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Mini-review

# Notch signaling: An emerging therapeutic target for cancer treatment

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ABSTRACT

The Notch pathway is involved in cell proliferation, differentiation and survival. The Notch signaling pathway is one of the most commonly activated signaling pathways in cancer. Alterations include activating mutations and amplification of the Notch pathway, which play key roles in the progression of cancer. Accumulating evidence suggests that the pharmacological inhibition of this pathway can overcome chemoresistance. Efforts have been taken to develop Notch inhibitors as a single agent or in combination with clinically used chemotherapeutics to treat cancer. Some Notch inhibitors have been demonstrated to have therapeutic efficacy in preclinical studies. This review summarizes the recent studies and clinical evaluations of the Notch inhibitors in cancer.



## Introduction

The Notch signaling cascade is critical for cell proliferation, differentiation, development and homeostasis [1]. Deregulated Notch signaling is found in various diseases, such as T-cell leukemia, breast cancer, prostate cancer, colorectal cancer and lung cancer as well as central nervous system (CNS) malignancies [2]. Recent evidence has demonstrated that Notch signaling is associated with esophageal and breast cancer stem cells [3,4]. Clinically oriented studies have further highlighted that Notch signaling impacts survival in human cancer [5].

Upon ligand binding, Notch receptors undertake two cleavage processes mediated by a member of a disintegrin and metalloproteases (ADAM) family and gamma-secretase, leading to the release of the Notch intracellular domain (NICD). As a result, it activates the transcriptional complex. Several small molecule inhibitors targeting the Notch pathway, including gamma-secretase inhibitor (GSI), siRNA and monoclonal antibodies (mAb) against Notch receptors and Notch ligands, have been developed and are currently in the clinical trials. Furthermore, Notch inhibitors have been tested in combination with conventional cytostatic agents or targeted drugs in phase I or phase II evaluations [6].

## Notch signaling pathway

Notch signaling is activated when a ligand binds to a Notch receptor. In mammals, there are four receptors, Notches 1~4, and five ligands, delta-like ligand 1 (DLL1), delta-like ligand 3 (DLL3), delta-like ligand 4 (DLL4), Jagged-1 (JAG1) and Jagged-2 (JAG2) [7]. The Notch receptors express on the surface of cell membrane, where they can be cleaved by a member of a disintegrin and metalloproteinase family (ADAM17 or ADAM10) of proteases and a presenilin-dependent gamma secretase complex. As a result, the Notch Intracellular Domain (NICD) is released and then translocates into the nucleus [8]. In the nucleus, NICD interacts with the ubiquitous transcription factor CBF-1/suppressor of hairless/Lag1 (CSL). CSL is a transcriptional repressor that can bind to the consensus DNA sequence in association with a SMART complex in the absence of NICD, and results in gene transcriptional activation, which is involved in two target genes family Hes (Hairy Enhance of Split) and Hey (Hairy/Enhancer of Spit related with YRPW motif). Notch signaling regulates p27cip1/waf1, cyclinD1, c-Myc, p21, Survivin, Slug and Nanog, and also activates the nuclear factor-kappa B (NF-κB) pathway (Fig. 1) [9]. DLL4-Notch signaling was found to play a key role in liver metastasis of human small cell lung cancer (SCLC) by regulating nuclear factor-kappa B (NF-κB) signaling [10] (Table 1).

Notch signaling is demonstrated to play an important role in embryo development through regulation of cell proliferation, differentiation and apoptosis. During mammalian heart development, Notch signaling is implicated in the maturation of arterial and ventricular cardiomyocytes and the development of the endocardium. In mouse models, Notch knockout can cause lethal cardiac defects, including ventricular septum defects, valve defects and cardiomyopathy [19]. Moreover, Notch signaling regulates stem cell differentiation and self-renewal. Loss of Bmil, a downstream target of Notch signaling, decreases murine intestinal stem cell proliferation and conversely increases differentiation to goblet cells [20]. However, during development, inhibition of the Notch pathway

