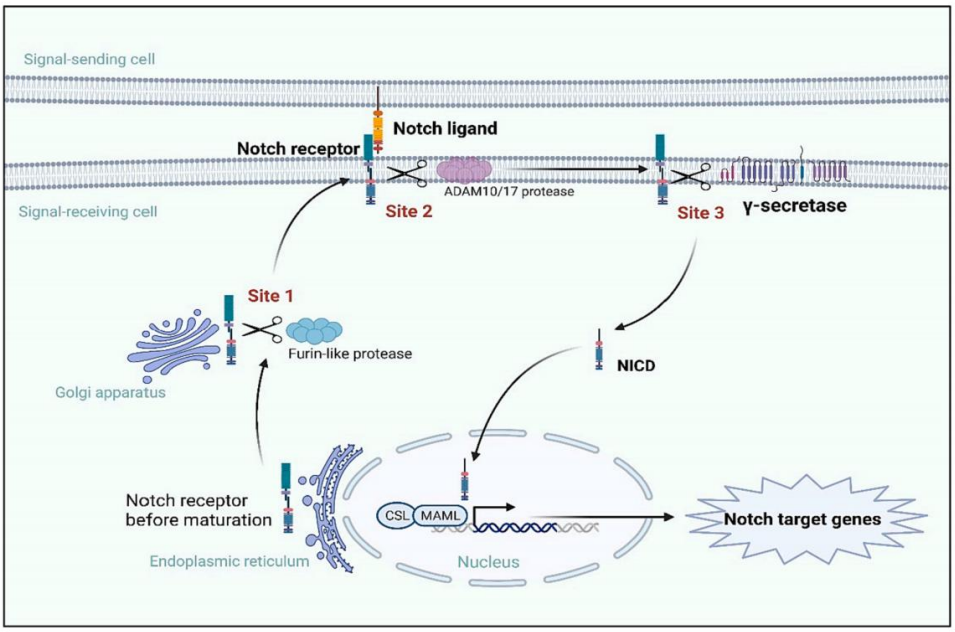


Fig. 1. Activation of the typical Notch pathway. The immature Notch receptor is transferred from the endoplasmic reticulum to the Golgi apparatus and sequentially sheared by furin-like protease, ADAM protease, and γ-secretase to release NICD, which translocate into the nucleus, where it binds to the CSL and recruits co-factors to initiate gene transcription and downstream gene expression.

the indispensable role of γ-secretase for this process.

The γ-secretase consists of four key subunits. The activation of the γ-secretase is initiated by units in the endoplasmic reticulum: Presenilin-1 (PSEN-1) or presenilin-2 (PSEN-2), nicastrin (NCST), anterior pharynx-defective (APH-1) and presenilin enhancer (PEN-2) [7,9,10]. Overall, the γ-secretase complex includes a horseshoe-shaped transmembrane structural domain and an extracellular structural domain of the NCST [11], extracellular structural domain functions as a substrate recruiter, allowing γ-secretase to cleave the transmembrane structural domain of the substrate (Notch receptor) in the hydrophobic environment of the lipid bilayer [10,12]. PSEN contains nine transmembrane structural domains that are the catalytic core of the γ-secretase complex mainly localized in the endoplasmic reticulum [10]. NCST is a type I integral membrane protein, which interacts with PSEN, this interaction is important for maintaining the enzymatic activity of the γ-secretase [13]. APH-1 has two isoforms in humans: APH-1A and B [14], hypoxia-inducible factor-1 (HIF-1) is a potential transcription factor regulating APH-1A [15], and the hypoxic environment of tumor cells can increase γ-secretase activity. In addition, APH-1 participates in the assembly and interaction with the substrate of the γ-secretase complex [14]. PEN-2 contains two transmembrane structural domains and plays an important role in the hydrolysis and stabilization of PSEN after cleavage [16]. The activation of the γ-secretase is initiated by the subsequent binding of NCST into APH-1 and PSEN to form a terpolymer which further binds to PEN-2 and breaks PSEN into a stable N-terminal fragment and a C-terminal fragment in the Golgi apparatus. This process promotes the activation of the γ-secretase complex and the formation of a catalytically active site with two transmembrane aspartic acids [10,17].

Activation of the Notch pathway requires multiple cleavages of proteases. It has been found that the cleavage of the Notch receptor by γ-secretase in the transmembrane region is key to the abnormal activation of the Notch pathway. When γ-secretase cleaves the Notch receptor, the carboxy-terminal β-chain of the Notch fragment forms a β-sheet with the β-chain of PSEN-1, which is the key to the cleavage of the carboxy-terminal of the Notch transmembrane helix [18]. In addition, PSEN-1 undergoes significant conformational rearrangements upon binding to substrates. Since GSIs can block the structural conformation and substrate binding of PSEN-1 by inhibiting the protease, they can stabilize the rearranged conformation caused by PSEN-1. Therefore, GSIs can prevent drug resistance mediated by abnormal activation of the Notch pathway [17].

3. Signaling pathway of γ-secretase/Notch activation to induce tumor drug resistance

In antineoplastic therapy, drug resistance can arise through two common scenarios: primary resistance and acquired resistance. Primary resistance refers to drug resistance that is already present in the cancer cells before treatment, while acquired resistance gradually develops as a result of factors such as drug therapy [19]. Clinically, the most of tumor chemotherapy resistance belongs to the acquired drug resistance. Therefore, understanding how acquired drug resistance developed is extremely important to improve the prognosis of cancer patients. There is increasing evidence that abnormal activation of the γ-secretase/Notch pathway is a key factor in the development of tumor resistance.

