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Current research of the Notch pathway in hepatocellular carcinoma

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Abstract

Notch signaling is a widely preserved communication pathway that supports essential cellular functions by allowing adjacent cells to interact. The Notch signaling pathway consists of Notch ligands (DSL proteins), Notch receptors, DNA-binding proteins, and downstream target genes. Hepatocellular carcinoma (HCC) represents the predominant cause of cancer-related deaths globally and poses a significant threat to human health. For highly malignant HCC, current treatment options, including chemotherapy, radiotherapy, immunotherapy, targeted therapies, and surgical procedures, often have poor prognoses. Therefore, there is a need to explore additional therapeutic strategies. Many studies have found that abnormal activation of the Notch signaling pathway contributes to tumor initiation and progression by promoting HCC proliferation, metastasis, stem cell-like properties, and drug resistance. In this research, we reveal the composition and activation mechanisms of the Notch signaling pathway, as well as the molecular mechanism underlying its aberrant activation in HCC. Furthermore, we summarize recent advances in targeting Notch signaling for the treatment of HCC. This review aims to highlight the promising potential of investigating the Notch pathway as a therapeutic target in HCC.

Keywords Notch signaling pathway, Hepatocellular carcinoma, Epithelial–mesenchymal transition, Stem-like properties, Proliferation

Introduction

The Notch gene was first discovered in 1917 during research on *Drosophila melanogaster* that displayed notched wings [1]. The Notch signaling pathway is highly conserved throughout evolution. Notch proteins serve as cell surface transmembrane receptors that mediate crucial cellular processes by facilitating communication between adjacent cells [2–4]. The Notch pathway consists of Notch ligands (DSL proteins), Notch receptors, DNA-binding proteins, and downstream target genes [5, 6]. It is involved in various physiological and pathological development processes in both vertebrates and invertebrates, such as muscle production, vascular production, hematopoiesis, skin development, and organ development. Additionally, Notch signaling also participates in other key cell processes, including cell proliferation and migration [7]. Therefore, abnormalities in the Notch pathway may result in the development of various diseases. Understanding the structure and function of the Notch pathway is vital to elucidate the mechanisms involved in the initiation and progression of disease.

Extensive research on the Notch signaling has noticed that the pathway is implicated in various aspects of cancer biology, such as cell proliferation, metastasis, and tumor immune evasion, and exhibits both tumor suppressor and carcinogenic activity [8]. For example, in

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T-cell acute lymphoblastic leukemia (T-ALL), the Notch1 receptor activates the transcription of Asb2α, which then facilitates the proliferation of T-ALL cells [9]. Similarly, in small-cell lung cancer, the Notch ligand delta-like ligand-3 (DLL3) promotes the proliferation of cancer cells and enhances their migratory and invasive capabilities [10].

Liver cancer is a significant global health concern and represents a leading cause of cancer-related mortality worldwide. Among the five deadliest cancers, it is the only cancer with an increasing annual incidence [11]. There are numerous risk factors for the development of liver cancer, such as hepatitis C virus, hepatitis B virus, diabetes, smoking, obesity, and non-alcoholic fatty liver disease [12–15]. Hepatocellular carcinoma (HCC) stands out as the predominant type of primary liver cancer [16, 17]. Over 80% of HCC develop in the context of chronic liver disease [18]. Study shows that non-alcoholic fatty liver disease (NAFLD) is the most prevalent chronic liver condition globally. The Notch signaling plays a key role in NAFLD and its progression to non-alcoholic steatohepatitis (NASH) and liver fibrosis. The Notch pathway is involved in the progression of NAFLD by regulating lipid metabolism, insulin resistance, oxidative stress and inflammatory responses [19]. In addition, it has also been shown that activation of the Notch pathway may be a key factor in the progression of NASH-to-HCC development [20]. For highly malignant HCC, the current treatment options, including chemotherapy, radiotherapy, immunotherapy, targeted therapy, and surgical intervention, such as hepatic resection and liver transplantation, often have poor prognoses. In addition, HCC has a high recurrence and metastasis rate, which greatly reduces the effectiveness of treatment. Therefore, we need to increase research and innovation in HCC treatment technologies to provide more effective treatment options for patients. Studies have established a strong correlation between the abnormal activation of Notch signaling and the development and progression of HCC [21]. In-depth investigation into the regulatory mechanism of the Notch pathway in HCC can enhance our understanding of its pathogenesis and provide new insights and methods for the treatment of this aggressive cancer.

Overview of the Notch signaling pathway

The Notch signaling pathway is a complex and evolutionarily conserved mechanism that facilitates communication between two adjacent cells after close contact. It plays a crucial role in various biological processes, such as organ formation, tissue repair, and cellular function [22]. In the following analysis, we describe the composition of Notch, activation of the classical and non-classical pathways (Fig. 1).

Notch signaling components

The main components of Notch pathway include Notch ligands, Notch receptors, DNA-binding proteins, and downstream target genes. Alterations in any of these components can disrupt the signal transmission within the pathway. Both Notch receptors and ligands are transmembrane proteins [23, 24], allowing them to interact directly with the cell surface.

Mammals possess four membrane-bound Notch receptors, namely, Notch1, Notch2, Notch3, and Notch4. Each receptor contains three fragments, the extracellular domain (NECD), the transmembrane domain (TMD), and the Notch intracellular domain (NICD) [25]. The NICD contains an RAM23 domain which boosts binding with the CSL [CBF1/RBPJ-kappa/Su(H)/Lag1] protein, a nuclear localization signal (NLS), seven domains with ankyrin repeats (ANK), and a PEST domain that contains high levels of proline, glutamic acid, serine, and threonine residues. Additionally, Notch1 and Notch2 have a transcriptional transactivation domain (TAD). The NECD is composed of between 29–36 epidermal growth factor (EGF)-like repeats (36 in Notch1 and Notch2, 34 in Notch3, and 29 in Notch4) and a region of negative regulation (NRR). The NRR domain is comprised of three cysteine-rich Lin12-Notch repeats (LNRs) and a heterodimerized region that is critical for S2 cleavage. A 'stop translocation' signal consisting of 3–4 Arg/Lys residues terminates the single TMD [2, 26–29].

The structure of the Notch ligand closely resembles that of the Notch receptor. In mammals, Notch receptors are activated by three delta-like ligands (DLL1, DLL3, and DLL4) and two Serrate/Jagged ligands (JAG1 and JAG2). These ligands contain between 6 and 16 EGF-like repeats in their NECD that determine the interaction with the corresponding receptors. The DSL domain is situated at the N-terminus of each protein, playing a crucial role in Notch signaling [30, 31]. Moreover, due to the increasing number of regulatory genes for each ligand corresponding to multiple genes and the Notch pathway, this signaling system is widely complex [32].