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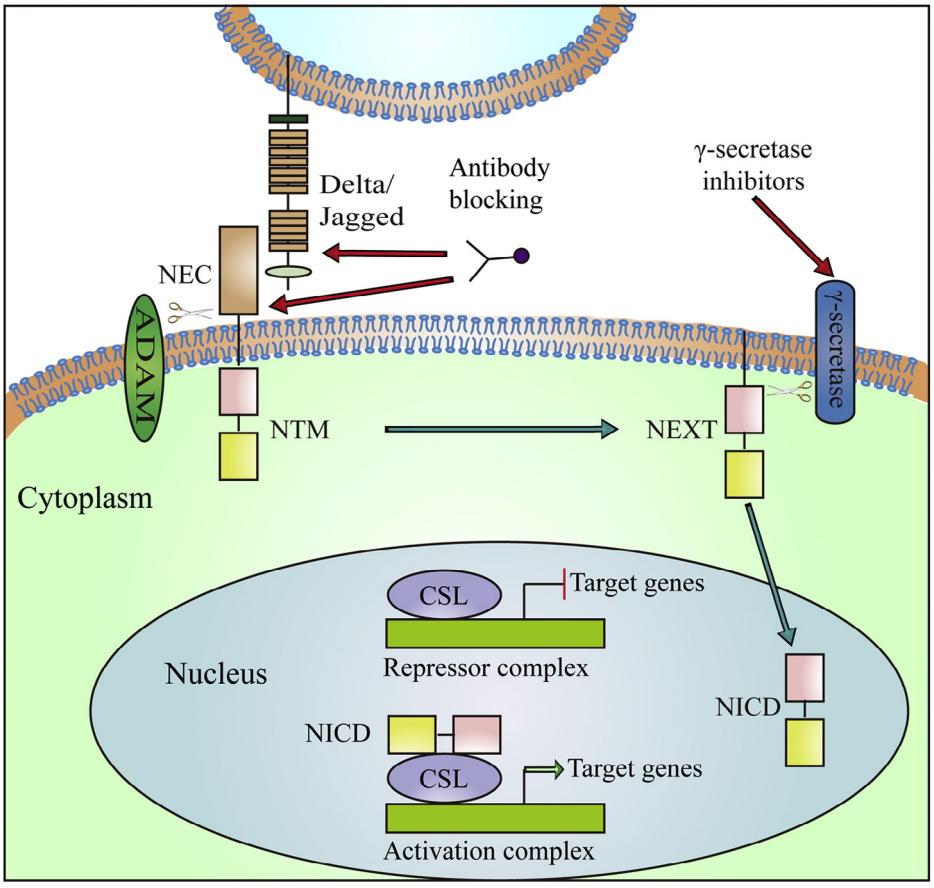



**Fig. 1.** Diagram of Notch receptor activation and therapeutic target in clinical development. Notch signaling is initiated by ligand binding to Notch receptor, which undergoes a two-step proteolytic cleavage by ADAM family proteases and γ-secretase, releasing the Notch Intracellular Domain (NICD). The NICD translocates to the nucleus where it binds to CSL and converts the complex from a repressor to an activator of Notch target genes. Notch signaling could be inhibited by two major classes of Notch inhibitors: γ-secretase inhibitors and monoclonal antibodies directing against Notch receptors or ligands. Abbreviations: NEC, Notch extracellular subunit; NTM, Notch transmembrane fragment; NEXT, Notch extracellular truncated; CSL, C protein binding factor 1/Suppressor of Hairless/Lag-1; NICD, Notch Intracellular Domain.