Aberrant activation of the Notch signaling pathway caused by γ-secretase is associated with tumor resistance to chemotherapy and radiotherapy [20]. It has been found that NCST overexpression activates the Notch pathway which mediates tumor drug resistance. Overexpression of NCST induced the activation of Notch-4 which made ERα+ breast cancer cells resistant to tamoxifen (Selleckchem, CAS No.: 10540-29-1, TX, USA) and led to changes in EMT phenotype and CSCs content [21]. After the knockdown of NCST, the cell invasiveness was reduced by 51.4 ± 1.7 %, and the number of CD44(+)/CD24(−) and the expression of acetaldehyde dehydrogenase 1 (ALDH1) in breast cancer stem cells (BCSCs) were reduced threefold and twofold, respectively [22]. It has been shown that the production of UDP through de novo pyrimidine synthesis is essential for the generation of UDP-GlcNAc, which is necessary for N-linked glycosylation and the stabilization of the NCST subunit in the γ-secretase complex. This, in turn, induces Notch cleavage, leading to the activation of c-Myc gene transcription. The upregulation of c-Myc, subsequently, encourages the expression of key enzymes for glycolysis, promoting the process. The increased rate of glycolysis, then, upregulates key enzymes for neo-pyrimidine synthesis, resulting in the development of chemoresistant gastric cancer cells [23], as depicted in Fig. 2A. Tumor radiotherapy leads to increased γ-secretase activity, which promotes excessive shearing of Notch receptors and thus induces increased intranuclear accumulation of NICD, which in turn induces drug resistance by abnormal activation of the Notch signaling pathway.

Notch receptors are evolutionarily and highly conserved single-channel transmembrane proteins that typically transmit signals upon binding to transmembrane ligands expressed on adjacent cells. The Notch receptor family includes four receptors: Notch-1, -2, -3, and -4. Notch receptors function in highly conserved intercellular signaling pathways and play an important role in the regulation of cell proliferation, differentiation, and apoptosis. Various tumor drug resistance may be mediated by different Notch receptors. The Notch-1 receptor is the most important receptor to mediate tumor drug resistance, it has been shown the activation of Notch-1 signaling promotes tamoxifen resistance in breast cancer xenograft tumors and resistance of melanoma cells to MAPK inhibitors [24]. In non-small cell lung cancer (NSCLC), Notch-1 activates the early transcription factor activator protein 1 (AP-1) to induce tumor resistance to paclitaxel (Selleckchem, CAS No.: 33069-62-4, TX, USA) via downregulating miR-451, which is a direct regulator of multidrug resistance protein-1 [25]. Mutation of the SCF E3 ubiquitin ligase FBWX7, which inhibits the growth of T-cell acute lymphoblastic leukemia (T-ALL) cells, prevents Notch-1 from being degraded by ubiquitination, resulting in upregulation of the Notch signaling pathway [26]. Moreover, the Notch-1 receptor is also associated with radiotherapy resistance [27]. As depicted in Fig. 2B, the studies suggested that targeting the Notch-1 receptor could be a crucial strategy to overcome drug resistance in tumors.

Notch-3 receptor may also be a key target for chemoresistance in progressive tumors [4,8]. Increased expression of the orphan nuclear receptor NR2F6 interacts with the promoter of Notch-3, causing the activation of the Notch-3 signaling pathway. This activation is achieved by enhancing p300 enrichment and histone acetylation on the promoter, ultimately leading to elevated expressions of Notch-3, NICD, and Hes-1. This phenomenon fosters a stem-cell-like behavior and mediates the resistance of epithelial ovarian cancer cells to cisplatin (Sigma-Aldrich, CAS No.: 15663-27-1, MO, USA) [28], as depicted in Fig. 2C. In addition, Notch-4 can mediate drug resistance in some tumors. Protein kinase Cα, a marker of poor prognosis in ERα(+/−) breast cancer, induces breast cancer drug resistance by increasing Notch-4 expression through AP-1 [29].

Although the association of drug resistance with the activation of Notch receptors-1, -3, and -4 has been well documented, as far as there are very few studies about Notch-2 tumor drug resistance, the role of Notch-2 receptors in tumor drug resistance is controversial. In addition to Notch receptors, it has been shown to increased expression of canonical ligand Jagged-1 is associated with poorer prognosis and drug resistance, as depicted in Fig. 2D. Lapatinib (Selleckchem, CAS No.: 2312779-2-2, TX, USA), a human epidermal growth factor receptor 2 (HER2) inhibitor, can increase the expression of Jagged-1 in cancer cell populations in HER2-positive breast cancer, the upregulation of Jagged-1 facilitates the activation of Notch and enhances the CSC population, leading to the development of lapatinib resistance [30]. The modulation of the Twist1-Jagged1/Krüppel-like factor (KLF4) axis has been suggested as an important strategy for therapeutic drug resistance in head and neck cancers. The induction of stem-like properties and drug resistance in head and neck cancer cells is achieved through the Twist1-

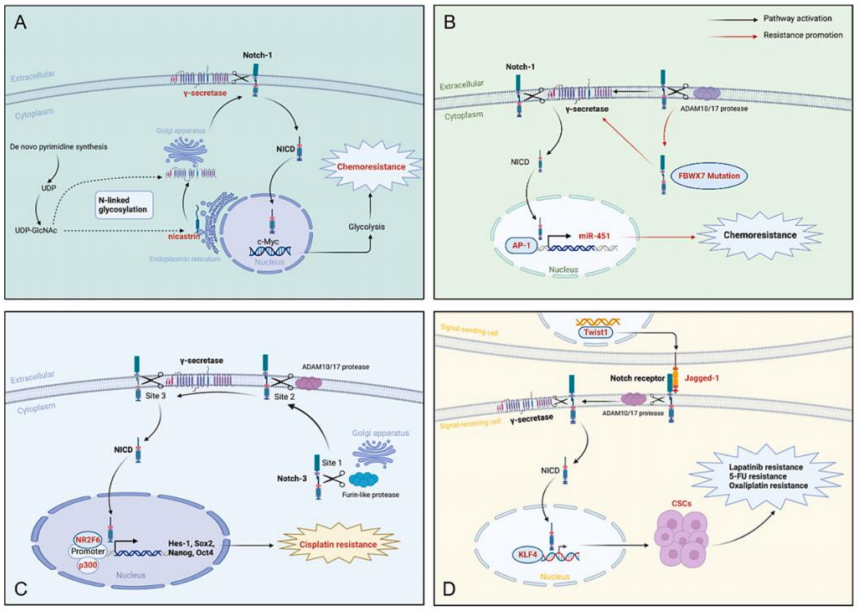


Fig. 2. Aberrant activation of the γ-secretase/Notch axis mediates tumor drug resistance. A. Excessive glycosylation of NCST increases γ-secretase activity that leads to abnormal activation of the NICD/Notch axis to mediate chemotherapy tolerance. B. Increased Notch-1 involves γ-secretase hydrolysis or modulation of miR-451 (a regulator of multidrug resistance protein-1), leading to tumor drug resistance. C. NR2F6 overexpression induces abnormal expression of downstream genes in the NICD/Notch-3 axis and cisplatin resistance. D. Twist1-Jagged1/KLF4 axis mediates tumor drug resistance through the regulation of CSCs.