Canonical Notch signaling

The canonical pathway is the most used Notch-related process. Conventionally, it is understood that it facilitates short-range communication between adjacent cells [30]. In the canonical pathway, the Notch receptor is produced within the endoplasmic reticulum followed by glycosylation of the EGF-like repeats. Notch receptors with newly attached glycans are subsequently transported to the Golgi complex where they undergo S1 proteolytic cleavage into two fragments: the NECD and the TMD [33, 34]. Subsequently, these fragments are conveyed to the cell

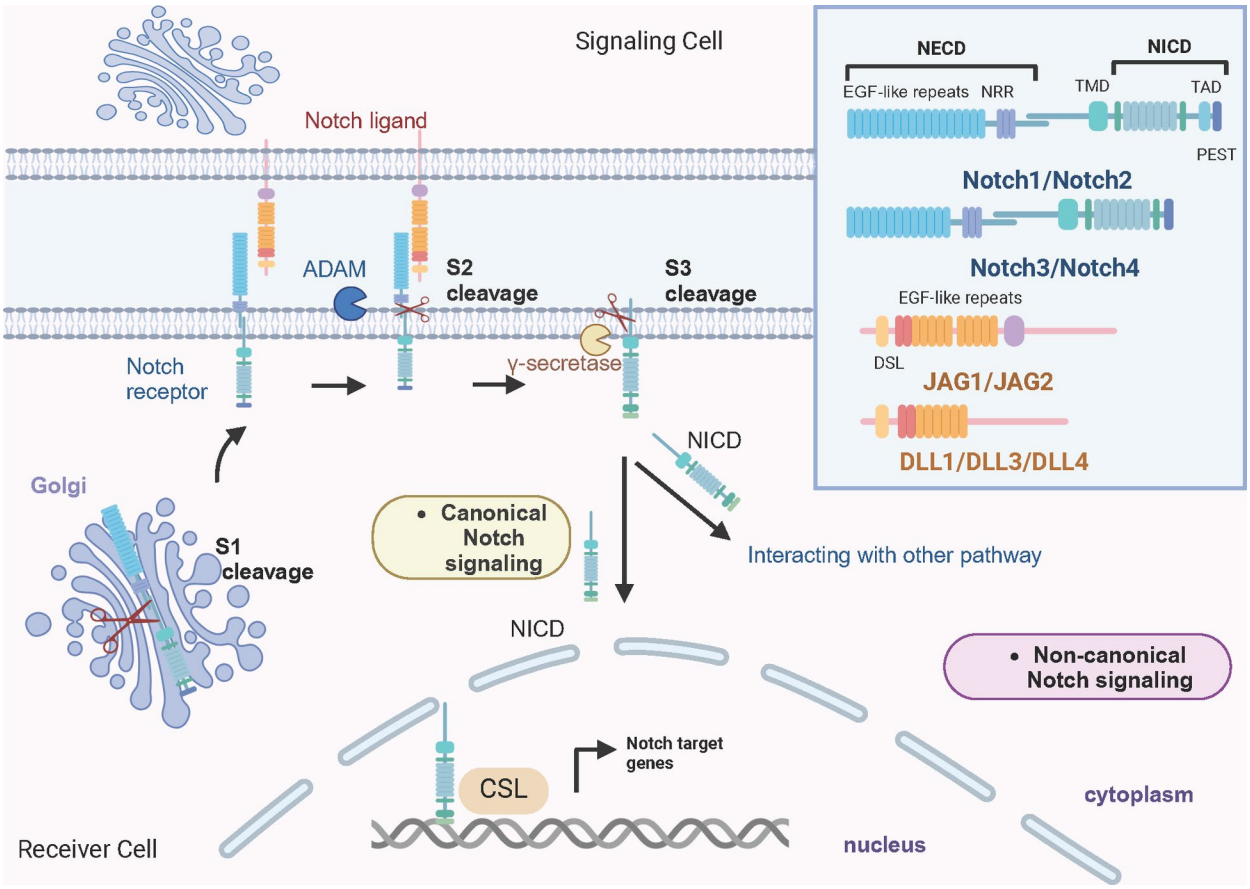

Fig. 1 The composition and activation of Notch signaling pathway. The main components of the Notch signaling pathway include Notch ligands, Notch receptors, DNA-binding proteins, and downstream target genes. Mammals possess four membrane-bound Notch receptors, namely, Notch1, Notch2, Notch3, and Notch4. In mammals, Notch receptors are activated by three delta-like ligands (DLL1, DLL3, and DLL4) and two Serrate/Jagged ligands (JAG1 and JAG2). Notch signaling is the activation effect of close contact between two adjacent cells, including canonical pathway and non-canonical pathway. Notch receptors are first produced in the endoplasmic reticulum and then transferred to Golgi for S1 cleavage. Notch receptors were cleaved into two fragments, NECD and TMD. These fragments are then transported to the surface of the cell membrane, where they interact with transmembrane ligands on neighboring signaling cells. Binding triggers ADAM cleavage, followed by S2 cleavage of the Notch receptor by ADAM. The cleaved portion is cleaved by the γ-secretory enzyme S3 on the cell membrane. This then leads to the release of NICD. In the classical pathway, the activated NICD is transported to the nucleus and binds to the transcription factor CSL, thereby regulating the expression of downstream genes. Some NICD that does not enter the nucleus can combine with other molecular pathways. The protein structure of the Notch ligand and receptor is shown in the upper right corner. NECD, extracellular domain; NICD, intracellular domain; ADAM, A protein containing a domain of disintegrin and metalloproteinases; γ-secretase, a membrane-bound protease responsible for S3 cleavage of Notch; NRR, a region of negative regulation; CSL,CBF1/RBPJ-kappa/Su(H)/Lag1;TAD, a transcriptional transactivation domain; PEST, a domain that contains high levels of proline, glutamic acid, serine, and threonine residues

membrane surface and form heterodimers. From here, these transmembrane receptors expressed on the signal-receiving cells interact with the transmembrane ligands found on the neighboring signal-sending cells [23]. Binding with DLL or JAG ligands induces a conformational change that enables a member of the ADAM (a protein containing a domain of disintegrin and metalloproteinases) family to cleave the receptor at site 2 (S2 cleavage), and the cleaved intracellular membrane-bound fragment is termed Notch extracellular truncation (NEXT). Subsequently, γ-secretase activates and further cleaves NEXT at site 3 (S3 cleavage), liberating the NICD which then translocates into the nucleus. Here, NICD binds to the transcription factor CSL, thereby regulating downstream gene expression [33–37].

Non-canonical Notch signaling

An atypical Notch signaling may be activated by non-traditional ligands, or when the Notch receptor is not cleaved, or in the absence of ligands. Some forms of atypical signaling do not require CSL and involve interaction with other nuclear or cytoplasmic effectors. For example,

T-cell receptor (TCR)-mediated self-amplification does not require ligand activation. The LCK-ZAP70PLCγ-PKC signaling axis can be activated by the TCR/CD3 complex. Subsequently, PKC activates ADAM-family and γ-secretase on endosomes, initiating S2 and S3 cleavage and Notch signaling [22]. The non-canonical pathway also plays an essential role in tumorigenesis and cancer progression. In addition, elevated levels of IL-6 have been linked to unfavorable outcomes in breast cancer patients, and evidence suggests that activation of the non-classical Notch signaling pathway regulates IL-6 expression [37–40]. These studies may provide additional therapeutic targets in the development of the disease.