**Table 1**
Significance of Notch pathway in cancer.

| | Function | Ref |
|---|---|---|
| Ligands | | |
| DLL 1 | Governing cell fate decisions and cell-to-cell communication | [7] |
| DLL 3 | Suppressing cell growth by apoptosis induction | [11] |
| DLL 4 | Activating NF-κB signaling to enhance VEGF secretion and promote metastasis | [10,12] |
| JAG 1 | JAG 1 activation of Notch enhances angiogenesis | [7] |
| JAG 2 | Interaction with Notch2 to promote cell survival and proliferation | [7] |
| Receptors | | |
| Notch1 | Transmembrane receptor involved in cell proliferation, invasion and chemoresistance | [5,13,14] |
| Notch2 | Constitutive Notch2 signaling induces hepatic tumors | [15] |
| Notch3 | Promoting proliferation and migration, and modifying chemotherapy response | [11] |
| Notch4 | Involved in endocrine therapy resistance and EMT in breast cancer | [16] |
| Targeted genes | | |
| Hes1 | Sequence-specific DNA binding transcriptional factor involved in cellular proliferation and differentiation | [11,17] |
| Hey1 | Hes-related transcriptional factor involved in neoplastic vasculature development | [18] |

promotes differentiation of the somatic cells and enables routine generation of human induced pluripotent stem cells (iPSCs) without non-core pluripotency factors KLF4 and c-Myc via suppressing p21 in a p53-independent manner in mouse and human keratinocytes [21].

Overwhelming evidence indicates that Notch signaling plays key roles in carcinogenesis and tumor progression, such as T-cell leukemia and breast cancer [16,22]. Notch1 signaling mediated hypoxia/HIF-1α induces cell proliferation, invasion and chemoresistance in T-cell acute lymphoblastic leukemia (T-ALL) [13]. Notch signaling is also involved in the establishment of mesenchymal phenotype during tumor progression and metastasis [23]. The role of Notch signaling in epithelial–mesenchymal transition (EMT) was first unraveled in cardiac valve and cushion formation during heart development, through downregulation of epithelial markers and upregulation of mesenchymal markers [24,25]. Over-expression of Jagged1 was found to reduce E-cadherin expression in human kidney epithelial cells, suggesting that Notch signaling plays quintessential roles in EMT [26]. In addition, the inhibition of Notch signaling by GSI reverses the EMT process [27]. Subsequently, Notch signaling was found to drive stemness in esophageal adenocarcinoma [3]. However, Notch signaling can be tumor suppressive in some cellular contexts, for instance, causing growth arrest by suppressing SIRT1 and activating p53 in Ewing sarcoma, which is also implicated in B-cell tumors and human keratinocytes [28].

During cancer progression, activating mutations occurred within and upstream of the PEST domains of Notch1, Notch2 and Notch3

receptors via several genetic mechanisms and reduced the function of the PEST domain, which was a negative regulator of the Notch signaling [29]. In addition, amplification of wild-type Notch receptors and ligands is also observed in various tumors. For instance, Notch1 activating mutation could be identified in over 50% of T-ALL tumors [30–32]. However, Notch4 and Notch ligands genes were mutated at low incidences [33]. Mutations and amplifications of the Notch signaling often increased the expression of canonical Notch target genes, resulting in the progression of cancer. Notch1 rearrangements related to high N1-ICD levels in triple-negative breast cancer xenografts correlated with responsiveness to GSI-based therapies. Deregulation of Notch signaling was further identified in other cancers [11,34,35]. In a transgenic mouse model, activated Notch1 was overexpressed in the alveolar epithelium and induced alveolar hyperplasia and pulmonary adenomas through regulating type II lung epithelial cells [14]. When crossed with mice expressing MYC, transgenic mice progressed to adenocarcinomas and metastases, indicating a synergistic effect between Notch1 and other oncogenes.

