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REVIEW

Canonical and noncanonical NOTCH signaling in the nongenetic resistance of cancer: distinct and concerted control

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Abstract **Therapeutic resistance in cancer is responsible for numerous cancer deaths in clinical practice. While target mutations are well recognized as the basis of genetic resistance to targeted therapy, nontarget mutation resistance (or nongenetic resistance) remains poorly characterized. Despite its complex and unintegrated mechanisms in the literature, nongenetic resistance is considered from our perspective to be a collective response of innate or acquired resistant subpopulations in heterogeneous tumors to therapy. These subpopulations, e.g., cancer stem-like cells, cancer cells with epithelial-to-mesenchymal transition, and drug-tolerant persisters, are protected by their resistance traits at cellular and molecular levels. This review summarizes recent advances in the research on resistant populations and their resistance traits. NOTCH signaling, as a central regulator of nongenetic resistance, is discussed with a special focus on its canonical maintenance of resistant cancer cells and noncanonical regulation of their resistance traits. This novel view of canonical and noncanonical NOTCH signaling pathways is translated into our proposal of reshaping therapeutic strategies targeting NOTCH signaling in resistant cancer cells. We hope that this review will lead researchers to study the canonical and noncanonical arms of NOTCH signaling as an integrated resistant mechanism, thus promoting the development of innovative therapeutic strategies.**

Keywords canonical NOTCH signaling; noncanonical NOTCH signaling; nongenetic resistance of cancer; cancer stem-like cells; epithelial-to-mesenchymal transition; drug-tolerant persisters; NOTCH inhibitors

Introduction

Cancer is a leading lethal disease worldwide. In 2022, 19 964 811 new cases and 9 736 779 cancer deaths were estimated to have occurred worldwide [1]. While lung cancer is the second most frequently diagnosed cancer type, it has remained the leading cause of cancer deaths for many years [2–5]. The occurrence of cancer generally arises from the accumulation of gain-of-function mutations in proto-oncogenes and loss-of-function mutations in tumor suppressor genes [6–8]. Recent advances in biomedical research have led to remarkable improvements in clinical diagnostics and anticancer therapies. In addition to surgery, the development of chemotherapy, radiotherapy, targeted therapy, and immunotherapy benefits patients with cancer [2,9–13]. However, the five-year survival rates of patients with advanced tumors have seen minimal improvement [14]. This clinical retardation is mostly attributed to the therapeutic resistance of cancer [3,15–18]. Therefore, deciphering molecular and cellular mechanisms underlying cancer resistance and developing additional mechanism-based strategies to overcome it are critical.

Therapeutic resistance is associated with genetic and nongenetic mechanisms. Mutations in genes encoding drug targets result in genetic resistance to targeted therapy. However, a growing body of evidence indicates that nongenetic resistance, which is unrelated to target mutations, plays an undeniable role in cancer therapy (reviewed in [19]). Despite limited insights into

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nongenetic resistance, it is likely associated with resistant cancer cells, which survive from treatments in heterogeneous tumors and are equipped with innate or acquired shields (traits) of drug resistance at molecular and cellular levels. From an epigenetic perspective, nongenetic reprogramming events in these resistant cancer cells shape their phenotypic states that are implicated in therapeutic resistance. An improved picture of nongenetic resistance needs to be drawn on the basis of recent advances in the field.

NOTCH signaling is responsible for regulating stem cells and differentiation, as well as tumorigenesis [20–24]. For example, NOTCH1 signaling controls T cell maturation through modulating the strength of T cell receptor (TCR) signals in the thymus [25]. Pathologically, aberrant NOTCH signaling plays a vital role in tumorigenesis. Genome-wide and single-cell RNA sequencing data revealed that NOTCH signaling was hyperactivated in lung adenocarcinoma (LUAD) [26–28]. Conversely, the ablation of *NOTCH1* in *Kras*-induced LUAD mice resulted in elevated p53-mediated apoptosis and remarkable tumor growth retardation [29,30]. Notably, the role of NOTCH signaling in cancer is highly complex and context dependent. For example, NOTCH signaling acts as a proto-oncogene in LUAD [27,29] but as a suppressor in lung squamous carcinoma and small-cell lung cancer [31–33].

NOTCH signaling also contributes to drug resistance. For instance, the mutations of the gene encoding epidermal growth factor receptor (EGFR) is commonly associated with lung tumors [34], which are treated with EGFR inhibitors, such as gefitinib. The upregulation of NOTCH1 or NOTCH3 in LUAD resulted in resistance to EGFR inhibitors, whereas their knockdown resensitized resistant tumor cells to tyrosine kinase inhibitors (TKIs) [35–37]. NOTCH signaling also induces chemoresistance in various types of cancer [38–40]. NOTCH activation appears to be linked to immunosuppressive environments, which are unfavorable for immunotherapy [41,42]. In this review, we focus on the canonical and noncanonical roles of NOTCH signaling in the regulation of resistant cell populations and their nongenetic resistance traits.

Resistant cell populations in cancer

Although the successful decoding of genetic resistance always attempts to convince us to understand nongenetic resistance at a molecular level, its molecular picture has never been satisfactory. Therefore, in this review, we propose considering nongenetic resistance as a collective response of resistant cancer cells to therapy. The known resistant populations discussed below are cancer stem-like cells (CSCs) [43], cancer cells with epithelial-to-mesenchymal transition (EMT) [44], partial EMT cells (also known as hybrid E/M cells in the intermediate states of EMT) [45], and drug-tolerant persisters (DTPs) [46]. Stable resistant cancer cells, as the fourth resistant population, are proposed to be the opposite of DTPs with reversible resistance but are omitted from this review due to limited evidence (reviewed in [19,47]). Whether these resistant populations are present simultaneously in tumors remains unclear.

CSCs, a rare population in heterogeneous tumors, play a crucial role in tumor initiation and nongenetic resistance, especially in resistance to chemotherapy and radiotherapy [48–51]. A $CD34^+CD38^-$ leukemia-initiating cell population in human acute myeloid leukemia was first identified by John Dick and his group in 1997 [52]. Similar populations were subsequently detected in solid tumors and proposed as CSCs or cancer-initiating cells [53,54]. We also identified $c\text{-}Kit^{mid}CD3^+Lin^-$ leukemia stem cells in a *Pten*-null T acute leukemia murine model, $CD166^+CD49f^{hi}CD104^-Lin^-$ CSCs in human NSCLC, and $CDC50A^+Lin^-$ CSCs in human ovarian tumors [38,55,56]. These populations, which are transformed by genetic mutations, are derived from tissue stem cells, transit-amplifying progenitors, or differentiated lineage cells [53,57]. Although the frequency of CSCs in heterogeneous tumors varies considerably, they are shown to be resistant to radiotherapy and chemotherapy, leading to relapse [38,43].

Epithelial cancer cells undergo EMT from the epithelial state to the mesenchymal state; this transformation is evolutionarily conserved in embryonic development as well as wound healing (reviewed in [58]). Epithelial cells establish a cell-cell layer as a physical barrier through their gap junctions, whereas mesenchymal cells with migratory properties are in loose contact with surrounding connective tissues. EMT cancer cells, which closely resemble mesenchymal cells, are characterized by the downregulation of the epithelial marker E-cadherin and upregulation of the mesenchymal marker Vimentin. As a result, these cells acquire the ability to invade and migrate into neighboring tissues or the circulation. In addition to their invasive property, these cells exhibit stem cell properties and therapeutic resistance and contribute to the development of an immunosuppressive microenvironment [59]. The TGF-β and WNT pathways cooperatively activate a regulatory transcription program involving transcription factors, such as Snail, Slug, TWIST1, and ZEB1, to secure the mesenchymal phenotype [59]. The reciprocal repression between miR-200c and ZEB1 further refines the EMT regulatory machinery at a transcriptional level [60,61]. Recent studies have demonstrated that certain cancer cells, which undergo a partial epithelial-mesenchymal conversion with varying expression levels of epithelial and mesenchymal markers, are considered as partial or hybrid EMT (reviewed in [62]). Although poorly defined, cancer cells with partial

EMT also show resistance to cancer therapy. Therefore, in terms of resistance, cancer cells with EMT or partial EMT are discussed as the same type of cells in this review.

DTPs are initially identified as a small population of cancer cells with reversible resistance to cancer therapy [46]. The DTP state is epigenetically reversible with activated IGF1 signaling and JARID1A-dependent chromatin alteration. Heterogeneous DTPs contain cycling and slow-cycling subpopulations [46,63–67]. A recent study using single-cell and bulk RNA sequencing has also demonstrated that DTP-related genes are implicated in nuclear division and cell cycle pathways [68]. The definition of the drug-tolerant population varies depending on the context. In various studies, DTPs in multiple types of cancer appear to be positive for ABCB5, CD133, CD271, JARID1A, and/or aldehyde dehydrogenase [69]. Similar to EMT cells or CSCs, some DTPs are reported to have the EMT phenotype or stemness property in addition to therapeutic resistance [69]. A strict distinction between DTPs and two other resistant subpopulations remains to be elucidated.

Molecular traits of resistant cancer cells

The genetic evolution of resistance is driven by sequential mutations in target genes, which greatly affect drug sensitivity. By contrast, nongenetic resistance is possibly associated with molecular traits in resistant cancer cells (Fig. 1), such as drug transport and metabolism; DNA repair; protein homeostasis; decreased cell death; and a hypoxic and an immunosuppressive microenvironment (reviewed in [43,70]). In this section, we discuss how these molecular traits as a whole support resistant cell populations.

Drug efflux by the ATP binding cassette (ABC) transporter family plays a crucial role in resistant cancer cells [71]. These ABC transporters control intracellular drug levels by transporting chemical compounds through cell membranes [72]. Among 48 ABC transporters, 28 were found to be inversely correlated with the response of NCI60 cancer cells to drugs obtained from the National Cancer Institute of the United States [73]. Collectively, at least 19 members were reported to contribute to the efflux of known anticancer drugs in the literature [74]. Of the 19 reported drug efflux transporters, 15 have putative binding sites in their promoters for EMT transcription factors, such as Snail, Slug, and TWIST1 [75]. Nine of them are indeed inactivated by the siRNA downregulation of the EMT transcription factors TWIST1 and ZEB1 in invasive breast cancer cells, resulting in reduced chemoresistance [75]. Compared with CD133$^-$ non-CSCs, CD133$^+$ lung CSCs are more resistant to cisplatin with the help of elevated ABCG2 (or the breast cancer resistance protein (BCRP)) [71]. ABCB1 (or multidrug resistance 1 (MDR1)) appears to mediate the resistance of NSCLC to TKIs, such as crizotinib and ceritinib; this resistance is abolished by *ABCB1* knockdown or the inhibitors of its encoded proteins [76].