induced the activation of Jagged-1/Notch/KLF4 signaling pathway [31]. It has been shown that Jagged-1 is associated with resistance to 5-fluorouracil (5-FU) (Selleckchem, CAS No.: 51-21-8, TX, USA) and oxaliplatin (Selleckchem, CAS No.: 61825-94-3, TX, USA) in colorectal cancer because silencing Jagged-1 is sufficient to restore the sensitivity of colorectal cancer cells to chemotherapy [32]. Furthermore, the upregulation of Hes-1 in the Notch pathway has been shown to contribute to multidrug resistance in tumors [33]. For instance, pancreatic stellate cells increase Hes-1 expression and promote chemoresistance in pancreatic cancer, and high expression of Hes-1 is considered as a biomarker of poor prognosis in pancreatic cancer [34].

Individual Notch family members play different, and even opposite, roles in cancer, depending on the cellular environment and tumor type. For example, Notch-1 and Notch-4 have been observed as oncogenes in breast cancer, while Notch-2 and Notch-3 have been found to be tumor suppressors [35,36]; Notch-1 and Notch-3 are oncogenic factors in T-ALL, lung adenocarcinoma and ovarian cancer [37–41]; Notch-1 and Notch-2 are highly expressed in B-chronic lymphocytic leukemia as well as gliomas and play an oncogenic role [42]. Surprisingly, Notch receptors also play a different role in tumor resistance, with Notch-1, Notch-3 and Notch-4 receptors all contributing to breast cancer resistance. No studies have shown the role of Notch-2 in breast cancer resistance, but its expression is positively correlated with B-cell lymphoma resistance. In ovarian cancer it is mainly Notch-3 overexpression that leads to resistance to chemotherapeutic agents. Drug resistance in prostate cancer, hepatocellular carcinoma (HCC), T-ALL, and NSCLC is mainly due to Notch-1 overexpression.

4. Potential mechanisms of γ-secretase/Notch activation to induce tumor drug resistance

4.1. The promotion of tumor cells transformation of CSCs

The expression of CSC-related genes plays an important role in tumor progression, and these genes mediate the resistance of tumors to chemotherapy and radiotherapy, as depicted in Fig. 3A. It has been demonstrated that cisplatin-induced tumor chemotherapy resistance in lung adenocarcinoma is achieved through the upregulation of p53-mediated the activation of Notch signaling pathway [43]. Inhibiting the Notch signaling pathway can decrease the expression of CSC genes, thereby improving chemotherapy sensitivity [44,45]. In contrast, some genes expressed in insulinoma stem cells, such as Oct4, Sox9, Sox2, CD133, and CD34, have shown strong resistance to 5-FU in both human and canine tumors [46]. Joon Tae Park et al. demonstrated that Notch-3 can increase the expression of embryonic stem cell-related genes, such as Nanog, Oct4, and ABCB1. Increased these genes may cause ovarian cancer cells resistant to carboplatin (Selleckchem, CAS No.: 41575-94-4, TX, USA) [47]. These results support the notion that the Notch signaling pathway regulates the expression of CSC genes.

Tumor radiotherapy resistance is also associated with Notch signaling pathway-regulated CSC gene expression. The activation of the Notch pathway increased the expression of these genes which mediates tumor radiotherapy resistance. Nanog may mediate radio-resistance in ALDH-positive breast cancer cells through the activation of Notch-1 and Akt pathways, and inhibition of ALDH activity reduces the resistance of breast CSCs to radiotherapy [48]. Meanwhile, Prabakaran et al. found that FTS silencing decreased CSC gene expression, radiation-induced

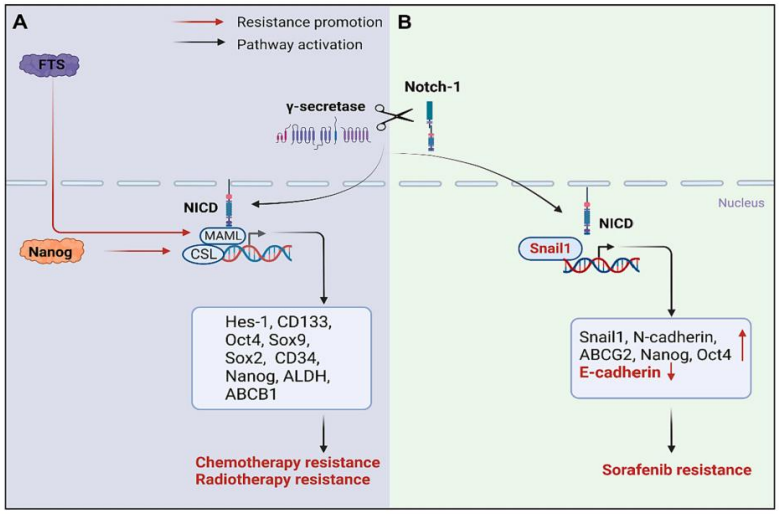


Fig. 3. The γ-secretase/Notch pathway promotes the conversion of tumor cells into CSCs and the EMT process to induce drug resistance. A. Nanog and FTS proteins induce γ-secretase/Notch axis activation, increase downstream CSC-related gene expression, and promote tumor drug resistance development. B. γ-secretase/Notch1-Snail1 axis regulates EMT and CSCs-related gene expression levels promoting tumor resistance to sorafenib.