Considerable studies have shown that Notch signaling is involved in tumor pathologic angiogenesis. Whole transcriptome sequencing revealed that Hey1, a Notch target, played a fundamental role in neoplastic vasculature development. Inhibition of Notch signaling decreased the production of new blood vessels in mice [18]. Notch1 in connection with VEGF-A has a significant prognostic impact, indicating that Notch pathway increased the possibility of metastasis and poor outcome through regulating tumor angiogenesis via crosstalk with VEGF-A in lung cancer [5]. In agreement, blockade of the DLL4-Notch pathway is associated with decreased angiogenesis and tumor growth in severe combined immunodeficiency (SCID) mice with renal cancer xenografts [12]. Importantly, combined targeting treatments of DLL4 and vascular endothelial growth factor (VEGF) signaling pathway resulted in enhanced tumor growth inhibition and a marked decrease in tumor perfusion. In addition, the clinical significance of Notch signaling has also been observed in lung cancer and breast cancer [11,36]. By conducting a meta-analysis, Notch1 and Notch3 were correlated with tumor progression and prognosis in NSCLC. Furthermore, patients with DLL3 and Hes1 overexpression had significantly poor overall survival (OS), indicating that Notch signaling may be a biomarker to predict progression and survival of NSCLC patients. Therefore, targeting Notch signaling may benefit patients with cancer [11].

## Targeting Notch signaling with gamma-secretase inhibitors (GSIs)

Currently, several classes of Notch inhibitors have been developed, mainly composed of GSI, siRNA and monoclonal antibodies against Notch receptors or ligands [37]. *In vitro* studies show that γ-secretase inhibitor (GSI) effectively represses cancer stem cells (CSCs) [38]. In a Kras(G12V)-driven NSCLCs mice model, γ-secretase inhibitor (GSI) blocked cancer growth by reducing HES1 levels and phosphorylated ERK [39]. Mechanically, GSI triggers apoptosis of tumor cells through inhibiting proteasome activity and enhancing endoplasmic reticulum (ER) stress [40]. Time-course studies suggest that initial apoptosis events induced by Notch inhibition are the result of the suppression of proteasome activity, concomitant with enhanced ER stress apoptosis signaling and Noxa expression, which precedes mitochondrial alterations in primary CLL cells [41]. At present, GSIs are the most extensively explored. The completed clinical trials of GSIs in cancer are shown in Table 2. The chemical properties and biological activity of GSIs are shown in Table 3.

### *RO4929097*

RO4929097, also known as 2,2-dimethyl-N-[(7S)-6-oxo-5,7-dihydrobenzo[d][1]benzazepin-7-yl]-N′-(2,2,3,3,3-pentafluoropropyl) propanediamide, is a novel small-molecular inhibitor of gamma secretase, which is found to decrease proliferation and impair the ability to form colonies in human primary melanoma cell lines. Moreover, RO4929097 affected the tumor formation and tumor growth of human primary melanoma xenografts, suggesting that RO4929097 suppresses the tumor initiating potential of cancer cells [49]. RO4929097 is well tolerated [44,50], and the most common treatment-related adverse events were nausea (53%), fatigue (41%), and anemia (22%) in patients with advanced cancer [50]. Preliminary evidence of anti-cancer activity was observed in three of nine recurrent ovarian cancer patients, with prolonged (≥3 months) stable disease (SD) [51]. Moreover, RO4929097 was also administrated in combination with other agents. In a phase I study, thirty patients with refractory cancer received RO4929097 in combination with capecitabine, and showed clinical benefit in cervical and colon cancer [46]. RO4929097 in combination with gemcitabine can also be safely tolerated and achieved clinical antitumor activity and >4 months stable disease in pancreas, tracheal, and breast primary cancers [47]. The combination of RO4929097 and Cediranib, a VEGF receptor tyrosine kinase inhibitor, showed an antitumor efficacy with prolonged disease stabilization in eleven patients (55%) with advanced solid tumors [52]. Co-administration of RO4929097 and temsirolimus (an mTOR inhibitor) increased clearance and reduced exposure to temsirolimus via a drug–drug interaction in refractory advanced solid tumors [48].