Mechanisms of Notch signaling in the development and progression of HCC

Increasing evidence suggests that the Notch signaling pathway is significantly involved in the progression of HCC, and aberrant activation or suppression is strongly associated with the proliferation, differentiation, and metastasis of HCC cells [41–43]. Numerous investigations have revealed multiple mechanisms that result in the irregular activation of the pathway and contribute to HCC progression, including its involvement in controlling epithelial-to-mesenchymal transition (EMT), obtaining cancer stem cell-like (CSC) characteristics, cell proliferation, and regulating other cellular and molecular processes. Following that, we summarize the molecular processes of the Notch pathway in tumorigenesis and advancement of HCC (Table 1).

Notch signaling and EMT

EMT refers to the transformation of epithelial cells into elongated cells with a mesenchymal phenotype, which can be involved in both physiological and pathological processes. EMT was primarily thought to be involved in the process of embryogenesis and tissue repair before the initial 80 s of the twentieth century. Subsequently, numerous studies have shown that EMT is involved in pathogenic processes, such as metastasis and carcinogenesis, and is today considered one of the most important mechanisms driving cancer metastasis [44–47].

The Notch pathway has been shown to significantly influence EMT regulation. Studies have shown that the Notch signaling is involved in the activation of EMT through multiple molecular mechanisms, which in turn promotes cancer invasion and metastasis (Fig. 2). The import of calcium into a cell is an established mechanism that drives cancer-promoting processes. Mitochondrial calcium uniporter regulator 1 (MCUR1) has been identified as a key molecule in HCC that promotes cancer cell survival. Jin et al. found that the MCUR1-mediated mitochondrial pathway activated the ROS/NRF2/Notch1 pathway, leading to EMT in hepatoma cells, and ultimately facilitating invasion and metastasis [48, 49]. Additionally, hepatitis virus infection is strongly associated with the incidence of HCC [50]. Xie et al. revealed that Tspan5 content significantly increased in HCC patients infected with a hepatitis virus and was strongly associated with tumor invasion. The results also showed that Tspan5 enhanced the Notch pathway by increasing cleavage of Notch1 receptor at the S3 site catalyzed, thereby promoting EMT and metastasis of HCC cells [51].

In addition, other molecules also play important roles in EMT and HCC metastasis through the Notch pathway. For example, KIAA1217 is a macromolecular protein with an uncertain function, which is extensively present in the cytoplasm and plays a crucial role in the metastasis of HCC [52]. Wang et al. demonstrated that KIAA1217-activated p-STAT3 was retained in the cytoplasm and subsequently activated the Wnt/β-catenin and Notch pathways to promote EMT induction and eventually leads to HCC metastasis [53]. Additionally, Wang et al. explored the relevant mechanisms of HCC using in vivo and in vitro methods. It was discovered that SMAD7 (mothers against decapentaplegic homolog) induces EMT and promotes HCC growth in vitro through activation of the YAP/Notch pathway, whereas in vivo it accelerates hepatocarcinogenesis. [54].

Another molecule is RNF187 (ring finger protein 187), a ubiquitin E3 ligase that contains an RING domain [55, 56]. A recent study revealed that the upregulation of Notch1 increased the expression of RNF187, which in turn promoted HCC metastasis by inducing EMT in HCC cells [57]. Furthermore, Xiao et al. observed that ACTL6A (actin-like 6A) upregulated Notch1 expression and stimulated the Notch signaling pathway by manipulating the expression of sex-determining region Y-box2 (SOX2), which ultimately promoted EMT and HCC metastasis [58]. Moreover, Nicastrin (NCSTN) serves as a fundamental component of the γ-secretase complex and has been implicated in driving tumor advancement. In their study, NCSTN facilitated the activation of β-catenin by promoting Notch1 cleavage and AKT phosphorylation, thereby initiating the transcription of Zeb1 and inducing EMT, leading to HCC cell growth and metastasis [59].

Collectively, the Notch pathway plays a central role in the regulation of EMT and promotes HCC metastasis through multiple molecular mechanisms. These studies not only deepen our understanding of the role of Notch pathway in tumor progression, but also provide an important theoretical basis for the development of future therapeutic strategies targeting EMT and cancer metastasis.

Table 1 Roles and mechanisms of the Notch signaling pathway in HCC

Biological process	Notch signaling component	Mechanism	Related molecule	Cell line/animal model	Refs.
EMT	Notch1	MCUR1 → Mitochondrial signaling → ROS/NRF2/Notch1 pathway → EMT → promote HCC metastasis	MCUR1, ROS, and NRF2	Human HCC cell lines BEL7402, and MHCC97L	[47]
	Notch1	Tspan5 → ADAM-10↑and activate Notch signaling → promote EMT → tumor metastasis of HCC	Tspan5	HL7702, BEL7402, Hep3B, HUH7, MHCC97H, MHCC97L, PLC, and QGY7701 SK-Hep1	[50]
	/	KIAA1217 → p-STAT3↑ → activate the Wnt/β-catenin and Notch pathways → promote EMT induction → HCC metastasis	KIAA1217, and p-STAT3	HCC cell lines	[52]
	/	SMAD7 → activate YAP/NOTCH pathway → include EMT → promote the growth of HCC	SMAD7	HLE, MHCC97H, SNU449, and Huh7 cell lines	[53]
	Notch1	Notch1↑ → RNF187↑ → EMT → HCC metastasis	RNF187	Subcutaneous tumor model	[56]
	Notch1	ACTL6A → enhance the expression of SOX2 → Notch1↑ → trigger Notch signaling pathway → promote EMT and metastasis of HCC	ACTL6A, and SOX2	PLC/PRF5, SMMC7721, HepG2, SHCC, SLHCC, and NHCC	[57]
	Notch1	NCSTN → Notch1 cleavage and AKT phosphorylation → β-catenin↑ → transcription of Zeb1 → EMT → HCC cell growth and metastasis	NCSTN, β-catenin, and Zeb1	HH3B, HH7, HHG2, HCL3, SNU449, and SNU387	[58]
Stem-like properties	Notch1, JAG1	Tm4sf1↑ → MYH9↑ → activate Notch signaling pathway → promote cancer stemness and chemoresistance in HCC	Tm4sf1, and MYH9	Hep-G2, Hep-3B, LM3, Huh7, and MHCC97H	[80]
	Notch1	SKA3 → activate Notch signaling pathway → promote cancer stem cell-like properties → HCC progression	SKA3	Human hepatic L02 cell line, Changliver cell line, HCC cell lines MHCC-97 h, and SNU-398	[72]
	Notch1	KCTD10 → inhibit Notch1 → inhibit Stem-like properties in HCC	KCTD10	MHCC97H, Hep3B, LX2, HepG2, and Huh7	[73]
	Notch1, JAG1	CD90 → activate Notch signaling pathway → increase stem-like properties of CD90 in HCC	CD90	SK-HH1, HH3b, HH-7, SMMC-7721, Mhc-97L, PLC/PRF/5, and Mhc-97H	[65]
	Notch1	CAFs → secrete high levels of IL-6 → STAT3 phosphorylation → activate Notch signaling pathway → promote stem cell-like properties in HCC cells	CAFs, and IL-6	PLC/PRF/5, MHCC-97H, and HLE	[75]