The involvement of drug metabolism in cancer resistance is more complex than that of drug efflux. Some antitumor drugs, such as prodrugs, require metabolic activation for their therapeutic effects, whereas some are inactivated or detoxified via drug metabolism in resistant cancer cells. Drug activation or inactivation is mediated by drug-metabolizing enzymes (DMEs), which include the cytochrome P450 (CYP) family, glutathione-*S*-transferase (GST) superfamily, and uridine diphosphate-glucuronide transferase (UGT) superfamily. Some DMEs are reported to be important in drug resistance. The CYP protein CYP1B1 was detected in 14 types of tumors, e.g., lung, breast, and colon cancers, but not in corresponding normal tissues [77,78]. For comparison, the expression of *CYP1A1*, *CYP27B1*, and *CYP27C1* was reported only in breast, lung, and colon cancers [78,79]. Interestingly, the expression of *CYP1A1* and *CYP1B1* increased in breast CSCs [80]. The knockdown of *CYP27C1* in the NSCLC cell lines A549 and H1975 resulted in an increased response to the chemotherapeutic drug vinorelbine and TKI SKLB610 [81], suggesting the important role of CYP27C1 in drug resistance. *GSTP1*, a GST family member, is upregulated in cisplatin-resistant or sphere-replating lung cancer cells [82,83]. Its inhibition by miR-133b or shRNA attenuated cisplatin resistance in the abovementioned resistant lung cancer cells. Enzymes in the UGT family contribute to inactivating the glucuronidation of 73 targeted and chemotherapeutic drugs, which have recently been summarized and reviewed [84]. Interestingly, the UGT family gene *UGT1A6* is a top upregulated gene reported in erlotinib-resistant tumors from patients with lung cancer [85]. This finding underscores the importance of UGT enzymes in drug resistance.

Resistant cancer cells show enhanced DNA damage response (DDR) and DNA repair. DDR is a highly conserved intracellular machinery for protecting cells from genotoxic damage (reviewed in [86–88]). After damaged DNA is recognized by the MRE11–RAD50–NBS1 complex, DDR is initiated by ataxia-telangiectasia mutated (ATM) protein kinase and ataxia-telangiectasia and Rad3-related (ATR) kinase, which activate the checkpoint serine/threonine kinases CHK1 and CHK2 for cell cycle arrest (or slow cycling), DNA repair, or p53-mediated apoptosis. Slow cycling is actually beneficial for CSCs and DTPs to run DNA repair for a prolonged time. Given that p53-mediated apoptosis is commonly blocked in resistant cancer cells (see the description below), these cells launch DDR or partial DDR to establish resistance to genotoxic therapy, e.g., chemotherapy [89]. L1CAM (CD171) is preferentially

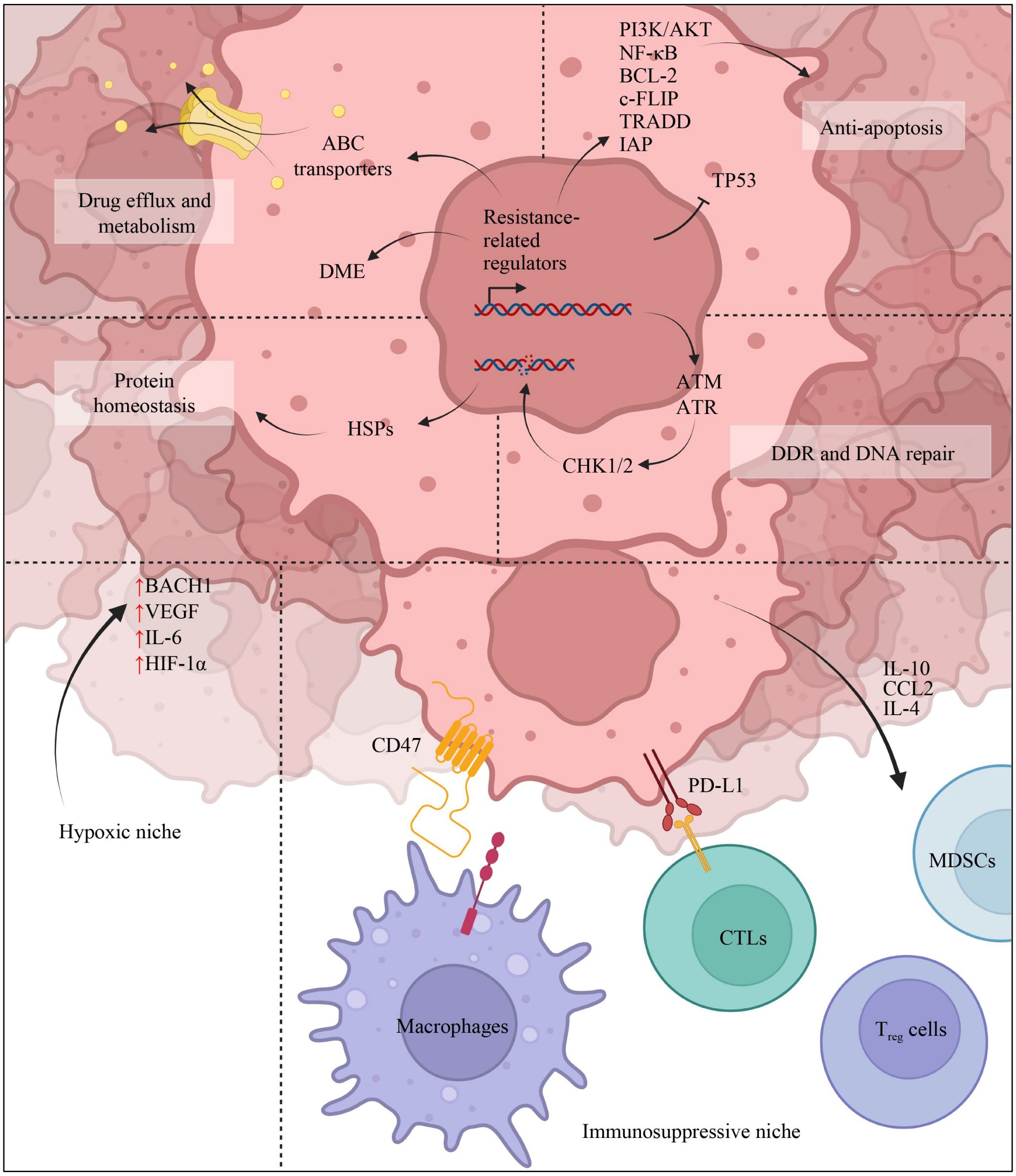

Fig. 1 Molecular traits associated with resistant cancer cells. Functional properties, including drug efflux and metabolism, protein homeostasis, DDR and DNA repair, and cell survival (antiapoptosis), as well as the hypoxic and immunosuppressive microenvironment, are involved in therapeutic resistance in resistant cancer cells. These resistance traits are controlled by functional machinery and signaling pathways. Drug efflux is mainly modulated by the ABC transporter family. Drug metabolism is regulated by DMEs, which include the CYP family, GST superfamily, and UGT superfamily. The regulation of protein homeostasis is mainly mediated by the molecular chaperones HSPs for protein folding. DDR is a conserved intracellular machinery for protecting cells from genotoxic damage. In DDR, DNA repair is sensed and initiated by ATM and ATR. The survival of resistant cancer cells requires the activation of antiapoptotic pathways (e.g., PI3K–AKT and NF-κB signaling) and antiapoptotic proteins (e.g., BCL-2, c-FLIP, TRADD, and IAP) and suppression of cell death mediated by p53 or other proapoptotic regulators. The hypoxic and immunosuppressive microenvironment supports cancer cells to develop resistance to radiotherapy, chemotherapy, targeted therapy, and/or immunotherapy. Created with BioRender.com.

expressed in glioblastoma stem cells (GSCs) and provides radiation protection to these cells by upregulating the expression of *NBS1* [90]. RAD50 is required for the enhanced DDR of triple negative breast CSCs in response to chemotherapy [91]. The upregulation of ATM in cisplatin-resistant lung cancer cells or by the EMT regulator ZEB1 in epirubicin-resistant breast cancer cells accounts for chemoresistance [92,93]. The activation of the DDR checkpoint CHK1 in CD133$^+$ lung CSCs and recurrent breast tumors is an indicator of chemoresistance [94] and radioresistance [95], respectively. As expected, the six DNA repair pathways are active in CSCs derived from various tumors, as summarized in a recent review [96].

Protein homeostasis is important for cancer development and resistance. Its regulation is mediated by heat shock proteins (HSPs), which include three HSP families, namely, HSPA (HSP70), HSPB (HSP90), and HSPC (small HSPs, e.g., HSP27), and serve as molecular chaperones for protein folding under stress (e.g., heat) and cancer [97]. Cancer development requires the accumulation of genetic mutations in oncogenes or tumor suppressors, which likely induce translated oncoproteins to become less stable than their wild-type counterparts. HSP70 and HSP90 contribute to the stabilization of mutated oncoproteins and protect cancer cells from any potential crisis of proteostasis. Mutated TP53 is stabilized by HSP70 for its dominant negative effect on gene transcription [98,99]. HSPs are also involved in therapeutic resistance. HSP70 and HSP90 function as chaperones for the regulatory R2 subunits of ribonucleotide reductase, a key enzyme that produces deoxyribonucleotides for highly active DNA synthesis and repair in chemoresistance [100]. HSP27 mediates the TGF-β-induced resistance of A549 cells to cisplatin [101] and resistance of lung CSCs to cisplatin and gemcitabine [102].

The survival of resistant cancer cells from chemotherapy and targeted therapy requires the activation of antiapoptotic programs. For example, antiapoptotic PI3K–AKT signaling and NF-κB signaling are upregulated in CSC populations of various tumors to prevent chemotherapy- and radiotherapy-induced cell death [103–106]. Similarly, antiapoptotic proteins (e.g., BCL2/BCL-xL, c-FLIP, and TNFR1-associated death domain protein) and inhibitors of apoptosis proteins (e.g., survivin) are activated in CSCs [107–109]. EMT transcription factors also regulate apoptotic programs, favoring drug resistance. In lung cancer cells, the EMT regulators Snail and Slug antagonize p53-mediated apoptosis [110]. ZEB1 is a transcriptional activator of the antiapoptotic BCL-2, which contributes to drug resistance [111,112].

Resistant cancer cells are generally protected and supported by the tumor microenvironment. In addition to nutrients and growth factors, hypoxia in the tumor microenvironment is a critical factor for tumor development and resistance [113,114]. Hypoxia favors the maintenance of resistant lung CSCs via elevating the expression of CSC signature genes and the cytokine genes *VEGF* and *IL-6* [115,116]. Importantly, hypoxia induces the expression of the transcription factor hypoxia-induced factor-1α (*HIF-1α*) in breast CSCs [117] and cancer cells [118]. HIF-1α is involved in the development of cancer resistance by facilitating drug efflux, promoting cell survival, and repairing DNA damage (reviewed in [119]). Interestingly, NOTCH signaling is activated in the hypoxic area of heterogeneous lung tumors [120] and accordingly required for the self-renewal and platinum resistance of lung CSCs [38].

Resistant cancer cells evade immune surveillance and resist immunotherapy by hijacking immune checkpoints and modulating immunosuppressive niches. CSCs are reported to have an increased expression of programmed cell death 1 ligand 1 (PD-L1), an immune checkpoint that interacts with its receptor programmed cell death 1 (PD-1) on the surface of cytotoxic T cells, to inhibit the cytotoxic activity of T cells [121–123]. Similarly, CSCs employ CD47 as a “don’t eat me” signal to escape from phagocytosis by innate macrophages [124,125]. These strategies protect CSCs from immune surveillance and enhance their resistance to immunotherapy. At the same time, CSCs generate an immunosuppressive microenvironment by recruiting immunosuppressive cells (e.g., macrophages, T_{reg} cells, and myeloid-derived suppressor cells (MDSCs)) and releasing immunosuppressive cytokines (e.g., TGF-β, CCL2, and IL-4) [126,127]. In turn, the recruited immunosuppressive immune cells release additional immunosuppressive cytokines, e.g., TGF-β and IL-10, to suppress the differentiation and cytotoxicity of T cells in the tumor microenvironment [126]. Such an immunosuppressive tumor microenvironment limits the efficacy of immunotherapy. For instance, TGF-β promotes the expression of the immunoinhibitory CD73 on $CD8^+$ T cells to facilitate resistance to anti-4-1BB/CD137 therapy [128–130].