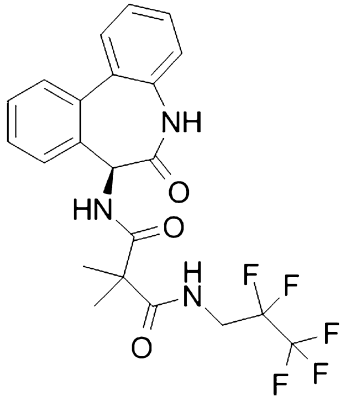
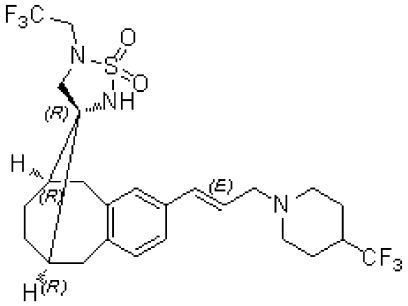
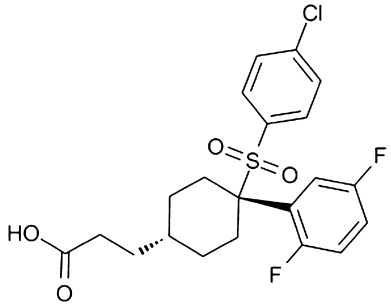
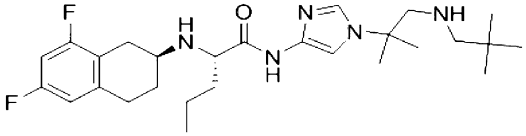
Moreover, RO4929097 significantly sensitized the putative breast cancer stem cells to ionizing radiation and reduced normal T-cell synthesis of inflammatory cytokines, suggesting that Notch pathway plays an important role in inflammatory breast cancer (IBC) stem cells, and that evaluation of inflammatory response may predict the

**Table 2**
Completed clinical trials of GSIs in cancer.

| Treatment | Trial type and tumor | Enrollment | Primary endpoint | Therapy effect | NCT trial number | Ref |
|---|---|---|---|---|---|---|
| MK0752 | Phase I; advanced solid tumor | 103 | MTD | 1 CR and 12 SD | 00106145 | [42] |
| MK0752 | Phase I; normal | 30 | Notch response signature | NA | 00803894 | NR |
| MK0752 + docetaxel | Phase I/II; breast cancer | 30 | DLT | 11 PR, 9 SD, and 3 PD | 00645333 | [43] |
| MK0752 + gemcitabine | Phase I/II; pancreatic cancer | 44 | Safety/MTD | NA | 01098344 | NR |
| RO4929097 | Phase II; renal cell carcinoma | 5 | Efficacy | NA | 01141569 | NR |
| RO4929097 | Phase II; pancreatic cancer | 18 | Survival rate | 3 SD, | 01232829 | [44] |
| RO4929097 | Phase II, colorectal cancer | 37 | Efficacy | 6 SD, | 01116687 | [45] |
| RO4929097 | Phase II; NSCLC | 6 | Efficacy | NR | 01193868 | NR |
| RO4929097 | Phase I; advanced solid tumor | 17 | Pharmacokinetics study | NR | 01218620 | NR |
| RO4929097 | Phase I; advanced solid tumor | 28 | Safety | NR | 01096355 | NR |
| RO4929097 + capecitabine | Phase I; refractory solid tumor | 30 | MTD | 3 PR, | 01158274 | [46] |
| RO4929097 + gemcitabine | Phase I; advanced solid tumor | 18 | Safety | 1 PR, 3 SD | 01145456 | [47] |
| RO4929097 + temsirolimus | Phase I; advanced solid tumor | 17 | Safety | 11 SD, | 01198184 | [48] |

Abbreviations: NR, not reported; MTD, maximum tolerated dose; DLT, dose limiting toxicity; NSCLC, non-small cell lung cancer.