Table 1 (continued)

Biological process	Notch signaling component	Mechanism	Related molecule	Cell line/animal model	Refs.
Cell proliferation	Notch1, Hes1, Hey1	CENPU↑ → activate Notch signaling pathway → facilitate HCC cell proliferation	CENPU	BL7402, SMC7721, HHG2, HCL3, Huh7, and L2	[89]
	Notch1	VPA → block Notch signaling pathway → reverse the Notch1-induced HCC cell proliferation	VPA	SK-HEP-1	[83]
	Notch1, NICD	KK-LC-1↑ → activate Notch signaling pathway → promote the HCC cell proliferation	KK-LC-1	QSD-7701, SMMC7721, HHG2, HH3B, HHF, and Huh7	[84]
	Notch1	EVs → PRDM16 → activate Notch signaling pathway → promote EMT → enhance HCC cell proliferation	EVs, and PRDM16	HSC cell line LX-2 (CL-0560), HCC cell lines HuH-7 (CL-0120), and Li-7 (CL-0139)	[86]
	Notch1	Quercetin → inhibit Notch and Hh signaling → inhibit HCC cell proliferation	Quercetin	Adult male Sprague Dawley rats model	[87]
	Notch1, NICD	HBx → activate Notch signaling pathway → enhance HCC cell proliferation	HBx	L02	[88]
	Notch1, NICD, Hes1, Hey1	NOR1 → activate Notch signaling pathway → promote HCC cell proliferation	NOR1	L02, MIHA, HepG2, and Hep3B	[82]
	Notch1, Notch4	HBx → activate Notch signaling pathway → enhance HCC cell proliferation	HBx	HepG2-pc, and HepG2X	[113]
Chemoresistance	Notch1HES1	VPA → down regulate Notch1 → suppress Akt signaling pathway → enhance the sensitivity of HCC cells to anti-tumor agents	VPA	HepG2	[98]
Chemoresistance	NICD	ZLDI-8 → inhibit Notch signaling pathway → inhibit EMT → enhance the sensitivity of HCC cells to anti-tumor agents	ZLDI-8	subcutaneous tumor model, intrahepatic tumor model, in vivo metastatic HCC model	[99]
Chemoresistance	Notch1, NICD	ZLDI-8 → inhibit Notch signaling pathway and inhibit EMT → enhance the sensitivity of HCC cells to anti-tumor agents	ZLDI-8	HepG2, and Hep3B	[124]
Metabolic reprogramming	Notch1, NICD, HES1, HEY1	INPP5F↑ + ASPH → activate Notch signaling pathway → enhance cell proliferation and aerobic glycolysis → promote HCC progression	INPP5F, and ASPH	xenograft model	[93]
Angiogenesis	DLL4, JAG1	TARAP → inhibit Notch signaling pathway → inhibit tumor angiogenesis	TARAP	HepG2, and xenograft model	[101]
Angiogenesis	Notch, DLL4, JAG2	EELC → inhibit Notch, DLL4, JAG2 → inhibit tumor angiogenesis in HCC	EELC	HepG2, and nude mouse xenograft	[102]