Canonical NOTCH signaling

NOTCH signaling in mammals is mediated by a family of four conserved receptors designated as NOTCH1, NOTCH2, NOTCH3, and NOTCH4 [131], which display specialized structural and functional features [132,133]. The extracellular domains of NOTCH1 and NOTCH2 contain 36 epidermal growth factor (EGF) modules, which are involved in the interaction between ligands and receptors [134]. By contrast, NOTCH3 and NOTCH4 possess 34 and 29 EGF modules, respectively. Among these repeats, EGF repeat 8 is responsible for ligand specificity. EGF repeats 11–12 facilitate interactions with ligands on neighboring cells (*trans* interactions), whereas repeats 24–29 enable interactions with ligands on the same cells (*cis* interactions) [135,136]. The intracellular domains of NOTCH3 and NOTCH4 are shorter than those of NOTCH1 and NOTCH2 due to the absence of a complete transactivation region [134]. The NOTCH receptors are activated by five NOTCH ligands in two subfamilies; these ligands include Jagged (JAG) 1, JAG2, Delta-like ligand (DLL) 1, DLL3, and DLL4 [131] (Fig. 2). The activation of NOTCH requires the binding of these ligands, except for DLL3, via their Delta/Serrate/LAG-2 (DSL) domain to NOTCH receptors. This ligand–receptor interaction is subject to fine-tuning by NUMB, whose expression is lost in roughly 30% of

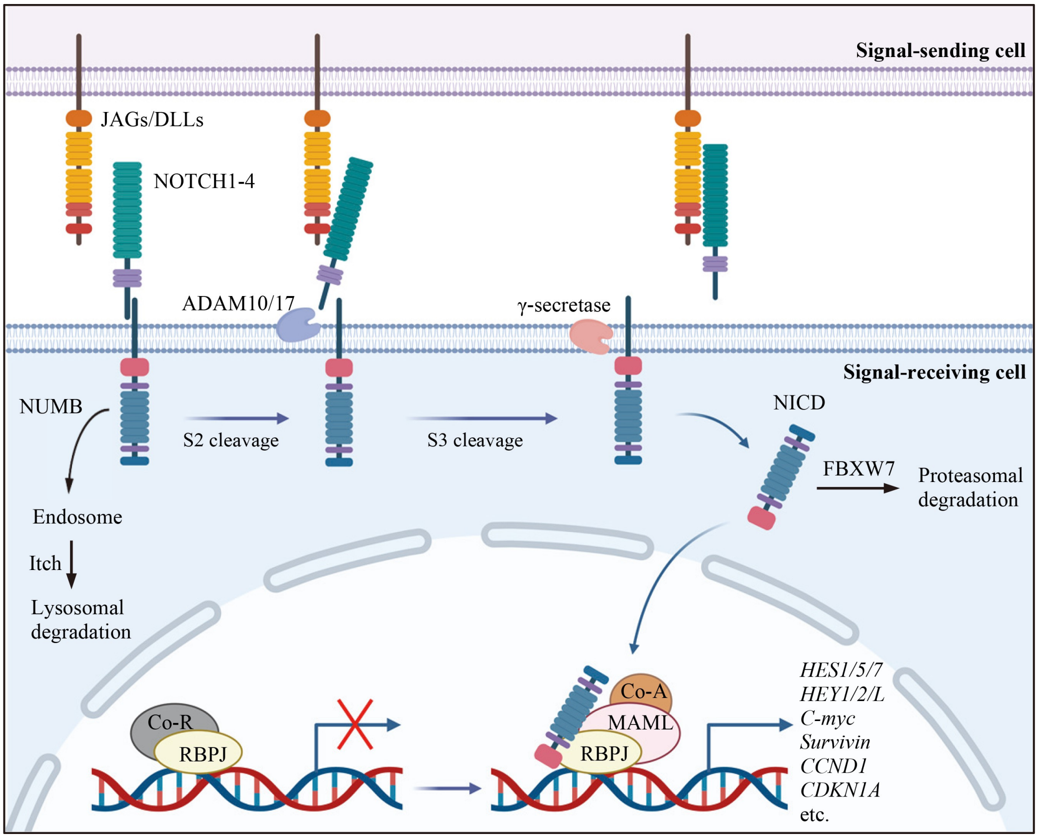

Fig. 2 Canonical NOTCH signaling pathway. In the canonical pathway, the interaction of NOTCH receptors and their ligands, including DLL1, DLL2, DLL4, JAG1, and JAG2, triggers two sequential steps of cleavage mediated by ADAM10/ADAM17 and γ-secretases, resulting in the release of NICD into the cytoplasm. In the absence of NICD, RBPJ interacts with ubiquitous corepressors (Co-R) and histone deacetylases (not shown) to inhibit the transcription of target genes. While NICD is transported into the nucleus and binds to RBPJ, the NICD–RBPJ complex activates MAML, which in turn recruits coactivators (Co-A) to transactivate the promoters of target genes, such as *HES1*, *HEY1*, and *c-MYC*. Furthermore, NUMB facilitates the endocytosis of NOTCH on the plasma membrane. This process is followed by Itch-dependent lysosomal degradation. The E3 ligase FBXW7, which is part of the ubiquitin–proteasome system, promotes the degradation of NICD. Created with BioRender.com.

patients with NSCLC [137]. NUMB facilitates the trafficking of NOTCH1 to late endosomes for degradation by the E3 ligase Itch, whereas the absence of NUMB permits the recycling of NOTCH1 to the plasma membrane [138]. Similarly, NUMB downregulates the stability and membrane accumulation of the NOTCH ligand DLL4 [139].

The interaction between ligands and NOTCH receptors triggers a series of proteolytic cleavages of NOTCH proteins. The S2 site on the transmembrane subunit of NOTCH is cleaved by the enzyme disintegrin and metalloprotease 10 or 17 (ADAM10 or ADAM17), and the complexes of ligands and cleaved extracellular portions of NOTCH are endocytosed into ligand-expressing cells [140]. A subsequent cleavage at the S3 site is performed by a γ-secretase, which releases the NOTCH intracellular domain (NICD) into the cytoplasm [141,142]. Notably, the second cleavage at Valine 1744 occurs at the plasma membrane or at Serine 1747 in endosomes [143,144]. The half-life of NICD is regulated by the ubiquitin–proteasomal system [145]. FBXW7, one of the most commonly mutated proteins in the ubiquitin–proteasome system in human cancer, is reported to mediate the degradation of NICD (reviewed in [146]). The FBXW7-mediated degradation of NICD requires phosphorylation by the cyclin C complex with CDK3, CDK8, or CDK19 [147,148]; GSK3α/β [149,150]; integrin-linked kinase [151]; or serum- and glucocorticoid-inducible kinase 1 (SGK1) [152].

In the absence of NICD, the DNA-binding partner RBPJ (recombination signal binding protein for immunoglobulin kappa J region, also known as CBF1/Suppressor of Hairless/LAG1 (CSL)) is inhibited by transcriptional repressors, such as FHL1C (KyoT2 in rodents) [153,154], SHARP [155], SMRT [156], and Groucho [157]. Upon translocation into the nucleus, NICD, which lacks a DNA binding domain, interacts with RBPJ and the cofactors Mastermind-like transcriptional coactivators (MAMLs) [133,158]. The resulting NICD transcriptional complex then activates the transcription of target genes. The important target genes of NOTCH signaling are hairy and enhancer of split 1/5/7 (*HES1/5/7*) and HES-related with YRPW motif 1/2/L (*HEY1/2/L*), all of which encode basic helix–loop–helix transcription repressors [159]. Additional target genes include *CD25* and *GATA3* in T cells [160,161], *c-MYC* and *survivin* in cancer cells [162,163], *CCND1* in a kidney cell line [164], and *CDKN1A* in keratinocytes [165]. The transactivation of NICD is inhibited by the interaction with the protein Yin Yang 1 (YY1) [166] or by SIRT1-dependent H4K16 deacetylation and LSD1-dependent H3K4 demethylation [167], whereas it is activated by the complex of histone acetyltransferases p300 and p300/CREB binding protein–associated factor [168].

Despite their analogous structures and signaling transduction, members of the NOTCH family often exhibit distinct functions in development and tumorigenesis. For example, NOTCH1, which is frequently mutated in lung cancer, drive tumorigenesis in $Kras^{G12D}$ NSCLC models [137,169]. In contrast to the oncogenic NOTCH1, in $Kras^{G12D}$ NSCLC models, NOTCH2 potentially suppresses tumor development by inhibiting MARK and β-catenin [169]. Similar to NOTCH1, NOTCH3 appears to be a critical driver in NSCLC, wherein it is more frequently mutated than NOTCH1 [27,170,171]. NOTCH4 is either mutated or overexpressed in numerous cancer types and positively correlated with tumor growth, stemness, invasiveness, and angiogenesis (reviewed in [172]). Nevertheless, the precise manner in which the four NOTCH receptors operate within the same tumors remains unclear.

Noncanonical NOTCH signaling

Noncanonical NOTCH signaling involves noncanonical partners or RBPJ-independent NOTCH activity after activation by canonical ligands (Fig. 3A and 3B). When released from the plasma membrane, NICD interacts with components in various signaling pathways, including the WNT, TGF-β, hypoxia, AKT, MAPK, ATM, NF-κB, Sonic hedgehog (SHH), JNK, SIRT1–p53, or cGAS–STING pathways. These noncanonical interactions of NICD are possibly abolished by its FBXW7-mediated degradation [173]. Interestingly, the crosstalk between NICD and its partners has either stimulatory or inhibitory effects on the NOTCH pathway, the partner pathways, or both. The noncanonical partners are classified into two groups: transcription factors (Fig. 3A) and signaling regulators (Fig. 3B). The interacting transcription factors in the first group include β-catenin in WNT signaling [174–177], SMAD3 in TGF-β signaling [178], HIF-1α in hypoxia signaling [179], and YY1 [166]. The interacting molecules in the second group include PINK1 for mTORC2–AKT signaling [180,181] and possibly for mTORC2–DUSP10–MAPK signaling [182–184], ATM for ATM signaling [185], IKKα/IKKβ for NF-κB signaling [180,186–188], GLI2 for SHH signaling [189–191], JIP1 (or officially known as MAPK8IP1) against JNK signaling [192,193], SIRT1 against TP53 signaling [194], and STING against cGAS–STING signaling [195]. The interacting partner Nur77 is a signaling molecule and transcription factor, and its interaction with NICD results in the suppression of TCR signaling [196]. Despite their varying effects on partner signaling pathways, the interactions between NICD and signaling molecules, if not all, appear to be linked to the inhibition of cell death. The interacting mechanisms and related effects are introduced in the following paragraphs.