**Table 3**
Chemical properties and biological activity of GSIs.

| Drug | Formula | Chemical structure | Target | IC50 | Ref |
|---|---|---|---|---|---|
| RO4929097 | C22H20F5N3O3 |  | Gamma-secretase | 4 nM | [44–55] |
| MRK-003 | C25H31F6N3O2S |  | Gamma-secretase | NR | [17,56–58] |
| MK-0752 | $C_{21}H_{21}ClF_2O_4S$ |  | Gamma-secretase | 5 nM | [42,43,59] |
| PF03084014 | C27H41F2N5O |  | Gamma-secretase | 6.2 nM | [60–65] |

Abbreviation: IC50, half maximal inhibitory concentration.

efficacy of Notch inhibitor [53]. Nevertheless, RO4929097 showed minimal single agent activity in patients with metastatic refractory colorectal cancer and childhood cancer [45,54]. A pharmacokinetic study demonstrated that RO4929097 is highly bound with α1-acid glycoprotein (AAG) in human plasma and that only unbound RO4929097 had pharmacokinetic activity in patients. It was found that plasma protein binding levels changed by concomitant drug which competitively binds to AAG or disease states, and that concomitant Hedgehog inhibitor GDC-0449 significantly increased unbound RO4929097 levels and improved RO4929097 *in vitro* Notch-inhibitory activity [55].

*MRK-003*

MRK-003, a γ-secretase inhibitor known as (3′R,6R,9R)-5′-(2,2,2-trifluoroethyl)-2-((E)-3-(4-(trifluoromethyl)piperidin-1-yl)prop-1-en-1-yl)-5,6,7,8,9,10-hexahydrospiro[6,9-methanobenzo[8]annulene-11,3′-[1,2,5]thiadiazolidine] 1′,1′-dioxide, induced caspase-dependent apoptosis and inhibited proliferation of multiple myeloma and non-Hodgkin's lymphoma cell lines by reducing the expression of NICD, Hes1 and c-Myc and up-regulating pAkt [17]. In a murine orthotopic glioblastoma xenograft model, weekly oral delivery of MRK003 resulted in significant inhibition of tumor growth, stem cell marker expression as well as clonogenicity, providing preclinical evidence for the application of MRK003 in malignant brain cancer patients [56]. Combining MRK-003 with trastuzumab, an ErbB-2 signaling inhibitor, induced tumor regression and prevented tumor recurrence post-trastuzumab treatment in ErbB-2-positive breast xenografts. Furthermore, MRK-003 was identified to partially reverse trastuzumab resistance *in vivo* [57]. Notably, MRK003, combined with gemcitabine, synergistically induced widespread hypoxic necrosis, resulting in prolonged survival of pancreatic ductal adenocarcinoma (PDA) in the LSL-Kras(G12D)(/+);Pdx-1-Cre mouse model [58].

*MK-0752*

MK-0752, known as 3-[4-(4-chlorophenyl) sulfonyl-4-(2,5-difluorophenyl)cyclohexyl]propanoic acid, is a potent oral inhibitor of γ-secretase. In a phase I study involving 103 patients with advanced solid tumor, preliminary antitumor efficacy was observed via modulation of Notch gene signature (Table 2) [42]. Treatment with GSIs MK-0752 in breast cancer reduced stem cell subpopulation *in vitro* and in human tissues from a clinical trial (Table 2) [43]. In addition, MK-0752 is well-tolerated and effective in children with refractory or recurrent CNS malignancies, supporting a rational application of MK-0752 in children [59]. However, the side effects of MK-0752 include diarrhea, nausea, vomiting, and fatigue.

*PF-03084014*

PF-03084014, known as (2S)-2-[[(2S)-6,8-difluoro-1,2,3,4-tetrahydronaphthalen-2-yl]amino]-N-[1-[1-(2,2-dimethylpropylamino)-2-methylpropan-2-yl]imidazol-4-yl]pentanamide, induced selective apoptosis of chronic lymphocytic leukemia cells from Notch mutated CLL patients, while it exhibited little apoptosis induction of normal T cells or T cells from Notch-unmutated patients, suggesting that PF-03084014 targeted CLL patients with Notch activating mutations [60]. In a preclinical model of T-cell acute lymphoblastic leukemia (T-ALL), PF-03084014 caused cell growth arrest and enhanced apoptosis by inducing cell cycle arrest at the G0–G1 phase [6]. Moreover, PF-03084014 altered endothelial cell tube formation and mammosphere formation *in vitro*, and exhibited antitumor and antimetastatic activity in breast xenograft model [61]. In a patient-derived CRC explant model with elevated Notch expression, PF-03084014 induced tumor growth arrest via down-regulation of the Notch pathway [62]. In a phase I trial, PF-03084014 showed drug tolerability and high rate of response in desmoid tumors [63]. When combined with gemcitabine, PF-03084014 treatment resulted in tumor regression in 3 of 4 pancreatic cancer xenograft models via targeting malignant cancer stem cells. Notably, the combined therapy further showed enhanced efficacy in the inhibition of tumor cell proliferation and angiogenesis, attenuating growth of primary tumor and controlling metastatic dissemination in a highly aggressive orthotopic model [64]. Unlike other agents in this class, the toxicities of PF-03084014 were generally mild or moderate, including diarrhea, nausea, fatigue, hypophosphatemia, vomiting, rash, and decreased appetite [65].