γ-secretase complex activity and Hes-1 expression, and increased Notch-mediated radiosensitivity of CSCs [49]. These findings indicate that there is a positive correlation between γ-secretase/Notch-mediated expression of CSC genes and radiotherapy resistance in tumors. Additionally, GSIs have been shown to decrease the expression of genes associated with "stemness", leading to increased sensitivity of cancer cells to radiotherapy [50].

4.2. The promotion of the EMT process

The EMT process is positively correlated with tumor recurrence and metastasis, and the EMT process is regulated by the γ-secretase/Notch pathway [50]. Epithelial HCC cells are more sensitive to sorafenib, whereas HCC cells activated by the EMT process are resistant to sorafenib (Sigma-Aldrich, CAS No.: 284461-73-0, MO, USA) [51]. Snail is a transcription factor that controls the expression of EMT-related genes, and aberrant activation of the Notch-1 pathway can upregulate Snail to promote EMT activation [52,53]. Studies on sorafenib-resistant HCC reveal that Notch-1 induces sorafenib resistance of HCC by down-regulation of E-cadherin expression and upregulation of N-cadherin, Snail1, ABCG2, Nanog, and Oct4 expression [51], which are known as EMT-related genes, as depicted in Fig. 3B. It is well known that tumor cells often live in a hypoxic environment, Notch signaling can convert hypoxic stimuli into kinetic energy that promotes EMT progression, accelerating tumor cell migration and invasion [54]. All the above-mentioned studies support that the γ-secretase/Notch pathway plays a regulatory role in EMT.

Reduced expression of E-cadherin and increased expression of Vimentin are the main features of EMT [55]. Ylenia Lombardo et al. discovered that a disrupted E-cadherin at cell–cell contact was present in an endocrine therapy-resistant breast cancer model. However, this disruption could be repaired by GSIs, anti-NCST monoclonal antibodies, siRNA Notch-4, and NCST [21]. Similarly, a study of paclitaxel resistance in prostate cancer found that enhanced Notch signaling down-regulated E-cadherin, resulting in chemotherapy resistance. E-cadherin overexpression can reverse chemotherapy resistance [56]. Therefore, these findings suggest that E-cadherin downregulation may be a phenotype of tumor drug resistance induced by γ-secretase/Notch/EMT axis regulation.

CSCs have epithelial-mesenchymal plasticity. Interestingly, EMT can induce the formation of CSCs [57,58], and the natural drug resistance of CSCs drives tumor insensitivity to drugs. Thus, the activation of Notch-1 can orientate to induce EMT and CSCs enrichment. Furthermore, the blockade of the Notch-1 signaling pathway by GSIs can reverse EMT and reduce CSC enrichment, which impedes tumor acquisition of drug resistance [55]. These results demonstrate a strong link between the γ-secretase/Notch axis-regulated EMT, CSCs, and tumor drug resistance.

4.3. Activation of PI3K/Akt, MEK/ERK and NF-κB pathways

The γ-secretase/Notch pathway activation of PI3K/Akt, MEK/ERK and NF-κB is required to enhance apoptosis resistance leading to drug resistance, as depicted in Fig. 4. It has been shown that Notch-1 is involved in survival signaling through the activation of Akt and Survivin, leading to drug resistance in basal-like breast cancer [59]. The carcinoma-inhibiting protein PTEN acts as a negative regulator of PI3K/Akt signaling, converting phosphatidylinositol-3, 4, 5-trisphosphate (PIP_3) phosphate produced by PI3K to phosphatidylinositol-4, 5-bisphosphate (PIP_2), which in turn reverses the PI3K/Akt pathway [60]. PTEN deficiency has been shown to contribute to tumor drug resistance and Notch pathway activation [61]. It has been shown that Notch-1, activates the ERK1/2 pathway and partially promotes the proliferation of trastuzumab-resistant HER2+ breast cells through inhibition of PTEN [62]. The inhibition of Notch and Hedgehog signaling can eliminate acquired docetaxel (Selleckchem, CAS No.: 114977-28-5, TX, USA) resistance in prostate cancer, and the underlying mechanisms may involve activation of the PI3K/Akt pathway by Notch, thereby inducing docetaxel resistance [63]. Furthermore, the development of chemoresistance may also involve the interplay of multiple pathways. The correlation between Notch and MAPK pathways has been linked to

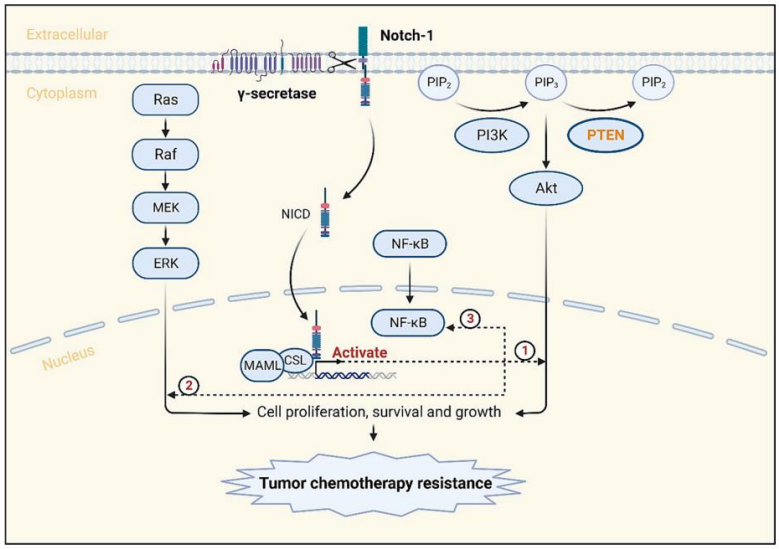


Fig. 4. The γ-secretase/Notch pathway regulates PI3K/Akt, MEK/ERK, and NF-κB to mediate tumor drug resistance. Inhibition of PTEN by the γ-secretase/Notch axis and activation of the PI3K/Akt, MEK/ERK and NF-κB pathways increase drug-resistant cells and lead to tumor resistance.