Another form of noncanonical NOTCH signaling is independent of NOTCH ligands [142,143] (Fig. 3C). Ligand-independent NOTCH signaling is activated by TCRs on T cells. TCRs induce the protein kinase C α (PKCα)- or PKCδ-mediated activation of ADAM10/17; this process is followed by the endosomal cleavage of NOTCH at S2 and S3 sites [197,198]. Moreover, the RAM domain of membrane-bound NOTCH physically interacts with β-catenin, leading to the NUMB-mediated degradation of the NOTCH–β-catenin complex in lysosomes and, as a result, the inhibition of WNT and NOTCH signaling [174–177]. This negative regulation is possibly compromised in lung, breast, and colon tumors carrying *NUMB* mutations or deficiency [27,199–201].

Noncanonical NOTCH signaling can also be activated by noncanonical ligands (Fig. 3C). D'Souza *et al.* reviewed a large class of noncanonical NOTCH ligands, including membrane-tethered proteins, glycosylphosphatidylinositol-linked membrane proteins, and secreted proteins [202]. Although these structurally diverse ligands lack the NOTCH binding DSL domain, they can still interact with NOTCH for the activation or inhibition of NOTCH signaling. For example, Delta-like noncanonical Notch ligand 1 (DLK1) on the plasma membrane contains a DOS domain but not a DSL domain. Given that JAG1 also carries a DOS domain, DLK1 has been proposed to antagonize JAG1-activated NOTCH signaling by competing with JAG1. The secreted protein CCN3 interacts with NOTCH via a tandem EGF binding domain at its C terminus, leading to the activation of NOTCH signaling.

Different roles of the canonical and noncanonical NOTCH signaling pathways in therapeutic resistance

In addition to driving tumorigenesis, NOTCH signaling confers therapeutic resistance to cancer cells, leading to cancer relapse. For example, NOTCH1 expression is positively correlated with the recurrence of lung

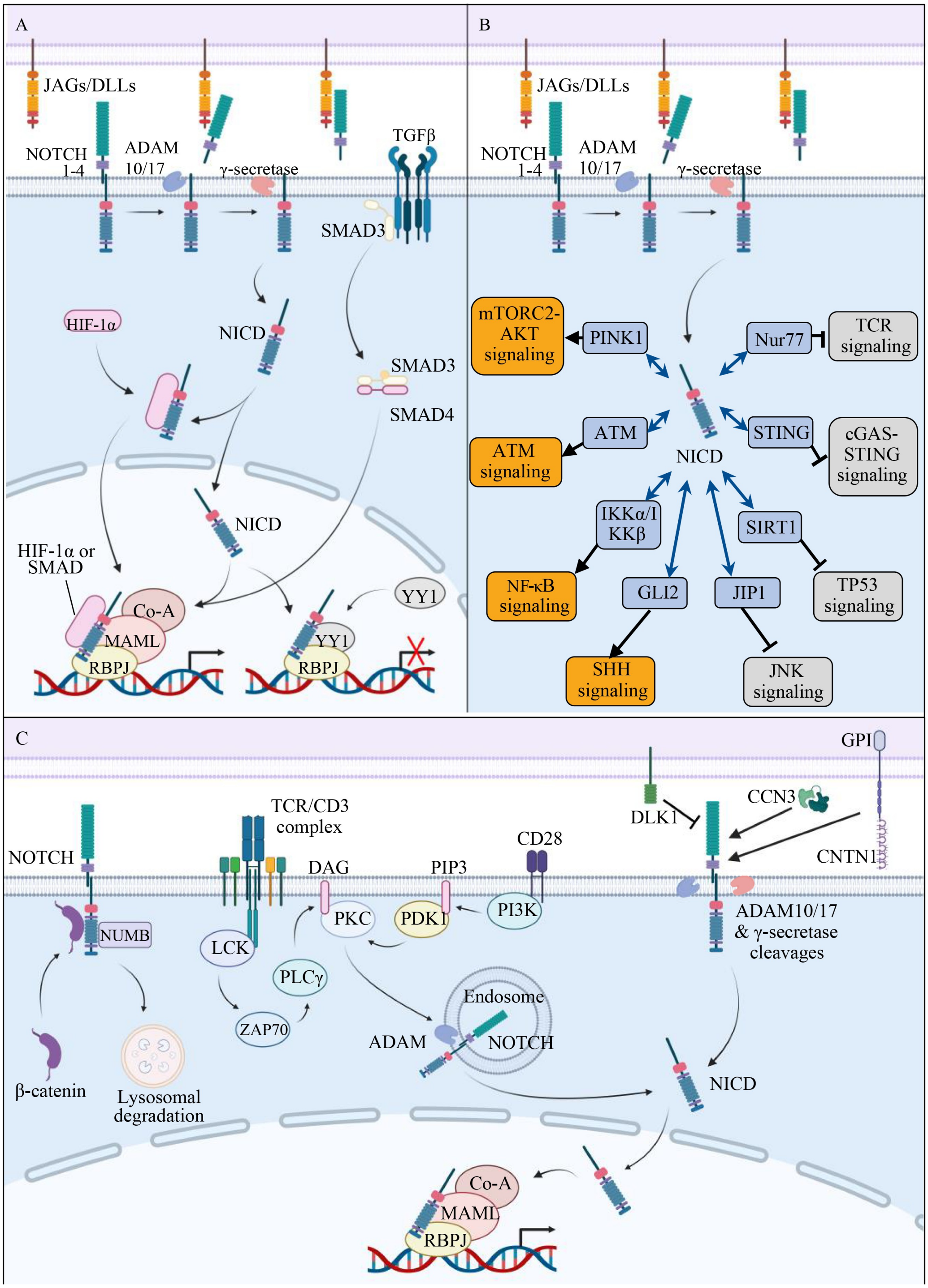

Fig. 3 Noncanonical NOTCH signaling pathway. Three types of noncanonical pathways exist: (1) the crosstalk of cleaved NOTCH (NICD) with noncanonical partners (A, B), (2) signaling regulation independent of ligands (C, left and middle panel), and (3) activation of NOTCH signaling by noncanonical ligands (C, right panel). (A) The interaction of NICD with transcription factors, including SMAD3 in TGF-β signaling, HIF-1α in hypoxia signaling, and YY1, promotes or inhibits the transactivation of NOTCH target genes. (B) NICD interacts with signaling regulators, including PINK1, ATM, IKKα/IKKβ, and GLI2, for the activation of corresponding pathways and with JIP1, SIRT1, STING, and Nur77 for the inhibition of partner pathways. Note that Nur77 is also a transcription factor. (C) Ligands are not needed for the NUMB-mediated degradation of NOTCH–β-catenin complex (left panel) and the TCR-mediated cleavage of NOTCH and NICD-mediated transactivation of NOTCH target genes (middle panel). In addition, NOTCH signaling can be activated by noncanonical ligands (right panel), including membrane-tethered proteins (e.g., DLK1), glycosylphosphatidylinositol (GPI)-linked membrane proteins (e.g., CNTN1), and secreted proteins (e.g., CCN3). DAG, diacylglycerol; PIP3, phosphatidylinositol 3,4,5-trisphosphate. Created with BioRender.com.

adenocarcinoma after chemotherapy with taxane [203]. The high expression of *NOTCH3* was associated with platinum resistance in a cohort of 594 patients with advanced NSCLC at stages III and IV [204]. The nuclear level of HES1, a surrogate marker for the activation of canonical NOTCH signaling, increased in relapsed LUAD tumors treated with EGFR TKIs and was associated with shortened progress-free survival [35]. Consistent with clinical observations, NOTCH1 and NOTCH3 were upregulated in lung cancer cells resistant to chemotherapeutic or targeted drugs [35,36,203,204]. The knockdown or pharmacological inhibition of NOTCH1 and/or NOTCH3 resensitized resistant lung cancer cells to chemotherapeutic or targeted drugs, underscoring the importance of NOTCH signaling in the therapeutic resistance of lung cancer. Although NOTCH-dependent therapeutic resistance has recently been reviewed [205,206], the different roles of the canonical and noncanonical NOTCH signaling pathways in therapeutic resistance remain unclear.

Our recent study has revealed that canonical NOTCH signaling regulates the self-renewal of lung CSCs, whereas noncanonical NOTCH signaling induces chemoresistance of the rare population [38]. Such different roles between the canonical and noncanonical NOTCH pathways were revealed through the pharmacological inhibition of NOTCH activation with different doses of GSI34 [38]. NOTCH inhibition using a high dose of GSI34 (10 μmol/L) resulted in the downregulation of *HES1* and *HEY1* and impeded the self-renewal of lung CSCs. Despite having no effect on the self-renewal regulator *HES1*, a low dose of GSI34 (1 μmol/L) suppressed the chemoresistance of lung CSCs. These unexpected observations prompted us to explore the different roles of the canonical and noncanonical NOTCH pathways in the regulation of therapeutic resistance. As discussed below, the canonical pathway of NOTCH appears to contribute to the maintenance (or homeostasis) of resistant cancer cells, whereas its noncanonical pathway likely regulates resistant functions in these cells.

Canonical NOTCH signaling induces or maintains resistant cancer cells

Canonical NOTCH signaling via the NOTCH1–HES1–STAT3 axis regulates the self-renewal of stem cells and lineage fate of T cells [38,207]. As demonstrated by our own research and that of other scientists, NOTCH1 signaling plays an important role in maintaining the self-renewal of chemoresistant CSCs [38,208] (Fig. 4). The signaling scaffold protein STRAP antagonizes the epigenetic silencing of *HES1* and *HES5* by impairing the assembly of polycomb repressive complex 2, thereby enhancing the NOTCH-mediated self-renewal of colon CSCs [209]. Accordingly, the glycosylation of NOTCH by the glycosyltransferase GnT-III or competitive binding of Vasorin to NOTCH1 disrupted the interaction between NUMB and NOTCH1 as well as the lysosome degradation of NOTCH1, facilitating the activation of the

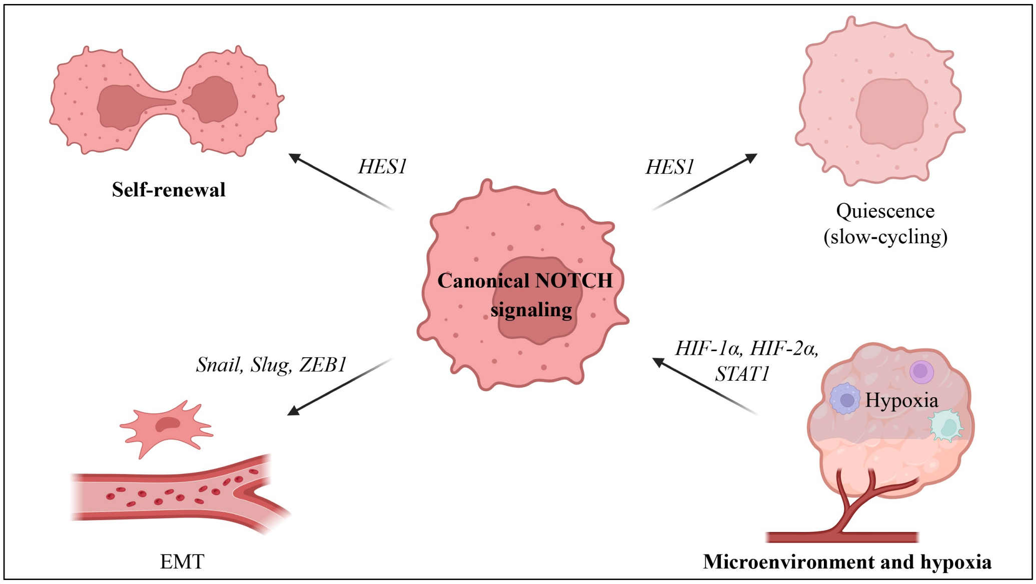

Fig. 4 Roles of the canonical NOTCH pathway in the induction and maintenance of resistant cancer cells. The canonical NOTCH pathway maintains the self-renewal and quiescence of CSCs (or slow-cycling of DTPs) via canonical downstream regulators, e.g., HES1. This pathway also controls EMT through modulating the transcription of the core regulators of EMT, e.g., *Snail*, *Slug*, and *ZEB1*. The activation of canonical NOTCH signaling appears to be promoted by the interaction of resistant cancer cells with the hypoxic microenvironment. Created with BioRender.com.