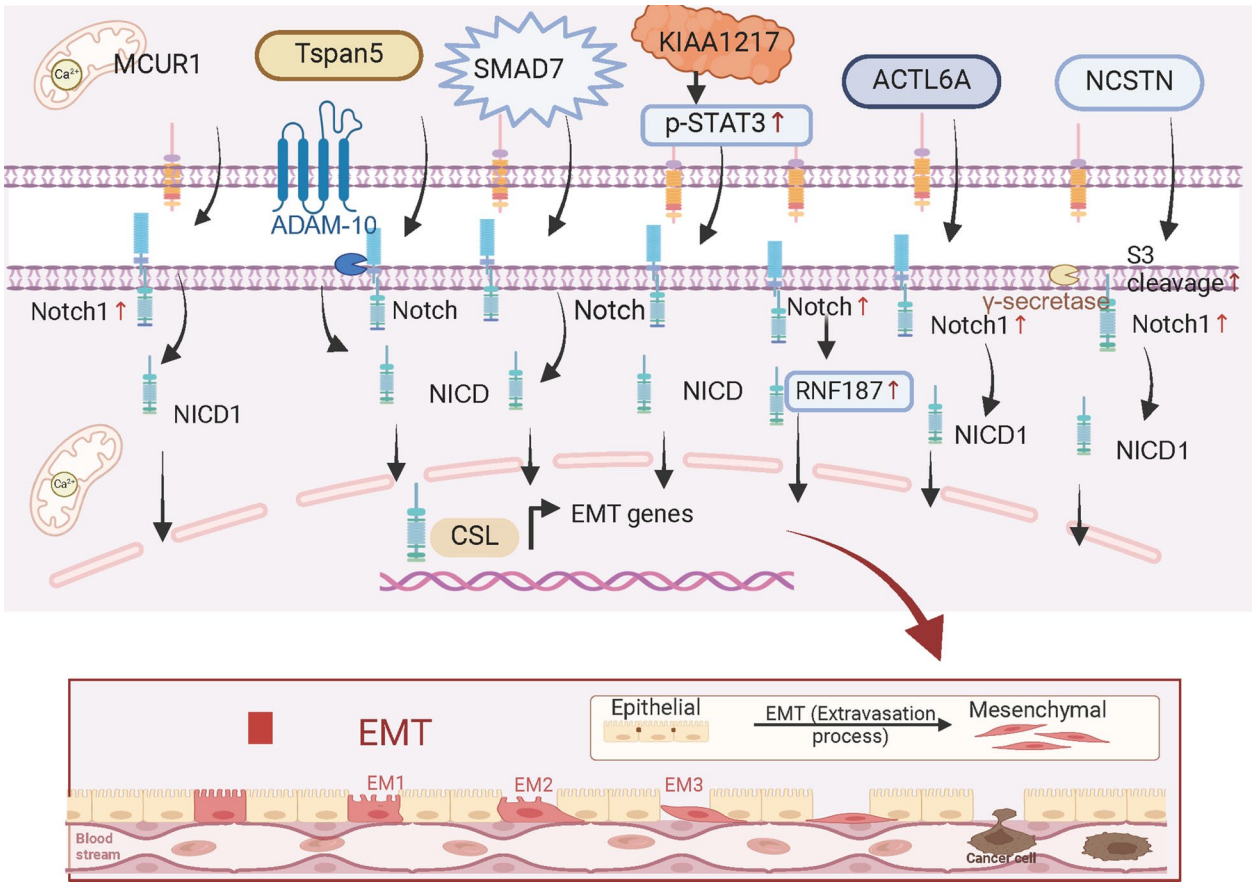

Fig. 2 EMT and Notch signaling pathway. EMT refers to the transformation of epithelial cells into elongated cells with a mesenchymal phenotype. EMT is involved in pathogenic processes, such as metastasis and carcinogenesis, and is today considered one of the most important mechanisms driving cancer metastasis. The Notch pathway has been shown to significantly influence EMT regulation. MCUR1, Mitochondrial calcium uniporter regulator 1; SMAD7, mothers against decapentaplegic homolog 7; ACTL6, actin-like 6A; SOX2, sex-determining region Y-box2; NCSTN, a fundamental component of the γ-secretase complex; KIAA1217, a macromolecular protein

Notch signaling and CSCs

CSCs are a distinct subpopulation of poorly differentiated neoplastic cells capable of self-renewal, tissue invasion, multi-directional differentiation, and unlimited proliferation. Studies have shown that CSCs play a key role in the occurrence, progression, and treatment resistance of HCC. They not only drive tumor growth and invasion, but also contribute to tumor recurrence, metastasis, and resistance to chemotherapy and radiotherapy [60–65]. CD90 has been identified as a marker for HCC CSCs as it contributes to the development of cancer by triggering the Notch pathway, increasing the stemness of CD90 + cells [66].

The SKA (spindle and kinetochore-associated) is a protein complex involved in regulating mitosis and is comprised of three subunits: SKA1, SKA2, and SKA3 [67, 68]. In the past few years, the association between SKA complexes and tumor proliferation and metastasis in a variety of cancers has received widespread attention [69–72]. Bai et al. demonstrated that SKA3 exhibited significant protumor effects in HCC cells. The knockdown of Notch1 significantly inhibited the increased stem cell-like properties induced by SKA3 overexpression, suggesting that SKA3 promoted HCC stem cell-like properties by modulating Notch1 [73]. This finding reveals a potential mechanism of action of SKA complexes in HCC.

Additionally, Ma et al. demonstrated that KCTD10 restrains the carcinogenicity of HCC cells and the formation of stem cells by blocking the activation of the Notch pathway [74]. Previous reports also revealed that IL-6 secreted from tumor-associated macrophages promoted HCC stem cell-like properties [75]. Xiong et al. also found that IL-6 released by cancer-associated fibroblasts (CAFs) activated Notch signaling through STT3 phosphorylation, which ultimately promoted HCC stem cell-like properties [76]. These studies revealed the important role of the tumor microenvironment in the regulation of HCC CSCs. Additionally, TM4SF1 is a

member of the transmembrane 4 super family and is significantly involved in both malignant and healthy human tissues [77–80]. Yang et al. revealed that the overexpression of TM4SF1 was significantly associated with the progression and poor prognosis of HCC by activating Notch through upregulation of MH9, a widely expressed cytoskeletal protein. This, in turn, promoted HCC stem cell-like properties and ultimately led to the development of lenvatinib resistance [81]. This research not only provided insights into the pathogenesis of HCC but also suggested that TM4SF1 may serve as a new focus for enhancing the clinical efficacy of lenvatinib in the treatment of HCC.

These studies provide new insights into the pathogenesis of HCC and lay the theoretical foundation for the development of therapeutic strategies targeting CSCs. In the future, interventions targeting these key molecules and pathways may lead to more effective therapeutic options for HCC patients.

Notch signaling and cell proliferation

The Notch pathway is crucial in regulating cellular proliferation and differentiation, and accumulating evidence has highlighted its involvement in the proliferation of HCC cells [82]. NOR1 is a newly discovered tumor suppressor. Recent findings indicate that there is a significant upregulation of NOR1 in HCC cells. Mechanistically, NOR1 enhanced HCC cell proliferation by activating the Notch signaling pathway [83]. The recently reported that valproic acid (VPA), an inhibitor of histone deacetylase, inhibited the growth of HCC cells. VPA increased the expression of tumor suppressors p21 and p63 by inhibiting Notch1 and its downstream target gene, HES1. Furthermore, the increase in cell proliferation induced by Notch1 was reversed by VPA treatment [84]. These studies revealed the regulatory mechanism of Notch pathway in HCC cell proliferation.

Furthermore, hypomethylation-induced overexpression of Kita-Kyushu lung cancer antigen-1 (KK-LC-1) was closely associated with HCC proliferation through the activation of Notch signaling [85]. Studies have indicated that hepatic stellate cells (HSCs) promoted HCC progression through the secretion of extracellular vesicles (EVs). The transcription factor positive regulatory domain I-containing protein 16 (PRDM16) is differentially expressed in HCC cells and plays a role in various biological processes, including cell fate determination and development [86]. HSCs contribute to liver fibrosis by releasing substances that maintain liver inflammation. HSC-derived EVs transport PRDM16 and activate Notch1-mediated signaling in HCC cells, promoting their proliferation and advancing HCC [87].

The natural compound quercetin may inhibit HCC cellular proliferation by downregulating Notch and Hedgehog signaling [88]. In addition, hepatitis B virus protein X (HBx) plays an important role in the progression of HCC. Emerging data have indicated that HBx is significantly contributed the progression of HCC by stimulating cancer cell proliferation through activation of the Notch signaling pathway [89]. Additionally, the previous report showed that aberrant centromere protein U (CENPU) expression is closely associated with HCC. Yu et al. revealed that the high expression of CENPU could activate the Notch pathway and promote the proliferation of HCC cells [90]. This study further revealed the critical role of Notch pathway in HCC cell proliferation. These studies not only deepen our understanding of the pathogenesis of HCC, but also provide an important theoretical basis for the development of therapeutic strategies targeting the Notch pathway.

Notch signaling and other biological processes

Metabolic reprogramming is one of the characteristic features of cancer and encompasses changes, such as increased glycolysis, mitochondrial biogenesis, amino acid and lipid metabolism, and activation of the pentose phosphate pathway [91, 92]. Cancer cells favor glycolysis even under normoxic conditions in comparison to normal cells [93]. Research has indicated that inositol polyphosphate 5-phosphatase F(INPP5F) is an enzyme involved in the occurrence and progression of tumors. Zhou et al. explored the function and potential mechanism of INPP5F in HCC and found that INPP5F activated the Notch pathway through its interaction with ASPH. This interaction leads to increased cell proliferation and aerobic glycolysis, ultimately contributing to the carcinogenic effects observed in HCC [94].