## Synergistic effect of GSI with chemotherapy, radiotherapy and other signal transducers

Based on published data from clinical trials, single agents of GSIs have therapeutic effects in cancers. Mechanically, the inhibitory effect of GSIs was especially significant in CD133 (+) cells, suggesting that Notch pathway blockade may be a strategy to target cancer stem cells (CSCs) [66,67]. In addition, Notch inhibition attenuated sphere formation and xenograft growth of CD44(+) CD24(low+) triple negative breast cancer initiating stem cells [68]. To achieve the best curative effect, the combination of GSIs with other therapies has also been studied.

*GSI with chemotherapy drug*

*In vivo* studies showed that Notch inhibitors inhibit tumor growth and sensitize cancer cells to a variety of chemotherapy drugs [69,70]. The treatment of NSCLC cells with platinum enriched CD133 (+) cells. The later is cross-resistant to chemotherapy. In these enriched CD133 (+) cells, Notch signaling is activated, and Notch inhibition enhanced the anti-tumor effect in transplanted tumors and cancer patients previously receiving cisplatin treatment [71]. Vincristine (VCR), an anti-microtubule agent, was also synergized with Notch inhibitor by augmenting VCR-induced apoptosis in HeLa cells [72]. Importantly, Notch inhibition was also found to sensitize to the targeted therapy [73]. Sorafenib (Nexavar), the exclusive clinically approved drug for advanced hepatic carcinoma, is a multiple kinase inhibitor. Inhibition of Notch3 signaling enhanced sorafenib-induced apoptosis via down-regulation of p21 and up-regulation of pGSK3βSer9 in HCC cells, suggesting that Notch3 inhibition increased the anti-cancer effect of sorafenib through overcoming drug resistance [74].

*GSI with ionizing radiation*

As ionizing radiation and Notch inhibition played key roles in suppressing tumor vasculature, the potential cooperativity between Notch inhibitors and ionizing radiation in tumor growth regression was explored in somatic tumors. In human colorectal carcinoma xenografts, administration of Notch inhibitors after ionizing radiation resulted in growth arrest, with increased tumor vessel density but reduced tumor blood flow, which promoted extensive tumor necrosis [75]. Mechanically, Notch inhibitor induced apoptosis of cancer cell via the regulation of MAPK and Bcl-2 family proteins, and that GSI administration blocked Notch-induced radiation resistance [76].