self-renewal program in ovarian cancer cells or hypoxic glioma stem cells [210,211]. The competitive binding of RFC4 to NICD1 prevented the CDK8-mediated phosphorylation and subsequent FBXW7-mediated degradation of NICD1; this effect consequently promoted the NOTCH-dependent stemness and metastasis of NSCLC [212]. The interaction between NDR1 and NICD resulted in the disruption of the FBXW7–NICD complex and FBXW7-mediated degradation of NICD, thereby enhancing the stemness of breast CSCs [213]. These observations support the notion that canonical NOTCH signaling is important for the homeostasis of CSCs, which are a primary contributor to nongenetic resistance. Given that some EMT cells function as CSCs in cancer metastasis [214], they are likely to be regulated by canonical NOTCH signaling [215].

Canonical NOTCH signaling controls stem cell quiescence via the downstream regulator HES1 in adult tissues [216–219] and CSCs [220] (Fig. 4). Quiescence protects tissue stem cells from replicative and genotoxic stress [221,222]. Although most tumor cells are proliferative, slow-cycling subpopulations (e.g., CSCs and DTPs), which are resistant to genotoxic chemotherapy or targeted therapy, exist in tumors [223]. Two interconvertible subsets of CSCs with differential cycling activities were observed in colon cancer: LGR5$^+$ fast-cycling CSCs (roughly 13% of the total CSCs) and BMI1$^+$ slow-cycling CSCs (87% of the total CSCs) [220]. Interestingly, active NOTCH signaling was present in slow-cycling CSCs but not in LGR5$^+$ fast-cycling CSCs. Consistent with the role of canonical NOTCH signaling in quiescence, its blockade by GSI or *JAG1* shRNA resulted in a decreased expression of *HES1* and *HES5* and a reduction in BMI1$^+$ slow-cycling CSCs. Conversely, the activation of NOTCH signaling accounted for the expansion of BMI1$^+$ CSCs. Similarly, a drug-persistent subset of GSCs exhibited NOTCH activation and slow-cycling properties [224]. GSI or a dominant-negative mutant of *MAML* blocked NOTCH signaling and reduced drug-persistent GSCs [224]. Slow-cycling DTPs in lung cancer or colon cancer were also positive for NOTCH1 and downstream HES1 and resensitized by *NOTCH1* knockdown and GSI to the EGFR TKI osimertinib or chemotherapy [63,225].

Canonical NOTCH signaling regulates the transition of epithelial cancer cells to the mesenchymal state via complex interactions with the core regulatory machinery of EMT, including TGFβ signaling, EMT-related transcription factors, and noncoding microRNAs (Fig. 4). For instance, the canonical NOTCH pathway contributes to TGFβ-induced EMT in cancer cells. The inhibition of NOTCH signaling by *JAG1* siRNA or GSI was reported to block TGF-β-induced EMT [226]. At the transcriptional level, NOTCH signaling and EMT-related transcription factors are mutually regulated. Components in NOTCH1 signaling are controlled by the miR200c–ZEB1 regulatory loop, which modulates the reversible transition between EMT and mesenchymal-to-epithelial transition (MET) (reviewed in [227]). The EMT-suppressive miR-141 and miR-200c, members of the miR200c family, translationally inhibited multiple genes in NOTCH signaling, e.g., *JAG1*, *MAML1*, and *MAML2*, whereas upregulated ZEB1 in resistant EMT cancer cells potentiated NOTCH signaling via inhibiting the miR-200c family [228]. By contrast, canonical NOTCH signaling directly induces the expression of EMT-related transcriptional factors, e.g., *Snail*, *Slug*, and *ZEB1*, to promote EMT. NOTCH has been reported to directly transactivate the promoter of *Snail* and indirectly stabilize its encoded protein in ovarian cancer cells under hypoxia [229]. Similarly, NOTCH signaling activates *Slug* expression in a RBPJ-dependent manner [230,231]. In NSCLC cells, NOTCH3 transcriptionally activated *ZEB1*, which encodes a key mediator of TGF-β-induced EMT [232]. As indicated above, the blockade of the CDK8/FBXW7-mediated degradation of NICD favored the NOTCH-dependent metastasis of NSCLC [212].

The interaction between CSCs and their microenvironment stimulates canonical NOTCH signaling to maintain resistant CSCs (Fig. 4). As represented by the increased expression of *HES1* and *HEY1* in lung CSCs, canonical NOTCH signaling was stabilized and activated in the hypoxic areas of lung tumors, thereby maintaining the stemness of CSCs [120,233]. This mechanism is consistent with the reported accumulation of CSCs in hypoxic areas of lung tumors [115]. Similarly, in the CSCs that resided in hypoxic areas of glioblastoma, the hypoxia-induced protein HIF-1α interacted with and stabilized NICD, thereby sustaining canonical NOTCH signaling [179]. HIF-1α and HIF-2α were shown to boost NOTCH signaling through a strong synergy with MAML1 [234]. In addition to hypoxia, immune and stroma cells contribute to the NOTCH-mediated maintenance of CSCs in tumors. The cytokine G-CSF secreted by breast CSCs induced the accumulation of immunosuppressive MDSCs in the CSC microenvironment, which in turn enhanced the self-renewal of CSCs by activating canonical NOTCH signaling [235]. Stroma cells were found to stimulate RIG-I-dependent antiviral signaling in breast cancer cells through the delivery of exosome-derived RNA. The transcription factor STAT1 downstream from RIG-I signaling cooperated with NOTCH3 signaling to upregulate the transcription of canonical NOTCH genes for the maintenance of resistant CSCs [236].

In addition, a limited number of reports have indicated that NOTCH signaling is directly involved in the regulation of resistant properties in a canonical manner. For example, NOTCH1 and the cofactor RBPJ were observed to interact directly with the promoter of *ABCC1* and activate its transcription in the etoposide-resistant breast cancer cell line MCF7/VP [237]. However, although the RBPJ-dependent transcriptional regulation of resistant phenotypes is possible, noncanonical NOTCH signaling may play a dominant role in their regulation. A good example is that FOXC2 is predominantly regulated by noncanonical NOTCH signaling in a prostate-specific *Pten* null mouse model, even though NOTCH/RBPJ binding elements are available on the *FOXC2* promoter [238].

Noncanonical NOTCH signaling regulates therapeutic resistance in resistant cancer cells

Although our recent experimental data linked drug resistance to noncanonical NOTCH signaling, our understanding of this novel link remains limited likely because most studies are focused on the role of canonical NOTCH signaling in cancer resistance. As stated in the previous section, the blockade of canonical NOTCH signaling generally results in the loss of resistant cancer populations, e.g., CSCs, leading to impaired resistance. Herein, we discuss a distinct role of noncanonical NOTCH signaling in drug resistance by summarizing the existing evidence in the literature and link the noncanonical NOTCH-interacting network with the aforementioned resistance traits (Fig. 5 and Table 1).

NOTCH signaling promotes drug efflux through the upregulation of ABC transporters, e.g., ABCB1, ABCC1, and ABCG2, as supported by observations showing that NOTCH inhibition affects efflux activity in chemoresistant cancer cells [239,240]. The NOTCH-mediated regulation of ABC transporters is achieved in a canonical and noncanonical manner. As described above, canonical NOTCH signaling transactivates the promoters of *ABCC1* in breast cancer cells [237] and *ABCG2* in retinal stem cells [241]. Conversely, *ABCB1* expression appears to be regulated by noncanonical NOTCH signaling (Fig. 5). Huang *et al.* demonstrated that

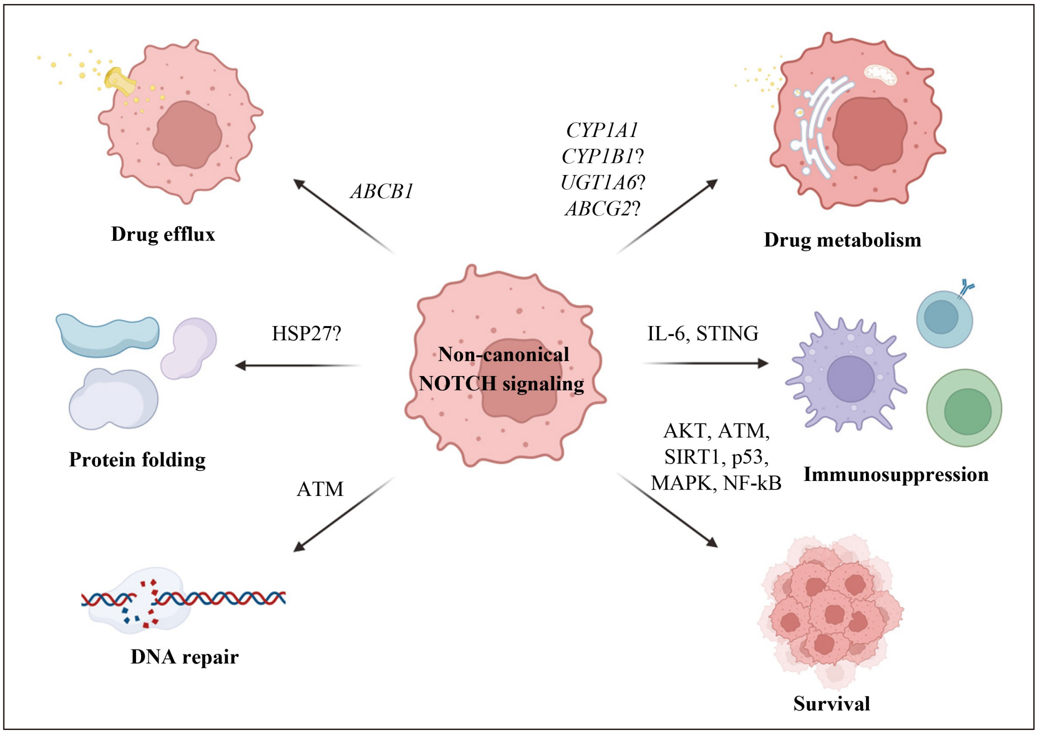

Fig. 5 Roles of the noncanonical NOTCH pathway in the regulation of resistance traits. The noncanonical NOTCH pathway cooperates with other signaling molecules or pathways to regulate resistance traits. Despite limited evidence, the resistant functions regulated by the noncanonical NOTCH pathway appear to involve drug efflux and metabolism, DNA repair, protein folding, survival, and immune response. *ABCB1* and *CYP1A1* are the known targets of the noncanonical NOTCH pathway in drug efflux and metabolism. The chaperone activity of HSP27 is hypothetically enhanced by the NOTCH1–mTORC2–AKT–HSP27 axis. DDR-induced DNA repair is stimulated by the interaction of NOTCH1 and ATM. The inhibition of apoptotic programs possibly results from MDM2 stabilization modulated by the noncanonical NOTCH–PINK1–mTORC2–AKT axis and the NOTCH–ATM axis, p53 inactivation by the interactions between NOTCH1 and SIRT1 and between NOTCH1 and p53, proapoptotic protein inhibition by the NOTCH1–mTORC2–DUSP10–MAPK axis, or antiapoptotic protein activation by the NOTCH1–IKKα axis. The immunosuppressive microenvironment is supported by the IL-6 and cGAS–STING signaling pathways, which are modulated by the noncanonical NOTCH pathway. Note that the hypothetic targets for the noncanonical NOTCH pathway are labeled with question marks. Created with BioRender.com.