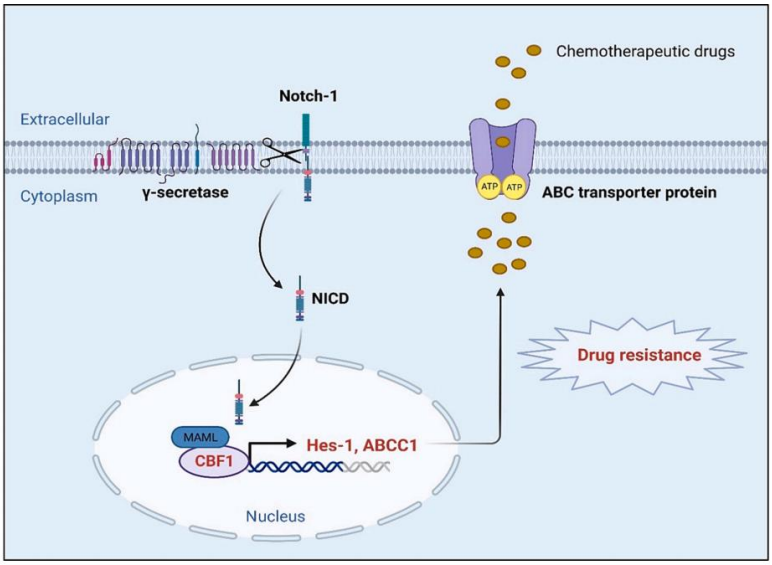


Fig. 5. Promotion of ABC transporter protein to accelerate the efflux of intracellular chemotherapeutic drugs. The γ-secretase/Notch pathway promotes the expression of ABC transporters, which accelerates the efflux of chemotherapeutic drugs and reduces the intracellular concentration of chemotherapeutic drugs.

MEK inhibitor resistance in BRAFV600E metastatic melanoma. On the other hand, the inhibition of Notch and MAPK pathways has been shown to extend the therapeutic impact of MEK inhibitors in such cells [64]. NF-κB signaling is located downstream of the Notch pathway, and the Dll1/Notch axis activates the NF-κB pathway, which exerts a protective effect against drug-induced cell death and DNA damage in breast cancer, leading to chemotherapy resistance [65].

4.4. Promotion of ABC transporter proteins to accelerate the efflux of intracellular chemotherapeutic drugs

ABC transporter proteins are a highly conserved class of transmembrane proteins, they function as a transporter responsible for transporting intracellular substances to cell outside. Abnormal activation of the γ-secretase/Notch pathway can promote the ABC transporter protein to expel chemotherapeutic drugs from cell inside into outside, reducing the concentration of chemotherapeutic drugs in tumor cells and thus inducing drug resistance [66,67], the activation of the γ-secretase/Notch pathway has been shown to increase the ability of ABC transporter protein to promote efflux of tumor chemotherapeutic drugs, resulting in drug resistance and tumor recurrence [68].

ABCC1 is a type of ATP-binding cassette transporter. Notch-1 can regulate ABCC1 expression through the transcription factor CBF1 [67], as depicted in Fig. 5. The inhibition of Notch-1 can reduce the intranuclear accumulation of NICD, and further downregulate the expression of ABCC1 in drug-resistant cells, and ultimately reverse tumor drug resistance. In addition, it has been reported that increased expression of multidrug resistance-associated protein-1, which is encoded by the ABCC1 gene, can also increase the efflux of chemotherapeutic drugs and promote resistance of breast cancer cells to chemotherapeutic drugs [69], Hes-1, a target gene of Notch can promote 5-FU resistance in colorectal cancer by inducing ABC transporter proteins [70]. These results support the notion that the upregulation of ABC transport proteins by Notch is one of the important mechanisms to induce tumor drug resistance. In addition, RLIP and RalBP1, as non-ABC transporters, are also key anti-apoptotic factors inducing drug resistance in tumors, but their association with Notch has not been elucidated. In addition, RLIP and RalBP1, as non-ABC transporters, are also key anti-apoptotic factors inducing drug resistance in tumors [71,72]. RLIP may affect the expression of genes downstream of Notch pathway, catalyze ATP-dependent efflux of unmetabolized drugs and toxins on the plasma membrane, and promote tumor progression [73,74]. RalBP1 has not

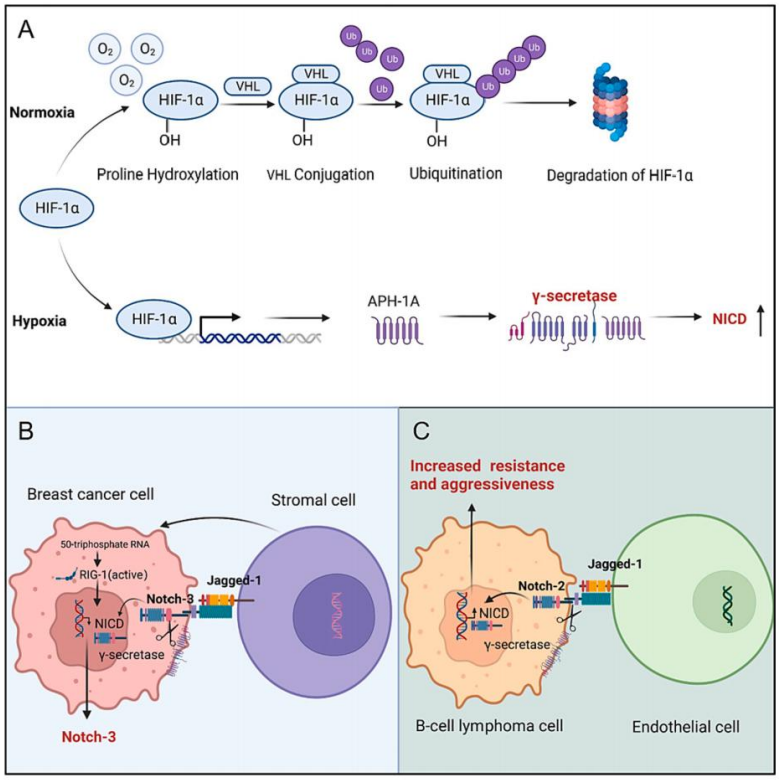


Fig. 6. TME alterations and their interaction with Notch can activate the γ-secretase/Notch pathway. A. Under normoxic conditions, HIF-1α is degraded by the proteasome, whereas HIF-1α in a hypoxic environment increases the activity of γ-secretase, resulting in abnormal activation of Notch. B. Stromal cell-mediated RIG-I/Notch-3 pathway co-drives tumor drug resistance. C. Intercellular contacts induce enhanced γ-secretase/Notch axis signaling and promote tumor drug resistance.

been studied for its association with Notch.