In HCC, aberrant Notch activation is closely associated with tumorigenesis, progression, and chemotherapy resistance [95]. VPA is an anti-epileptic drug that has been used in recent years for anti-tumor activity [96–98]. Yang et al. demonstrated that VPA increased cancer cell sensitivity to sorafenib treatment by downregulating Notch1 expression, thereby inhibiting the Akt pathway [99]. Another study revealed that ZLDI-8 may serve as a potential novel therapeutic agent that increases tumor cell susceptibility to anti-tumor drugs, thereby reducing multi-drug resistance (MDR) in liver cancer. Researchers found that ZLDI-8 inhibited Notch signaling by suppressing the activation of ADAM-17 and blocked the accumulation of nuclear NICD in HCC cells. Furthermore, ZLDI-8 also inhibited EMT in HCC cells, enhancing their sensitivity to chemotherapy drugs [100]. These findings suggest that inhibition of Notch signaling improved the sensitivity of HCC cells to anti-cancer

therapies. Therefore, targeting the Notch pathway alone or in combination with other drugs is a promising strategy to improve the efficacy of HCC treatment.

Notch signaling is crucial for physiological angiogenesis. Aberrant stimulation contributes to tumor angiogenesis and metastasis [101], and researchers have investigated the role of natural compounds in suppressing this mechanism. A previous report showed that treatment with total alkaloids of Rubus alceifolius Poir (TARAP) inhibited angiogenesis in HCC by downregulating the Notch signaling pathway [102]. In addition, studies have shown that treatment with extract of Livistona chinensis seeds (EELC) also inhibited tumor angiogenesis by significantly reducing the expression of Notch, DLL4, and JAG1 in HCC mouse tumor tissues [103].

Notch signaling and tumor suppression

Notch has primarily been associated with malignant growth. However, some studies have indicated that Notch signaling also functions as a tumor suppressor in HCC. For example, Notch1 inhibited the growth of human HCC by altering the balance between Bcl-2 and p53 to induce cell cycle arrest and subsequent apoptosis [104]. In addition, activation of the Notch signaling pathway via retinoblastoma pathway inhibition was shown to reduce cell proliferation and tumor growth in HCC [105, 106]. In TKO liver cells, Notch signaling acts as a tumor suppressor feedback mechanism, responding to the activation of E2F transcription factors. While this negative feedback is insufficient to prevent the development of cancer, activating Notch may significantly restrict the spread of tumor cells in the body [106]. Chronic hepatitis B virus (HBV) infection is one of the primary causes of HCC. Prior research has indicated that the expression of HBx in hepatoma cells resulted in the reduction of endogenous proteins within the intracellular domain of Notch1 and a concomitant decrease in messenger RNA expression of its downstream target genes. This led to the promotion of cellular proliferation, induction of cell cycle progression, and attenuation of senescence-like growth arrest, both in vitro and in vivo [107]. In addition, Liu et al. evaluated the differential expression of Notch1 and observed significant reduction in tumor tissues compared to adjacent non-tumor tissues. Despite the tumor's suppressive capabilities, further evidence is emerging to support the oncogenic role of Notch in the development of HCC.

Clinical potential of the Notch signaling pathway in HCC

HCC is a prevalent cancer globally and a serious threat to human health [108]. Despite extensive research that has advanced our understanding of the molecular mechanisms involved in the development and progression of HCC, the prognosis of advanced-stage HCC remains poor. Therefore, there is an urgent requirement for novel and efficient therapies to enhance patient clinical results [109]. An increasing amount of data indicates that the Notch pathway is significantly involved in the progression of HCC [110]. There has been extensive research into the expression and clinical potential of Notch family members in HCC (Table 2). The four Notch receptors are all expressed in HCC cells and have different distributions in cell subcells. First, both Notch1-4 can be expressed in the cytoplasm. Second, Notch1 and Notch4 can also be expressed in the nucleus [105]. Analysis of Notch and its target genes in HCC revealed that Notch3 and Notch4 were abnormally expressed in cancerous tissue compared with para-cancer tissue [111]. Another study corroborated these findings, indicating that normal liver tissues hardly express Notch3 and Notch4, whereas human HepG2 cell lines exhibited high expression levels of Notch3 and low expression levels of Notch4 [112]. Ann and colleagues studied 288 patients with HCC and showed that Notch1, Notch3, and Notch4 proteins were overexpressed in HCC compared to normal liver tissues. In addition, this study also demonstrated that Notch1 and Notch4 may be utilized as immunohistochemical biomarkers to identify patients with shorter disease-specific survival [113]. In a study conducted by Gao et al., it was observed that HBx upregulated the expression of cytoplasmic Notch1 and nuclear Notch4 in HepG2X cells. Furthermore, Notch1 upregulation by HBx was mediated by the p38 MAPK pathway [114]. A previous study conducted also found that a strong correlation between elevated JAG1 expression and HBx presence in HCC tissues [115]. Combined with the previous studies, it has been found that both Notch1 and Notch2 may promote the occurrence of liver cancer in humans [116]. Moreover, Hayashi et al. suggested that Notch2 played an essential role in promoting the aggressiveness and morphological transformation of HCC cells and supported that only Notch2 was found to be significantly associated with advanced clinical staging in primary HCC [117]. Dill et al. investigated the results of constitutive Notch2 signaling in the oncogenic model of DEN, which reported that constitutive Notch2 signaling accelerated the growth of HCC. Moreover, Notch3 and Notch4 were not expressed in chronic hepatitis and normal liver tissue surrounding HCC but were aberrantly expressed in HCC tissues. In addition to protein expression levels, studies have observed an upregulation of Notch3 mRNA in HCC [116, 118]. Similarly, Notch3 had also been reported to be overexpressed in HCC [119]. Studies has implicated a robust association between the presence of HBx and the expression of JAG1 in HCC

Table 2 Clinical potential of Notch signaling pathway in HCC

Notch component	Expression	Clinical feature	Clinical application	Refs.
Notch1	Upregulated	Disease-specific survival	Predicting poor prognosis	[112]
Notch2	Upregulated	Clinical stages	Predicting poor prognosis	[116]
Notch3	Upregulated	TNM stage, overall survival	Predicting poor prognosis	[118]
Notch4	Upregulated	Disease-specific survival	Predicting poor prognosis	[112]
JAG1	Upregulated	Differentiation grade	Predicting poor prognosis	[114]
JAG2	Upregulated	Advanced TNM stage and intrahepatic metastasis	Predicting poor prognosis	[120]
DLL4	Downregulated	/	/	[119]
NICD	/	ZLDI-8 improves chemotherapy sensitivity and inhibits tumor growth	Clinical targets	[99]
Notch2	Upregulated	miR-148a treatment effectively decreases tumor growth and prevents tumor development	Clinical targets	[122]
Notch1	Upregulated	ZLDI-8 reduces the resistance of HCC cells to sorafenib and inhibits tumor growth	Clinical targets	[124]
Notch1, HES1	Upregulated	ZLDI-8 inhibits the proliferation and metastasis of HCC	Clinical targets	[125]
Notch1	Upregulated	GSI-I + IL-24 downregulated Notch1 to promote apoptosis of HCC cells and reduce the migration and invasion ability of HCC cells	Clinical targets	[127]
JAG1	Upregulated	GSI-I inhibits HCC cell growth	Clinical targets	[128]
Notch1, HES1	Upregulated	DAPT inhibits tumor growth	Clinical targets	[129]
Notch1	Upregulated	SIL inhibits the growth of HCC cells	Clinical targets	[131]