Table 1 Interacting partners of NOTCH and resistance-related functions

Category	NOTCH partners	Signaling pathways	Functions	References
Transcription factors	HSP70, HSP90	NOTCH signaling	Stabilization of NICD	[254,255]
	HIF-1α	NOTCH signaling	(1) Stabilization of NICD in hypoxic areas; (2) upregulation of *ABCB1*	[179,243]
	SMAD3	TGFβ and NOTCH signaling pathways	Coactivation of genes with RBPJ- and SMAD-binding motifs in their promoters	[178]
	YY1	NOTCH signaling	Inhibition of NOTCH target genes	[166]
	β-catenin	WNT/β-catenin signaling	Inhibition of WNT/β-catenin signaling	[174–177]
Signaling regulators	ATM	ATM signaling	Blocking the ATM-mediated activation of TP53-associated apoptosis	[185,253]
	ASK1	p38 signaling	(1) Inhibition of ASK and p38 signaling; (2) suppression of ROS-induced apoptosis	[318]
	GLI2	SHH signaling	(1) Activation of antiapoptotic bcl-2; (2) suppression of TRAIL-induced apoptosis; (3) transcriptional activation of *ABCB1*	[189–191,319]
	IKKα/IKKβ/NF-κB	NF-κB signaling	(1) Activation of NF-κB signaling; (2) suppression of TNFα-induced apoptosis; (3) induction of IL-6 expression in macrophages for the immunosuppressive microenvironment	[187,274–278]
	JIP1	JNK signaling	(1) Inactivation of JNK signaling; (2) inhibition of TNFα and UV-induced apoptosis; (3) stabilization of *ABCB1* mRNA	[192,193]
	Nur77	TCR signaling	Suppression of TCR-induced apoptosis in T cells	[196]
	p53	TP53 signaling	Transcriptional inhibition of p53-regulated apoptotic genes	[271]
	PINK1	mTORC2–AKT signaling	(1) Suppression of proapoptotic BAX; (2) stablizatin of MDM2; (3) inhibition of TP53-induced senescence and apoptosis; (4) activation of HSP27-mediated protein homeostasis	[181,272]
	PINK1?	mTORC2–DUSP10–MAPK signaling	Inhibition of proapoptotic BIM	[182–184]
	SIRT1	TP53 signaling	(1) Deacetylation of TP53; (2) suppression of p53-induced senescence and apoptosis	[194]
	STING	cGAS–STING signaling	(1) Inhibition of STING activation; (2) suppression of IRF3-induced apoptosis; (3) impairment of immune response and NK immunotherapy	[195,279]
	XIAP	Caspase-mediated apoptotic pathway	(1) Inhibition of XIAP degradation; (2) suppression of caspase-mediated apoptosis	[320,321]
	Unknown	AHR signaling	(1) Stimulation of AHR signaling; (2) induced expression of *CYP1A1*; (3) suppression of UV-induced apoptosis	[248,322]

upregulated NOTCH1 in LUAD induced taxane resistance by stabilizing *ABCB1* mRNA, which was targeted by miR-451 for degradation [203]. That is, NOTCH1 inhibited the phosphorylation and activation of c-Jun, a major component of AP-1, and thus the AP-1-mediated transcription of miR-451. In line with these results, the physical association of NOTCH1 with the scaffold protein JIP1 interfered with JIP1-mediated JNK activation and hence the JNK phosphorylation of c-Jun [192,193]. Moreover, in various contexts, NOTCH signaling has been reasonably predicted to be capable of regulating *ABCB1* expression via interacting with NF-κB [242], HIF-1α [179,243], YY-1 [244], or GLI2 [189–191] in a noncanonical manner.

The NOTCH-mediated regulation of drug metabolism in cancer resistance remains to be understood further. The DME CYP1A1 is reported to be upregulated by NOTCH signaling in multiple myeloma and contributes to NOTCH-induced resistance to bortezomib, an FDA-approved proteasome inhibitor [245]. Its expression is transcriptionally controlled by aryl hydrocarbon receptor (AHR), which is frequently overexpressed in cancer cells [246] and associated with drug resistance [247]. Interestingly, Alam *et al.* reported that NOTCH signaling stimulated AHR via an unidentified pathway to drive the transcription of *IL-22* and *CYP1A1* in CD4$^+$ murine T cells [248]. RBPJ deficiency accounted for an approximately 60% reduction in *CYP1A1* mRNA in these cells, indicating that the canonical and noncanonical NOTCH signaling pathways are involved in the expression of *CYP1A1* (Fig. 5). Given that the drug metabolism genes *CYP1B1*, *UGT1A6*, and *ABCG2* are validated transcriptional targets of AHR [80,249,250], NOTCH signaling may modulate the expression of these genes in the same fashion.

Noncanonical NOTCH signaling enables damaged cells to conduct DNA repair by blocking the ATM-induced activation of apoptosis (Fig. 5). The DDR sensor ATM plays dual roles in cells with DNA damage: promoting DNA repair and inducing p53-mediated apoptosis. Interestingly, NOTCH1 specifically impairs the apoptosis-inducing activity of ATM kinase in human cancer cells and gonad germ cells of *Caenorhabditis elegans* [251,252], underscoring the importance of this conserved mechanism. Independent of its transcriptional activity, NOTCH1 physically interacts with the regulatory FATC domain of ATM; this physical interaction disrupts the binding of FOXO3a to the FATC domain and abolishes the formation of an ATM–FOXO3a–KAT5/Tip60 complex [185]. Considering that FOXO3a is critical for linking ATM to TP53-mediated apoptosis [253], these lines of evidence favor a novel role for noncanonical NOTCH1 signaling in the molecular choice of DDR-induced DNA repair over cell death in response to genotoxic therapy.

The interaction between NOTCH signaling and regulators of protein homeostasis has been partially understood thus far (Fig. 5). The physical interaction of Hsp70 and NICD1 is required for the activation of NOTCH and transcription of NOTCH target genes in $CD4^+$ T cells [254]. Hsp90 also interacted and stabilized NOTCH1 for the transcription of NOTCH target genes, contributing to T cell leukemogenesis [255]. Although whether the interaction of NOTCH and HSP proteins benefits NOTCH-regulated resistance has not yet determined, some clues are available. GO analysis linked NOTCH to protein stability in chemoresistance and indicated a role for NOTCH in protein ubiquitination and processing through HSPA5, HSP90AA1, and other HSP members in the endoplasmic reticulum [239,240]. HSP27 phosphorylation, mainly at three serine residues (S15, S78, and S82), is critical for reversible conversion between the small dimers of phosphorylated HSP27 and the large oligomers of unphosphorylated HSP27 [256]. Dimeric HSP27 has high chaperone activity and antiapoptotic activity to promote drug resistance [256]. In resistant CSCs, NOTCH1 interacts with the PINK1–mTORC2–AKT complex on the surface of mitochondria for the activation of AKT [181], which may in turn phosphorylate HSP27 and confer resistance [257]. This hypothetical regulation of the NOTCH1–mTORC2–AKT–HSP27 axis is supported by observations in murine epidermal differentiation [258,259] and human cancer resistance [181,257,258,260] but remains to be experimentally determined.

Resistance-promoting NOTCH signaling induces cancer cell survival by modulating core apoptotic programs, such as p53-mediated apoptosis. The apoptosis-inducing p53 is the central sensor for internal and external stresses and is tightly regulated by the positive regulator p19ARF and negative regulator MDM2 (reviewed in [261]). Given that *PTEN*, which encodes a negative regulator of AKT, is transcriptionally suppressed by HES1, NOTCH1 is believed to block p53 activity in its canonical manner via inducing the AKT-mediated stabilization of MDM2 [262,263]. However, NOTCH signaling also employs its noncanonical partners to suppress programmed cell death in diverse contexts (Fig. 5). For example, the AKT-mediated stabilization of MDM2 and suppression of p53-dependent apoptosis are possibly induced by the noncanonical NOTCH–PINK1–mTORC2–AKT axis [181]. This hypothetical mechanism is actually supported by observations on starved cancer cells [264], tumor cells under oxidative stress [265,266], and eIF4E-associated chemoresistant leukemia cells [267,268]. In cancer cells with DNA damage, the interaction between NOTCH1 and ATM as described above promotes the ATM-mediated stabilization of MDM2 and inhibits the formation of the ATM–FOXO3a–KAT5/Tip60 complex, which both contribute to the suppression of p53-dependent apoptosis [29,269,270]. Alternatively, NOTCH1 may recruit the deacetylase SIRT1 to deacetylate and inactivate p53, as reported in an unreviewed paper [194]. Kim *et al.* observed that ectopically expressed NICD1 interacted with overexpressed p53 in *p53*-null HCT116 and, as a result, inhibited the transcription of p53-regulated apoptotic genes [271]. In addition, NOTCH1/3 contributes to antiapoptotic regulation by promoting the AKT-mediated inhibition of proapoptotic BAX [272], mTORC2–DUSP10–MAPK–mediated inhibition of proapoptotic BIM [182–184], and IKKα-mediated activation of antiapoptotic NF-κB [187].

Noncanonical NOTCH signaling plays a suppressive role in cancer immunity and immunotherapy (Fig. 5). A bioinformatic study on four cohorts of patients with NSCLC and *EGFR or ALK* mutations revealed that the deleterious (inactivating) mutations of NOTCH1-3 were correlated with the infiltration of M1 macrophages, activation of $CD8^+$ T and NK cells, and improved clinical outcomes for immune checkpoint inhibitors [273]. These findings can be explained by experimental evidence using the noncanonical NOTCH pathway. For example, the expression of IL-6, a major anti-inflammatory and immunosuppressive cytokine, is mainly activated through noncanonical NOTCH and IKKα/IKKβ signaling pathways in breast tumor cells and possibly in macrophages [186]. In addition to its promoting activity for stemness, EMT, and resistance [274–276], the secreted IL-6 either switches the differentiation of monocytes from dendritic cells to macrophages or maintains dendritic cells in an immature state [277,278]. These effects collectively lead to the development of tumor-associated macrophages and immune suppression. Moreover, the noncanonical NOTCH pathway interferes with the cGAS–STING innate immune pathway and possibly impairs immune response and immunotherapy in glioblastoma [195,279]. cGAS is stimulated by double-stranded DNA (e.g., viral or damaged DNA) and produces the cyclic dinucleotide GMP–AMP as the second messenger, which binds to the cyclic dinucleotide binding (CDNB) domain of STING and triggers the STING-induced transcription of proinflammatory type I interferons, cytokines, and chemokines via interferon regulatory factor 3 and NF-κB [280]. However, NICD inhibits the cGAS–STING pathway by interacting with the CDNB domain of STING [195], contributing to the development of the immunosuppressive microenvironment.