*GSIs with other signal transducers*

A role for Notch signaling in cancer progression and survival suggests that targeting this pathway alone or in combination with other pathways represents a promising therapeutic strategy. Since Notch signaling and janus kinase 2 (JAK2)/signal transducers and activators of transcription 3 (STAT3) pathways have been shown to participate in the initiation and progression of pancreatic ductal adenocarcinoma (PDAC), targeting these two pathways simultaneously through dual treatment of gamma-secretase inhibitor IX (GSI IX) and JAK2 inhibitor (AG-490) dramatically impaired growth and invasion of human pancreatic cancer cell and attenuated tumor progression *in vivo* compared to monotherapy, indicating that combined inhibition of Notch and JAK2/STAT3 pathways exceeded either agent alone [77]. γ-Secretase inhibitor has been shown to efficiently induce apoptosis via induction of Noxa, a pro-apoptotic Bcl2-homology 3 domain (BH3)-only protein of the Bcl-2 family. The biologic effects of γ-secretase inhibitor GSIXII combined with BH3-mimetic inhibitor of antiapoptotic proteins Bcl-2/Bcl-xL (i.e., ABT-737) have been evaluated. This study showed a synergistic apoptotic response [78]. Interestingly, in a gastric cancer xenograft model, combined treatment of extracellular signal-regulated kinase (ERK) inhibitor PD98059 and Notch inhibitor induced additive anti-cancer effects than a single inhibitor [79]. Moreover, the combination treatment of the γ-secretase inhibitor compound E, proteasome inhibitor bortezomib and histone deacetylase inhibitor romidepsin significantly inhibited tumor growth and prolonged survival in a murine model of human ATL, compared with all other treatment groups [80].

## Other inhibitors of Notch signaling

In addition, other receptor-specific approaches can reduce the invasion of cancer, for instance, siRNA-mediated inhibition of Notch1 has been found to induce tumor growth arrest through nanoparticle encapsulation [81]. Furthermore, monoclonal antibodies against Notch signaling have also been developed [82,83]. MEDI0639, an antibody targeting DLL4 that inhibits the binding of DLL4 to Notch1, was found to promote human umbilical vein endothelial cell growth and human vessel formation [84]. In addition, γ-secretase, a transmembrane protease that is composed of four subunits encoded by four genes, PSEN1, PSENEN, NCSTN and APH1, can be inhibited using

specific mAbs targeting NSTN. Importantly, NCSTN can be used as a molecular marker for the targeted therapy [85].

The natural agents, including curcumin, 3,3′-diindolylmethane (DIM), resveratrol, 3,5-bis(2,4-difluorobenzylidene)-4-piperidone (DiFiD) and epigallocatechin-3-gallate (EGCG), have been reported to be alternative strategies for the treatment of cancer via repressing Notch signaling [86,87]. Honokiol, a traditional Chinese medicine, was also found to increase the sensitivity of colon cancer stem cells to ionizing radiation (IR) via suppression of activated Notch signaling. Furthermore, the combination of honokiol and IR significantly suppressed tumor xenograft growth, which was coupled with reduced expression of cancer stem cell marker and Notch signaling in xenograft tissues, suggesting that honokiol is a potent inhibitor of cancer growth that targets the stem cells by inhibiting the Notch signaling pathway [88].

Furthermore, inhibitors of aspartate β-hydroxylase (ASPH), a cell surface protein that catalyzes the hydroxylation of epidermal growth factor (EGF)-like repeats in Notch receptors and ligands, were developed and discovered to reduce prostate cancer growth by a process that relies on the downregulation of the Notch signaling pathway [89]. In addition, the activation of Notch signaling involves the process of Notch receptor endocytosis toward acidic compartments, which required vacuolar H(+) ATPase (V-ATPase) for acidification of endocytic organelles. Inhibition of V-ATPase reduced growth of breast cancer cells via downregulation of Notch signaling [90].

## Conclusion

Notch signaling is a conserved cell fate determining factor in embryo development. However, the deregulation of Notch signaling is frequently observed in many cancers through mutations and amplification of the components of the Notch signaling pathway. In addition, transgenic mice with liver-specific activation of Notch2 are sufficient to induce HCC formation and biliary hyperplasia [15]. This provides an opportunity for the development of targeted therapy. Ample evidence has demonstrated that inhibition of Notch induces tumor growth arrest. Moreover, combined therapy of chemotherapy or radiotherapy with Notch inhibitors also results in a synergistic effect, suggesting Notch inhibitors may improve chemotherapy response. Finally, based on the stratification of patients by Notch activating mutation and amplification, Notch inhibitors combined with chemotherapy or radiotherapy hold great promise for cancer control.

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## Conflict of interest

The authors have no conflicts of interest to disclose.

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