4.5. The activation of the γ-secretase/Notch pathway by the interaction of TME and Notch pathway

TME is composed of the extracellular matrix, soluble factors, and other non-tumor cells (e.g., immune cells, fibroblasts) [75]. Because rapid growth of tumor cells often causes tissue hypoxia, which activates transcriptional factor hypoxia-induced factor-1α (HIF-1α), HIF-1α can promote APH-1A transcription and translation, leading to an increase in APH-1A concentration and an enhancement in γ-secretase activity, ultimately results in the activation of Notch signaling [15,20], as depicted in Fig. 6 A. In addition, chronic hypoxia induces high expression of HIF-2α, which activates the Notch pathway to promote the drug resistance of BCSCs [76].

On the other hand, TME remodeling abnormally activates the Notch pathway, while TME remodeling also increases the adaptation of tumor cells to chemotherapeutic agents, leading to tumor resistance [77]. The interaction between stromal cells with breast cancer cells can promote drug resistance in breast cancer cells. As depicted in Fig. 6B, the interaction of stromal cells with breast cancer cells activates RIG-I antiviral signaling, which further activates the Notch signaling pathway, leading to excessive binding of Notch-3 to Jagged-1. As a result, the transcriptional response of Notch-3 is promoted, leading to an increase in breast cancer drug resistance [78].

The activation of Notch in tumor cells promotes the secretion of soluble factors, which affects the angiogenic and immunosuppressive environment of cells and causes TME remodeling. At the same time, TME remodeling enhances the activation of the Notch pathway and induces drug resistance in breast tumors [79]. Notch signaling can also promote tumor drug resistance by regulating cell–cell contacts. Excessive binding of Notch-3 and Jagged-1 promotes contact between tumor fibroblasts and breast cancer cells, further increasing the accumulation of CD44 (+)/CD24 (-) tumor-initiating and drug-resistant cells leading to chemoresistance [80]. Likewise, the binding of Jagged-1 on endothelial cells and of Notch-2 on B-cell lymphoma cells induces drug resistance and increased invasiveness of cancer cells [81], as depicted in Fig. 6C. It has been shown that enhanced communication between cancer cells and non-cancer cells by the activation of the γ-secretase/Notch pathway, this communication alters the tumor microenvironment which leads to drug resistance.

5. GSIs target the γ-secretase/Notch axis

In 2020, the atomic resolution cryo-electron microscopy structures of γ-secretase-bound three GSIs were reported for the first time [9]. The whole process of γ-secretase binding drugs provides a strong foundation for the design and optimization of the next generation of substrate-selective GSIs and also provides ideas for analyzing the mechanism of GSIs targeting γ-secretase/Notch axis reversal resistance. GSIs that have been proven to be effective in reversing tumor resistance in combination therapy include PF-03084014 (Selleckchem, CAS No.: 1290543-63-3, TX, USA) [82], BMS-708163 (Selleckchem, CAS No.: 1146699-66-2, TX, USA) [83], LY-411575 (Selleckchem, CAS No.: 209984-57-6, TX, USA) [84], RO4929097 (Selleckchem, CAS No.: 847925-91-1, TX, USA) [85], DAPT (Selleckchem, CAS No.: 208255-80-5, TX, USA) [86], GSI-XII (MedChem Express, CAS No.: 161710-10-7, NJ, USA) [87], MK-0752 (Selleckchem, CAS No.: 471905-41-6, TX, USA) [88], etc. Based on the mechanism of inhibition, GSIs can be categorized into transition state analogs (TSA) such as L-685458 (Selleckchem, CAS No.: 292632-98-5, TX, USA), and non-transition state analogs (non-TSA) such as DAPT and BMS-708163. TSA directly binds to the PSEN-1 active site and can helically bind to the substrate, acting as an inhibitor by preventing the formation of key interactions necessary for the initiation of substrate cleavage [89]. Although TSA L-685458 eliminates γ-secretase activity at nanomolar concentrations, this inhibitor has not been reported in terms of reversing tumor resistance. Compared with TSA, non-TSA is more effective in reversing tumor resistance, which may be related to its inhibition mechanism targeting γ-secretase. Non-TSA DAPT does not make contact with the active site of γ-secretase and is the most commonly used GSI to eliminate tumor resistance in preclinical studies. DAPT binds tightly to γ-secretase in the spacious cavity formed by TM2, TM3, and TM5 of PSEN-1, acting as an inhibitor by blocking the pathway from the substrate to the active site [90].

Some GSIs, such as LY-411575 and RO4929097 [91,92], do not target γ-secretases alone but bind to signal peptides peptidase (SPP) and signal peptides peptidase-like (SPPL) proteases that are structure-like to γ-secretase. However, GSIs showed significant differences in the inhibition rates of γ-secretase and SPP/SPPL protease activities [93]. At a certain concentration, GSIs can inhibit γ-secretase but have little effect on SPP/SPPL protease, so the effect of SPP/SPPL protease on reversing tumor resistance is negligible. Studies have shown that LY-411575 and RO4929097 can reverse tumor resistance, further supporting the above view. There are also differences between PSEN and SPP/SPPL proteases. For example, the structures of the active site subsites of the two are different [94]; compared with PSEN, the topological structure of SPP/SPPL protease is overall reversed [95]. Because of these differences, not all GSIs target both γ-secretase and SPP/SPPL proteases. For example, DAPT does not effective on SPP/SPPL proteases. DAPT specifically targets the PSEN C-terminal fragment, which is only present in the γ-secretase complex but not in the binding site of SPP/SPPL proteases, and does not block the catalytic activity of SPP/SPPL family members [95].