Therapeutic targeting of NOTCH signaling in resistant cancer cells

Three classes of inhibitors of NOTCH signaling (Table 2) were developed to target γ-secretase, interactions between NOTCH receptors and their ligands, or the formation of the NOTCH transcription activation complex to address the clinical challenges posed by NOTCH-driven tumorigenesis and resistance [38,281,282]. The first class is GSIs, which inhibit the γ-secretase-mediated S3 cleavage of NOTCH receptors and their activation [283]. Several GSIs, including RO4929097, PF-03084014, LY900009, MK0752, BMS-906024, BMS-986115, and LY3039478, have been tested in clinical trials [284–294]. The second class includes monoclonal antibodies recognizing the ligand binding domain of NOTCH receptors or their ligands (DLL3 and DLL4). Some of them, such as MEDI0639 (antiDLL4) [295], enoticumab (or REGN421, anti-DLL4) [296], rovalpituzumab tesirine (or SC16LD6.5, a DLL3-targeted antibody–drug conjugate) [297–299], tarextumab (or AMG 757, anti-NOTCH2/3) [300,301], and brontictuzumab (anti-NOTCH1) [302], have been approved for clinical trials. The third-class inhibitor CB-103 targeting the transcriptional complex of NOTCH and RBPJ is at the clinical trial I/IIa stage [303,304].

To date, no NOTCH inhibitor has passed phase II of clinical trials, possibly due to two issues: severe toxicity [305] and resistance due to limited dosing windows [205]. We would like to propose three alternative therapeutic strategies to address this dilemma: (1) increasing targeting specificity; (2) lowering the dosage of NOTCH inhibitors only to reverse the resistance induced by noncanonical NOTCH signaling but not to eliminate resistant cancer cells; and (3) targeting regulators downstream from noncanonical NOTCH signaling.

The first strategy is to limit the effect of NOTCH inhibitors only to hypoxic resistant cancer cells (Fig. 6A). Given that resistant CSCs or EMT cells reside in hypoxic areas of tumors, the prodrug hypoxia-activated GSI (HA-GSI), which is enzymatically activated under hypoxic conditions, could be developed to target specifically hypoxic resistant subpopulations [115,116,306]. Although HA-GSI prodrugs are not yet available, the hypoxia-activated prodrugs (HAPs) TH-4000 (a hypoxia-activated EGFR TKI) and PR-104 (a hypoxia-activated DNA damage inducer) showed promising results in the phase II/III of clinical trials for NSCLC patients [306]. These showcased HAPs encourage us to develop anti-NOTCH HAPs.

The second approach is to reduce the dosage of NOTCH inhibitors to inhibit the noncanonical NOTCH pathway instead of the canonical NOTCH pathway (Fig. 6B). Although the strategy is no longer capable of eradicating resistant cancer cells, it is effective in mitigating the adverse effects of GSI-induced toxicity in patients and resensitizing resistant cancer cells to chemotherapy. As narrated previously, our recent findings have revealed that a considerably reduced dose of GSI (1 μmol/L GSI34) is effective in abolishing the therapeutic resistance induced by noncanonical NOTCH signaling in lung CSCs and resensitizing the resistant population to chemotherapy [38]. The dose-reducing approach mitigates the clinical toxicity associated with NOTCH inhibitors, e.g., GSIs. This strategy has also been supported by GSI treatment for other resistant populations. DTPs resistant to osimertinib were considerably resensitized by GSI-XX at the dose of 1 μmol/L, which is only 1/10 of its IC50 [225]. Similarly, a low dose of GSI-I (1–2 μmol/L) had little cytotoxic effect on ALK$^+$ anaplastic large-cell lymphoma cells but remarkably enhanced the sensitivity of these cells to bortezomib [307].

Targeting the downstream regulators of the noncanonical NOTCH signaling network is also feasible (Fig. 6C) and supported by observations that AKT is highly activated in patients with NSCLC resistant to MEK inhibitors [308,309] and ATM is activated in the resistance to cisplatin [92]. As shown in Table 3, the inhibitors against the NOTCH-interacting pathways, e.g., mTORC2–AKT, ATM, IKK-NF-κB, TP53–apoptosis, JAK–STAT, ATM–FOXO3, or SHH signaling pathways could be used in combinatorial strategies with chemotherapy, targeted therapy, or immunotherapy to intervene with resistant tumors. For example, in clinical trials, AKT inhibitors (e.g., capivasertib and MK-2206) were used in combination with chemotherapy, targeted therapy, or endocrine therapy for the treatment of resistant breast cancer [310–312]. Inhibitors of ATM and ATR signaling were employed to overcome cisplatin resistance [92,313]. The JAK1/2 inhibitor ruxolitinib abolished chidamide resistance in T cell/natural killer lymphoma and T cell lymphoblastic leukemia [314,315]. Combinatorial therapy with the SHH inhibitor glasdegib and chemotherapy is being tested to substitute for traditional intensive chemotherapy. The survivin inhibitor

Table 2 Inhibitors of NOTCH signaling and their clinical trials

Inhibitor type	Compounds	Cancer	Adverse effects	Clinical trials	References
GSI[a]	RO4929097	NSCLC[b]	Severe cardiac disorders, malignant and unspecified neoplasms, mild blood and lymphatic system disorders, gastrointestinal disorders, fatigue, infections and infestations, dyspnea, hyponatremia, hypomagnesemia, musculoskeletal and connective tissue disorders	II	[294]
	RO4929097	Advanced solid tumors (e.g., melanoma, colorectal, and sarcoma)	Diarrhea, erythema, rash, pruritus, fatigue, headache, hypophosphatemia, nausea, vomiting	I	[284]
	RO4929097 + capecitabine	Advanced solid tumors (e.g., colorectal and biliary tract)	Anemia, anorexia, chills, diarrhea, dry skin, fatigue, headache, hypokalemia, hypophosphatemia, nausea, leg pains, vomiting, weight loss	I	[285]
	RO4929097 + temsirolimus	Advanced solid tumors (e.g., sarcoma, neuroendocrine, and squamous cell carcinoma of the head and neck)	Fatigue, mucositis, anorexia, rash, nausea, dysgeusia, vomiting, diarrhea, headache, cardiac disorders, anemia, neutropenia, thrombocytopenia, metabolic disorders	Ib	[286]
	R04929097 + gemcitabine	Advanced solid tumors (e.g., breast and pancreas)	Nausea, fatigue, vomiting, hypophosphatemia, anorexia, transaminitis, maculopapular rash, hypomagnesemia, acneiform rash, diarrhea	I	[323]
	RO4929097 + cediranib	Advanced solid tumors (e.g., colorectal, renal cell, and leiomyosarcoma)	Severe hypertension and hypophosphatemia, mild diarrhea, hypertension, fatigue, nausea, headache, hypothyroidism, hypophosphatemia, metabolic disorders	I	[324]
	PF-03084014	Advanced solid tumors (e.g., colorectal, desmoid, and breast)	Diarrhea, nausea, vomiting, fatigue, hypophosphatemia, rash, anorexia, mucosal inflammation, headache, hypokalemia, pruritus, dyspepsia	I	[287]
	LY900009	Advanced and/or metastatic solid tumors (e.g., colorectal, endometrium, and ovarian) and lymphoma	Diarrhea, vomiting, anorexia, nausea, fatigue, rash acneiform, oral mucositis, hypophosphatemia	I	[288]
GSI	MK-0752	Advanced solid tumors (e.g., breast, colorectal, and glioblastoma)	Diarrhea, vomiting, nausea, fatigue, decreased appetite, headache, rash	I	[289]
	MK-0752 + dalotuzumab	Advanced solid tumors (e.g., colorectal and ovarian)	Severe anemia; pain in extremities; nausea; elevated AST[c], ALT[d], and GGT[e]; dehydration; rash; diarrhea; vomiting; nausea; fatigue; hypokalemia; hypophosphatemia and deep vein thrombosis; mild blood system, gastrointestinal, general, metabolic, dermatological, respiratory, and vascular disorders	I	[325]
	MK-0752 + gemcitabine	Pancreatic ductal adenocarcinoma	Anaemia, lymphocyte reduction, nausea, fatigue, vomiting, neutropenia, thrombocytopenia, elevated ALT and AST, dysphagia, fatigue, hypokalemia, hypophosphatemia, hemorrhage, debility	I	[292]
	BMS-906024	Solid tumors (e.g., NSCLC and TNBC[f])	Not available	I	NCT01292655①
	BMS-906024 + chemotherapy	Solid tumors (e.g., NSCLC and TNBC[f])	Not available	I	NCT01653470①
	BMS-986115	Advanced solid tumors (e.g., colorectal, adenoid cystic carcinoma, and cholangiocarcinoma)	Diarrhea, nausea, vomiting, abdominal pain, colitis, ileus, fatigue, hypokalemia, hypophosphatemia, hyponatraemia, decreased appetite, dehydration, hypocalcaemia, pruritus, cough, urticaria	I	[291]
	LY3039478	Advanced and/or metastatic solid tumors or lymphoma	Diarrhea, nausea, vomiting, decreased appetite, fatigue, increased ALT and AST, hypophosphatemia, hypokalemia, dyspesia, hypophothsphatemia, stomatitis, acute kidney injury, rash	I	[293]
Inhibitors of the ligand-NOTCH interaction	MEDI0639 (anti DLL4)	Advanced solid tumors	Anaemia, leukocytosis, thrombocytopenia, acute coronary syndrome, diplopia, constipation, nausea, vomiting, fatigue, noncardiac chest pain, infections and infestations, decreased appetite, hypercalcemia, cerebral hemorrhage, acute kidney injury, dyspnea, pleuritic pain	I	[326]

(*Continued*)

Inhibitor type	Compounds	Cancer	Adverse effects	Clinical trials	References
	Enoticumab (or REGN421, anti DLL4)	Advanced solid tumors (e.g., colorectal, ovary, and pancreas)	Fatigue, nausea, vomiting, hypertension, headache, and anorexia, elevated brain natriuretic peptide and troponin I, right ventricular dysfunction and pulmonary hypertension, left ventricular dysfunction and pulmonary hypertension	I	[296]
	Rovalpituzumab Tesirine (DLL3-targeted antibody-drug conjugate)	SCLC[g] and large-cell neuroendocrine carcinoma	Thrombocytopenia, pleural effusion, increased lipase, thrombocytopenia, serosal effusions, skin reactions	I	[298]
		SCLC	Fatigue, photosensitivity reaction, pleural effusion, peripheral edema, decreased appetite	II	[299]
	Brontictuzumab (antiNOTCH1)	Advanced, selected solid tumors (e.g., colorectal cancer, adenoid cystic carcinoma, and cholangiocarcinoma)	Diarrhea, nausea, vomiting, decreased appetite, fatigue, increased ALT and AST	I	[302]
	Tarextumab (anti NOTCH2/3) + nab-paclitaxel and gemcitabine	Metastatic pancreatic adenocarcinoma	Diarrhea, nausea, thrombocytopenia	II	[301]
Inhibitors of NOTCH transcription	CB-103	Adenoid cystic carcinoma and hematologic tumors	Elevated γ-glutamyl transferase activity, visual changes, elevated liver function, anemia	I	[304]

Abbreviations: GSI[a], γ-secretase inhibitor; NSCLC[b], nonsmall cell lung cancer; AST[c], aspartate aminotransferase; ALT[d], aspartate aminotransferase; GGT[e], γ-glutamyl transpeptidase; TNBC[f], triple-negative breast cancer; SCLC[g], small cell lung cancer. ①, Clinical Trials. gov ID.