tissues, with significantly higher levels of JAG1 observed in HCC tissues compared to adjacent on-tumor liver tissues [115]. Interestingly, the expression levels of DLL4 in tumor tissues were notably reduced compared to adjacent non-tumor tissues, and DLL4 expression was independent of any clinical parameters [120]. However, the role of DLL4 in HCC is largely unknown. Compared to normal tumor-adjacent tissues, JAG2 protein expression was significantly upregulated in HCC tissues. Additionally, JAG2 was significantly associated with intrahepatic metastasis and advanced TNM staging [121]. Conversely, evidence suggests that DLL3 expression negatively regulates HCC cell growth by suppressing Notch, andDLL3 is silenced by methylation in human HCC [122]. These studies reveal the key regulatory roles of Notch receptors and ligands in the development of HCC, highlighting their potentials therapeutic targets and prognostic indicators for HCC.

Additional research has emerged regarding inhibitors of the Notch pathway. For example, a study suggested that miR-148a may function as a suppressor of Notch, thereby inhibiting tumor growth and development in HCC [123]. At present, chemotherapy drugs are used to treat HCC. However, resistance to such treatment often develops, presenting a significant challenge for patients. Sorafenib, an oral multikinase inhibitor, is an effective first-line treatment for advanced-stage liver cancer. Despite promising results, the development of sorafenib resistance is becoming more common, and alternative therapies must be explored [124]. In the Notch pathway, ADAM-17 is an essential enzyme responsible for activating and cleaving the Notch protein. Studies have shown that ZLDI-8, a novel ADAM-17 inhibitor, can increase the sensitivity of HCC cells to sorafenib and inhibit tumor growth by suppressing the Notch pathway, specifically Notch1 [100, 125]. Additionally, another report corroborated these findings, revealing that ZLDI-8 blocked Notch and subsequently suppressed HCC proliferation and metastasis [126]. Therefore, ZLDI-8 maybe a potentially effective tool for the treatment of MDR HCC.

As previously mentioned, γ-secretase is a membrane-bound protease responsible for S3 cleavage of Notch. Due to the significant role in the Notch pathway, there has been growing interest in γ-secretase inhibitors (GSIs) as cancer therapeutics [127]. Han et al. found that GSI-I combined with IL-24 downregulated Notch1, promoting apoptosis of HepG2 cells while reducing their migration and invasion abilities [128]. Furthermore, Shen et al. compared the effects of four different GSIs and showed that GSI-I was more effective than GSI-IX, GSI-X, and GSI-XXI in inhibiting the growth of HCC cells. Researchers attributed the inhibition of cell growth to the suppression of the Notch signaling pathway. However, the results indicated that the effect of GSI-I depended on the presence of JAG1 [129]. These studies suggest that GSIs may be a promising treatment strategy for HCC.

DAPT represents another widely used GSI in cancer therapy. Qiu et al. explored the potential efficacy of DAPT in HCC. They found that DAPT markedly blocked Notch1/HES1 signaling and inhibited HCC cell

proliferation and migration, supporting the anti-tumor effects of DAPT [130]. Accumulating evidence suggests that DAPT-mediated Notch inhibition may modulate the effects of other protein molecules involved in HCC [131]. For example, silybin (SIL), an antioxidant compound, can reduce the expression of Notch1 and exert hepatoprotective and anti-tumor effects. When combined with DAPT, SIL exhibited significantly enhanced anti-tumor activity [132].

These investigations have shown that inhibitors targeting Notch signaling can effectively suppress the development of HCC (Fig. 3). However, research on various receptor and ligand inhibitors are insufficient, and large-scale clinical trials are necessary to verify the efficacy and safety of these targeted therapies in HCC treatment.

Conclusion

HCC is a highly aggressive disease with a high mortality rate [133]. In HCC, the Notch signaling pathway is aberrantly expressed. In this review, we discussed how Notch components are implicated in the development, progression, and prognosis of HCC by modulating cell proliferation, CSC properties, EMT, and drug resistance. Specific mechanistic processes of Notch activation provide a new direction for HCC treatment. However, Notch is highly complex, and controversial reports suggest that Notch is a tumor suppressor in HCC. Moreover, therapeutic strategies targeting Notch signaling, such as γ-secretase inhibitors, have shown promise in inhibiting the development and progression of HCC and increasing drug sensitivity. However, further investigation is required to uncover the diverse molecular mechanisms of Notch in HCC and to develop more effective therapies. And targeting the clinical and therapeutic potential of Notch signaling in HCC is an important direction for future research. Future studies need to further explore the molecular mechanisms of the Notch signaling pathway in HCC, including its specific role in tumor development and interactions with other signaling pathways. In addition, new drugs and therapeutic approaches need to be developed and tested to more precisely target the Notch signaling pathway to improve the efficacy of HCC treatments and reduce side effects.