6. Therapeutic strategies for reversing tumor resistance with inhibition of the γ-secretase/Notch pathway

Over the past two decades, many approaches to inhibit the aberrant activation of the Notch pathway have been studied and developed, such as GSIs, ADAM inhibitors, monoclonal antibodies and natural small molecule compounds. Among them, GSIs are the first Notch pathway inhibitors to be proposed by scientists and successfully developed. Although GSIs treatment alone has shown promise in reversing tumor chemoresistance, more studies have confirmed that GSIs combined with conventional therapy (GCCT) can significantly improve tumor sensitivity to chemotherapy. Conventional therapy is essential to inhibit tumor growth and proliferation and promote tumor cell apoptosis, while GSIs can enhance the effect of conventional therapy, and reverse the tolerance of conventional drugs. Therefore, the scientific development and rational application of GSIs are the key to reversing drug resistance to conventional therapy.

The γ-secretase/Notch axis serves as a regulatory hub for CSCs, EMT, ABC transporter proteins, the PI3K/Akt, MEK/ERK and NF-κB pathway, and TME, with different mechanisms in the treatment of drug resistance in different types of cancer. For breast cancer, reversal of breast cancer resistance has been reported for DAPT, PF-03084014, and RO4929097 [69,96,97], and mechanisms of action have been demonstrated for CSCs, EMT, ABC transporter proteins, the PI3K/Akt, MEK/ERK and NF-κB pathway and TME. In prostate cancer studies, targeting the γ-secretase/Notch axis will result in inhibition of the PI3K/Akt pathway, altered TME, and decreased EMT and CSCs, thereby reversing resistance [98–100]. Sorafenib resistance is common in the clinical management of HCC. γ-secretase/Notch axis blocks EMT and CSCs progression by inhibiting the transformation of human mesenchymal stem cells to HCC cells, blocking the activation of EpCAM, and inhibiting the expression of EpICD and Notch1-Snail1 are important for the reversal of HCC resistance [101]. Drug resistance in lung adenocarcinoma and NSCLC is mainly closely related to the PI3K/Akt pathway and CSCs regulated by the γ-secretase/Notch axis [102]. GSIs increase the sensitivity of lung cancer to chemotherapeutic agents by inhibiting the activation of the PI3K/Akt pathway and reducing the enrichment of CSCs [43,103–105]. By comparing the mechanistic changes in the γ-secretase/Notch pathway in drug resistance studies in different cancers, we propose that

there is greater potential for the use of GSIs in the drug-resistant treatment of breast cancer.

Compared with the above multiple mechanisms to induce tumor resistance, the mechanism of regulating T-ALL and ovarian cancer resistance by the γ-secretase/Notch axis is relatively simple. Notch activation mutations of Notch-1 are present in more than 50 % of T-ALL patients [87]. There is evidence showing that GSIs in combination therapies reduce tumor resistance by targeting the inhibition Notch-1 receptor. GSIs inhibit Notch-1 signaling by inducing the expression of Bim (the BH3 gene required for glucocorticoid-induced apoptosis); Meanwhile, treatment with glucocorticoid-induced CCND2 transcriptional increases reversing intestinal toxicity after GSIs treatment [106,107]. GCCT treatment of ovarian cancer resistance reduces the activity of CSCs and increases the sensitivity of CSCs to the drug by targeting Notch-3 [108,109].

GCCT reversal of drug resistance not only has the advantage of clear objectives but also has sufficient theoretical basis and high feasibility, as shown in Table 1. Although most of the clinical studies on reversing tumor resistance by GCCT remain in phase I, the clinical effects of GCCT indicate that it has broad development prospects. Recently, M. Gounder and colleagues conducted an international Phase III, double-blind, randomized, placebo-controlled trial in patients with progressive fibroma, the results of which confirmed the safety and efficacy of GSIs. PF-03084014 treatment resulted in a 71 percent reduction in the risk of disease progression or death, with 41 percent of patients having a clear objective response and 7 percent having a complete response, with mostly low-grade and transient adverse events [110]. The GSIs that have been used to treat breast cancer resistance through GCCT and have entered clinical studies include RO4929097, MK-0752, and so on. Among them, RO4929097 is more frequently used in clinical studies for the treatment of breast cancer resistance, with 95 % of treatment-related toxicity of grade 1 or 2 [111], well tolerated, and has a greater potential for combining with conventional drugs in the treatment of breast cancer resistance.

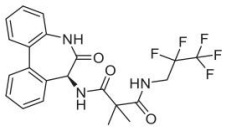
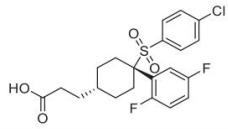
Based on the strategy of combining GSIs with chemotherapeutic drugs, it is also possible to further enhance the effect of GSIs to reverse the tolerance of chemotherapeutic drugs by optimizing the therapy. The optimization of therapies aims to address the limitations and leverage the benefits of GSIs through supplementary methods. Drug delivery system based on solid lipid nanoparticles contains GSIs with surface-modified death receptor-5 mAb and DLL-4 mAb to block the Notch signaling-mediated activity of BCSCs, thereby reversing drug resistance [112]. This method has three advantages: (1) reducing the non-targeting side effects of GSIs and improving the precision of treatment; (2) synergistic action of GSIs and DLL-4 mAb to block Notch signaling enhances tumor sensitivity to the drug [112].