YM155 in combination with either docetaxel on NOTCH-positive melanoma xenograft tumors or erlotinib on NSCLC tumors was well tolerated and more effective than any single agent alone [316,317].

Closing marks and future perspectives

In this review, we discuss the canonical and noncanonical roles of NOTCH signaling in the nongenetic resistance of cancer, which in our opinion is associated with at least three types of cancer cell subpopulations, namely, CSCs, EMT cells, and DTPs. Whether these resistant populations are overlapping or simply share some cellular and molecular characteristics is still unclear. Despite this uncertainty, these populations do share at least six resistance traits. Interestingly, a growing body of evidence indicates that NOTCH signaling is involved in the regulation of resistant populations and their resistance traits. As discussed in this review, we believe that canonical and noncanonical NOTCH pathways actually play distinct roles in resistance regulation. The canonical NOTCH pathway mainly maintains resistant cancer populations through the transcriptional programs of stemness, EMT, and quiescence. By contrast, the noncanonical NOTCH pathway appears to modulate the molecular traits of resistant cancer populations via RBPJ-independent interactions or cooperation with regulators in other signaling pathways. Such a new understanding of NOTCH signaling in nongenetic resistance will lead us to develop improved therapeutic strategies using NOTCH inhibition. These strategies could possibly address the severe toxicity and unsatisfactory efficacy observed in previous clinical trials.

The three distinct resistant subpopulations discussed in the review share common resistant properties, although their degree of resistance varies substantially. At the cellular level, resistant cancer cells show (1) therapeutic resistance, (2) slow cycling (quiescence), (3) clonal expansion or self-renewal, and (4) enhanced survival. At the molecular level, they exhibit (1) the activation of stress response signaling (e.g., NF-κB and BCL-2), (2) activation of NOTCH, TGF-β, and/or Wnt signaling, and (3) increased activity of detoxifying programs (e.g., ABC transporters and CYP450). These shared molecular and cellular properties indicate a common state of resistance. Of course, cancer cells in the resistant state could exhibit varying degrees of resistance to cancer therapy. The following question remains: What cellular or developmental state(s) do the resistant states of cancer resemble? A recent report attempted to address this question and showed that chemotherapy-resistant DTPs in colorectal cancer enter a diapause-like state that is reminiscent of the embryonic survival program diapause [63]. Systems biology with single-cell resolution will help us answer the above question.

As shown in our review, the canonical and

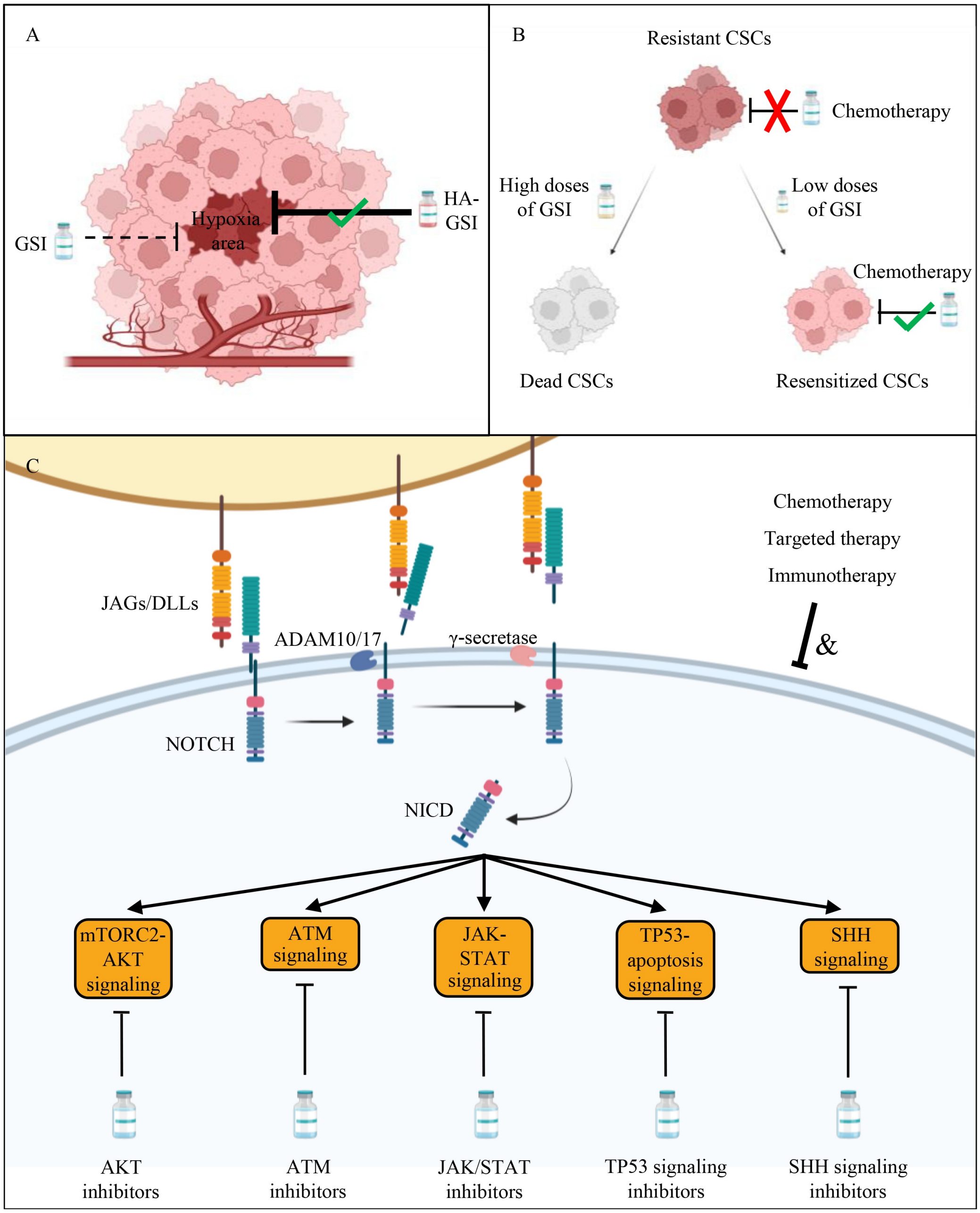

Fig. 6 Potential therapeutic strategies suppress noncanonical NOTCH signaling in resistant cancer cells. Three therapeutic strategies are proposed in this review. (A) The first strategy is to limit the effect of NOTCH inhibitors to hypoxic resistant cancer cells. HA-GSI is a good candidate. (B) The second strategy is to reduce the dosage of NOTCH inhibitors to inhibit the noncanonical NOTCH pathway and resensitize resistant CSCs to chemotherapy. (C) The third strategy is to target downstream regulators of the noncanonical NOTCH signaling network in combination with chemotherapy, targeted therapy, or immunotherapy. Created with BioRender.com.

noncanonical NOTCH signaling pathways appear to play distinct but synchronized roles in the regulation of cancer resistance. However, numerous reports in the literature failed to experimentally distinguish the canonical and noncanonical functions of NOTCH signaling, especially in therapeutic resistance, either because the difference between canonical and noncanonical functions was not considered or because clear-cut genetic settings (e.g., genetic disruption of the *RBPJ* gene) were not employed. In the future, an enhanced picture of NOTCH signaling in nongenetic resistance will be drawn on the basis of improved conceptual considerations and experimental designs. We also want to ask an important question: Why do the canonical and noncanonical NOTCH pathways converge toward nongenetic cancer resistance? Possibly, the dual arms of NOTCH-mediated control are indeed an efficient and concerted system for cancer resistance. As such, in line with Lamarck's induction model of

Table 3 Inhibition of the noncanonical NOTCH signaling network in preclinical and clinical studies

NOTCH-interacting signaling	Inhibitors of partner pathways	Chemotherapeutic or targeted drugs	Cancer	Clinical trials	References
AKT signaling	Capivasertib (AKT inhibitor)	Fulvestrant	HR[a]+, HER2- advanced breast cancer (resistant to aromatase inhibitors)	Approved	[310]
	Everolimus (mTORC1 inhibitor)	Fulvestrant	HR+, HER2- metastatic breast cancer (resistant to aromatase inhibitors)	II	[311]
	MK-2206 (AKT inhibitor)	Paclitaxel (+ trastuzumab if HER2+)	HER2+/− and/or HR+/− breast cancer	II	[312]
ATM signaling	AZD0156 (ATM inhibitor)	Irinotecan [+ 5-FU]	Colorectal cancer	Preclinical	[327]
	AZD1390 (ATM inhibitor)	Radiation	Brain tumors	Preclinical	[328]
	CP466722 (ATM inhibitor)	Cisplatin	NSCLC[b]	Preclinical	[92]
JAK–STAT signaling	Ruxolitinib (JAK1/2 inhibitor)	Chidamide	NK[c]/T cell lymphoma, T-ALL[d]	II	[314,315]
	INCB052793 or itacitinib (JAK1 inhibitor)	Azacitidine	Relapsed/refractory multiple myeloma and AML[e]	I & II	[329]
SHH signaling	Glasdegib (smoothend inhibitor)	Cytarabine	*De novo* and secondary AML	II	[330]
	Vismodegib or sonidegib (smoothend inhibitor)	Temozolomide or local radiotherapy	Recurrent medulloblastoma with PTCH1 mutations	II	[331]
TP53–apoptosis signaling	Idasanutlin (MDM2 inhibitor)	Ixazomib citrate and dexamethasone	Relapsed multiple myeloma	I & II	NCT02633059①
	YM155 (survivin inhibitor)	Erlotinib (EGFR inhibitor)	NSCLC	I	[317]
	YM155 (survivin inhibitor)	Docetaxel	Melanoma	Preclinical	[316]

Abbreviations: HR[a], hormone receptor; NSCLC[b], nonsmall cell lung cancer; NK[c], natural killer; T-ALL[d], T cell acute lymphoblastic leukemia; AML[e], acute myeloid leukemia. ①, Clinical Trials. gov ID.

resistance, the noncanonical arm of NOTCH signaling employs posttranslational regulation for a fast and adjustable response to external stress and cell death threats. Conversely, the canonical arm of NOTCH signaling applies transcriptional regulation for the long-term maintenance of resistant cancer cells. This behavior is reminiscent of Darwin's adaptation model for resistance. A deepened understanding of NOTCH signaling and cancer resistance is definitely needed to answer the above question.

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Compliance with ethics guidelines

Conflicts of interest Xianzhe Huang, Wenwei Chen, Yanyan Wang, Dmytro Shytikov, Yanwen Wang, Wangyi Zhu, Ruyi Chen, Yuwei He, Yanjia Yang, and Wei Guo declare that they have no conflict of interest.

This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

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