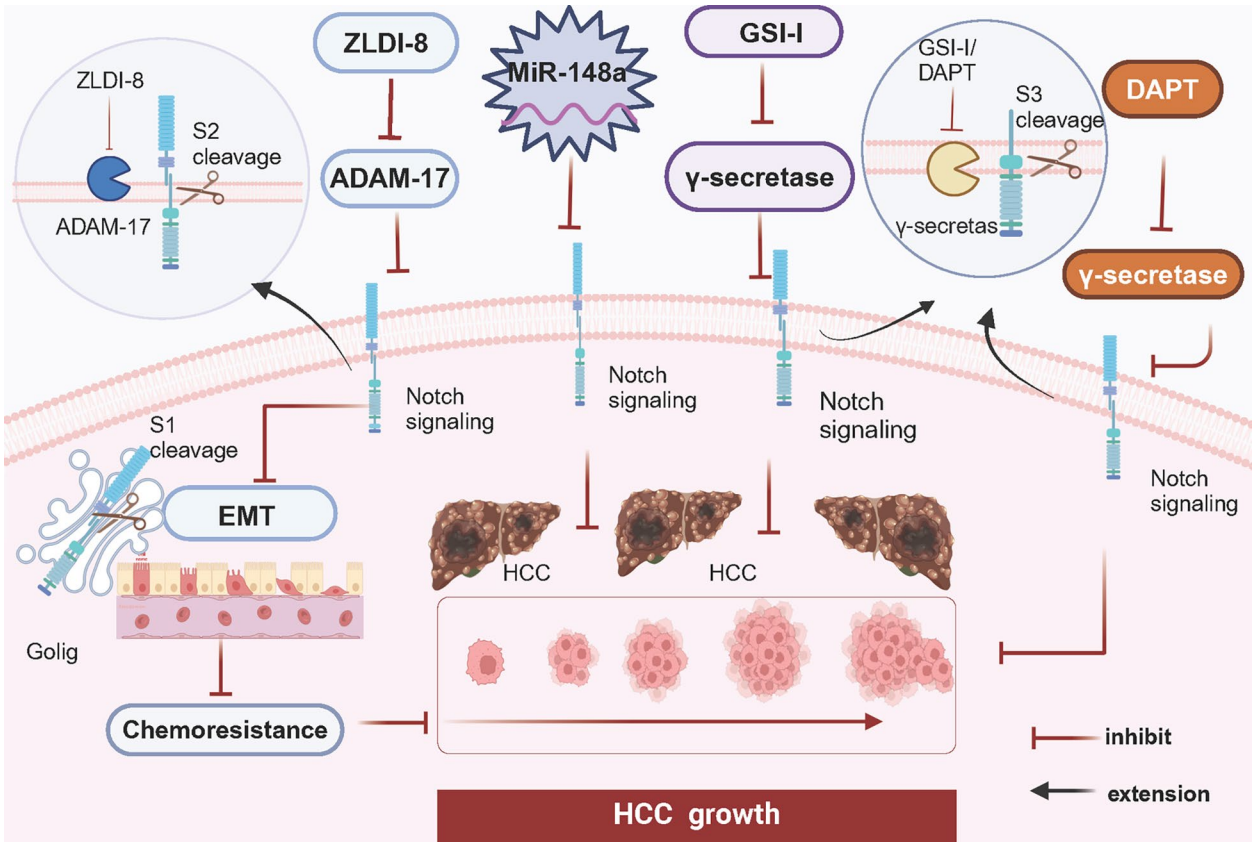

Fig. 3 Treatment strategies for Notch signaling pathway in HCC. ADAM-17, an essential enzyme responsible for activating and cleaving the Notch protein; ZLDI-8, a novel ADAM-17 inhibitor; Mir-148a, noncoding RNAs; γ-secretase, a membrane-bound protease responsible for S3 cleavage of Notch; GSI-I, γ-secretase inhibitors; DAPT, γ-secretase inhibitors

Immunotherapy is widely used as a novel therapeutic approach in the treatment of tumors and has shown some effectiveness in the treatment of HCC, but approximately 30% of HCC exhibits resistance to immune checkpoint inhibitors (ICIs), which necessitates new therapeutic combinations. It has been suggested that aberrant regulation of the Notch signaling pathway may affect immune cell responses, and therefore, therapeutic strategies targeting Notch signaling may be combined with immunotherapy to improve therapeutic efficacy [134]. Macrophages play a crucial role in the tumor microenvironment, especially in HCC, where they are not only involved in tumor progression and metastasis, but are also closely associated with the immunoregulation of the tumor microenvironment [135]. The Notch pathway, as an intercellular communication mechanism, plays a central regulatory role in macrophage polarization and function. It has been shown that activation of Notch signaling induces macrophage differentiation toward pro-inflammatory M1 type, which is involved in inflammatory response and anti-tumor activity; whereas blocking Notch signaling leads to macrophage polarization toward immunosuppressive M2 type, which inhibits inflammatory response and promotes tumor growth [136]. In addition, the Notch pathway plays an essential role in the regulation of a subpopulation of tumor-associated macrophages (TAMs) in HCC. In HCC, Notch blockade inhibited monocyte differentiation to TAMs, but promoted the proliferation and pro-tumor phenotype of kclTAMs. Blockade of the Notch pathway led to higher expression of IL-10 and PD-L1/2 by kclTAMs, which may have suppressed the anti-tumor immune response and promoted HCC progression [137].

Although there have been a number of therapies targeting the Notch signaling pathway that have shown potential, there are continuing challenges. For example, the development of chemoresistance is a major problem in the treatment of HCC, and further research into the role of the Notch signaling pathway in the development of chemoresistance is needed, as well as the development of new strategies to overcome drug resistance. Connexins are a group of tetraspan membrane proteins that form intercellular channels and are widely involved in the processes of tumorigenesis, progression, and chemoresistance. Hepatocytes predominantly express Cx32 and Cx26, and it has been shown that the expression of Cx32 and CX26 is closely related to the sensitivity of HCC to chemotherapeutic drugs, and that CX32 downregulation may enhance cell survival by activating the PI3K/Akt signaling pathway and the Src/FAK signaling pathway [138].

In addition, the integration of Notch-targeted approaches into clinical practice for HCC may require multiple efforts. First, the safety and efficacy of these treatments need to be validated through large-scale clinical trials. Second, personalized medicine strategies may need to be developed to select the most appropriate treatment regimen for different patients. Finally, awareness and acceptance of these emerging treatments need to be increased.

Abbreviations

HCC	Hepatocellular carcinoma
T-ALL	T-cell acute lymphoblastic leukemia
DLL3	Delta-like ligand-3
NECD	Notch extracellular domain
TMD	Notch transmembrane domain
NICD	Notch intracellular domain
TAD	Notch transcriptional transactivation domain
NRR	A region of negative regulation
LNRs	Lin12-Notch repeats
DLL1	Delta-like ligand-1
DLL3	Delta-like ligand-1
DLL4	Delta-like ligand-4
JAG1	Jagged ligand-1
JAG2	Jagged ligand-2
NEXT	Notch extracellular truncation
EMT	Epithelial-to-mesenchymal transition
CSC	Cancer stem cell-like
MCUR1	Mitochondrial calcium uniporter regulator 1
RNF187	Ring finger protein 187
ACTL6A	Actin-like 6A
SOX2	Sex-determining region Y-box2
NCSTN	Nicastrin
SKA	Spindle and kinetochore-associated
CAFs	Cancer-associated fibroblasts
TM4SF1	A member of the transmembrane 4 super family
NOR1	The oxidored-nitro-domain containing protein 1
VPA	Valproic acid
HES1	Notch downstream target gene
KK-LC-1	Kita-Kyushu lung cancer antigen-1
HSCs	Hepatic stellate cells
EVs	The secretion of extracellular vesicles
PRDM16	The transcription factor positive regulatory domain I-containing protein 16
HBx	Hepatitis B virus protein X
INPP5F	Inositol polyphosphate 5-phosphatase F
HBV	Hepatitis B virus
HepG2	Human Hepatoma Cell Line
TNM	Tumor Node Metastasis Classification

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Chen Xue and Juan Li conceived the idea and wrote the manuscript. Leiya Fu, Xinyu Gu and Na Lou drafted and conceptualized for the manuscript. Leiya Fu designed the figures and revised the manuscript. Leiya Fu and Na Lou completed the tables. All authors have read and agreed to the published version of the manuscript.

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Declarations

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