7. Conclusion and prospects

Tumor resistance is a dilemma in the field of cancer therapy, it has been shown that the activation of the γ-secretase/Notch signaling pathway can promote tumor drug resistance. The activation of the Notch pathway results in enhancement in small number of drug-resistant cells and stem-cell-like features in the tumor, promote EMT and the transformation of tumor cells into CSCs, increment in the expression of ABC membrane-bound proteins, activation of PI3K/Akt, MEK/ERK, and NF-κB pathways, as well as regulating TME, the above mechanisms will lead to drug resistance in breast cancer. There are three main ways to inhibit the aberrant activation of the Notch pathway: (1) Inhibition of three proteases involved in Notch receptor cleavage, such as furin-like protease, ADAM protease and γ-secretase; (2) Blocking the transcription of target genes, inhibiting the expression of CSL or MAML [113,114], or changing the function of the Notch ternary complex formed by CSL, NICD and MAML [115]. (3) Monoclonal antibodies targeting receptors or ligands. (1) and (2) do not address the issue of non-specific targeting of Notch receptors or ligands. This problem is addressed by developing monoclonal antibodies that target specific receptors and ligands. Currently, mature drugs targeting Jagged-2, Dll-1, and Notch-4 have not been reported, but there has been progress in the study of monoclonal antibodies targeting Notch receptor-1/-2/-3 and other ligands of Notch [42]. It is worth mentioning that GSIs can reverse tumor cell resistance to chemotherapy drugs or increase chemotherapy sensitivity through GCCT strategies, it can also induce tumor cell apoptosis and synergistically inhibit tumor cell growth with conventional chemotherapy drugs. GSIs are the most mature drugs targeting the γ-secretase/Notch axis, PF-03084014 has entered clinical phase III, which portend a promising application of GSIs in reversing drug resistance.

Surprisingly, the Notch pathway is not only associated with tumor drug resistance, but also plays an important role in tumor immune response [116]. Notch activation significantly correlates with immune checkpoint blockade in small cell lung cancer [117,118]. Overexpression of Notch-2 receptor induces anti-tumor immune response in CD8(+) T cells and reduces tumor load in mice [119]. On the contrary, Notch-1 promotes immune escape of melanoma cells by upregulating

Table 1
GSIs that have reversed tumor resistance through GCCT strategies and have undergone clinical studies.

Agent	Chemical structure	Type of cancer	Study stage	Outcome
RO4929097		ERα + metastatic breast cancer	Phase I	RO4929097 + Exemestane (Selleckchem, CAS No.: 107868-30-4, TX, USA): of the 14 patients, 1 PR, 6 SD and 7 PD [126].
		Triple negative breast cancer	Phase I	RO4929097 + Neoadjuvant Paclitaxel and Carboplatin: of the 14 female patients, 9 ORR (64 %) and 5 pCR (36 %) [127].
		Advanced solid tumors	Phase I	RO4929097 + Cediranib (Selleckchem, CAS No.: 288383-20-0, TX, USA): of the 20 patients, 11 SD and 1 PR [128].
		Advanced solid tumors	Phase I	RO4929097 + Temsirolimus (Selleckchem, CAS No.: 162635–04-3, TX, USA): of the 17 patients, 11 SD (73 %) [129]
		Recurrent Malignant Glioma	Phase I	RO4929097 + Bevacizumab (MedChem Express, CAS No.: 216974-75-3, NJ, USA): of the 12 patients, 2 RR, 1 CR, and 1 PR [130].
MK-0752		Breast cancer	Phase I	MK-0752 + Docetaxel: of the 24 participants, 11 PR, 9 SD, and 3 PD [88].

Note: pCR, pathological complete response; ORR, overall response rate; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; RR, radiographic responses.

TGF-β1 [120]. GSIs combined with immunotherapy as a novel strategy has not been investigated in the treatment of tumor resistance. GSIs in combination with immunotherapy is considered a more challenging and promising treatment strategy than combination with chemotherapy and radiotherapy.

However, GSIs have not achieved the expected results in clinical research on reversing cancer chemotherapy resistance, which may be related to the following reasons: (1) The selectivity of GSIs towards substrates needs to be improved. There is literature indicating that in addition to Notch receptors, GSIs also inhibit APP cleavage; In addition, unlike other subtypes of Notch, the increased activity of Notch-2 receptors has anti-tumor effects [8,77]. (2) Excessive inhibition of the Notch pathway may also trigger protective autophagy in tumor cells, leading to tumor resistance. (3) GSIs treatment can increase the expression of KLF4 and promote the accumulation of goblet cells in the intestine, resulting in gastrointestinal side effects [106]. To address the challenges of GSIs in treating tumor resistance, the following solutions have been proposed: (1) Improvement of specific inhibition of Notch receptors by optimization of GSIs design strategies, such as optimizing drug sequence length and altering target site selection. A similar effect can be achieved by screening suitable GSIs concentrations from Notch substrate inhibitory profiles. In addition, the development of substrate-selective GSIs may address this issue. (2) In the GSIs treatment regimen, supplementing with PKC inhibitors alleviates the potential cellular protective autophagy associated with GSIs [121]. (3) Intermittent administration [100] or the preparation of GSIs into nanoparticles can reduce gastrointestinal side effects during treatment. [122]. Although there are still some controversies over the reversal of drug resistance by GSIs, the vast majority of studies support that GSIs can effectively reverse tumor drug resistance.

Cancer chemotherapy resistance is a huge obstacle. In preclinical studies, drug activity tends to be overestimated when treated alone, and combination therapy is an improvement on the above approach. In implementing combination therapy, patients need to be categorized using biomarkers that identify γ-secretase activity to select which patients are suitable for GCCT treatment. Thus, finding genes or markers that reflect γ-secretase activity is key to combination therapy. In addition, phenotypic screening of tumors using patient samples can provide useful information to guide the development of next-generation GSIs, as well as for evaluating tumor cells for targeting natural components. Natural products with better pharmacokinetics and safety are the direction of drug development. The research and application of GSI derived from natural products in Alzheimer's disease is more in-depth compared to tumor resistance therapy. For example, natural source Dihydroergocristine, it is a type of γ-secretase inhibitors, which is approved by the FDA for the treatment of hypertension and dementia, no gastrointestinal toxicity has been found so far [123]. Besides, Sulforaphane increased the effectiveness of chemotherapeutic agents on CSCs by inhibiting Notch-1 activity, and organ toxicity in mice was not found [124]. Our research team confirmed that Cimigenoside was isolated and purified from Cimicifuga dahurica (Turcz.) Maxim, can target the inhibition of the γ-secretase/Notch pathway, and show the activity of reversing paclitaxel resistance in triple-negative breast cancer [125]. Although the development of GSIs from natural active ingredients for the reversal of chemoresistance holds some promise, there are still many challenges in bringing such novel GSIs from bench to bed.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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