Journal of Translational Medicine

REVIEW

Open Access

Notch signaling in the tumor immune microenvironment of colorectal cancer: mechanisms and therapeutic opportunities

Jiachun Sun[1], Yi Chen[2], Ziyi Xu[1], Weizheng Wang[1] and Penghui Li[3*]

Abstract

Colorectal cancer (CRC) remains a leading cause of cancer-related morbidity and mortality worldwide, driven by a complex interplay of genetic, environmental, and immune-related factors. Among the pivotal pathways implicated in CRC tumorigenesis, the Notch signaling pathway is instrumental in governing cell fate decisions, tissue renewal, homeostasis, and immune cell development. As a highly conserved mechanism, Notch signaling not only modulates tumor cell behavior but also shapes the immune landscape within the tumor microenvironment (TME). Aberrant Notch signaling in CRC fosters immune evasion and tumor progression through its effects on the balance and functionality of immune cells, including myeloid-derived suppressor cells (MDSCs) and tumor-associated macrophages (TAMs). Elevated Notch pathway activation correlates with advanced clinicopathological features and poorer clinical outcomes, highlighting its relevance as both a prognostic biomarker and a therapeutic target. Therapeutic approaches aimed at inhibiting the Notch pathway, such as γ-secretase inhibitors (GSIs) or monoclonal antibodies (mAbs) in combination with other therapies, have demonstrated promising efficacy in preclinical and clinical settings. This review examines the impact of Notch signaling on CRC immunity, elucidating its regulatory mechanisms within immune cells and its role in promoting tumor progression. Additionally, this review discusses therapeutic strategies targeting Notch signaling, including GSIs, mAbs, and potential combination therapies designed to overcome resistance and improve patient outcomes. By elucidating the multifaceted role of Notch within the CRC TME, this review underscores its potential as a target for innovative therapeutic strategies.

Keywords Notch signaling, CRC, Immune, Prognosis, GSIs

Background

Colorectal cancer (CRC) is the third most prevalent malignancy globally, accounting for 9.6% of all cases, and stands as the second leading cause of cancer-related mortality, responsible for 9.3% of cancer deaths, according to Global Cancer Statistics 2022 [1–3]. CRC results from complex interactions between genetic mutations and environmental factors, driving progressive changes in cell growth, invasion, and immune evasion [4–6]. Recent molecular profiling has identified four distinct consensus molecular subtypes (CMS) for CRC, each associated with unique biological behaviors and patient

*Correspondence:
Penghui Li
lph0819@163.com
[1]Henan Key Laboratory of Cancer Epigenetics, Cancer Institute, The First Affiliated Hospital, College of Clinical Medicine, Medical College of Henan University of Science and Technology, Luoyang 471003, China
[2]Department of Children's gastroenterology, Anhui Children's Hospital, Hefei, Anhui 230000, China
[3]Department of Gastrointestinal surgery, The First Affiliated Hospital, College of Clinical Medicine, Henan University of Science and Technology, No. 24 Jinghua Road, Jianxi District, Luoyang, Henan 471000, China

© The Author(s) 2025. **Open Access** This article is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License, which permits any non-commercial use, sharing, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if you modified the licensed material. You do not have permission under this licence to share adapted material derived from this article or parts of it. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by-nc-nd/4.0/.

survival [7–9]. Among these, the CMS4 subtype is characterized by aggressive clinical features and the poorest relapse-free and overall survival rates, underscoring the need for tailored therapeutic strategies [10–13]. A critical determinant of CRC progression and patient prognosis is the tumor immune microenvironment (TME), where dynamic interactions between immune and tumor cells reshape immune responses and influence therapeutic outcomes [14–17]. One key regulatory pathway within the TME is the Notch signaling pathway, which plays a multifaceted role in tumor progression and immune modulation [18–21].

The Notch signaling pathway is an evolutionarily conserved intercellular communication mechanism that regulates vital processes such as proliferation, differentiation, and apoptosis [22]. Notch signaling operates through receptor-ligand interactions between adjacent cells, influencing cell fate decisions across various tissue types [23]. In the immune system, Notch signaling is essential for hematopoiesis and immune cell development, affecting the balance between innate and adaptive immune responses. By guiding immune cell differentiation, activation, and function, Notch signaling is essential for maintaining effective immune surveillance and responses to tumorigenesis [24, 25]. In CRC, Notch signaling has emerged as a critical regulator of both tumor biology and the TME [26–28]. Dysregulation of the Notch pathway—whether through aberrant activation or suppression—disrupts immune cell populations and their functions, leading to immune escape mechanisms that support tumor growth and metastasis [27, 29, 30]. High levels of Notch signaling in CRC are associated with adverse clinical features and poorer prognosis, highlighting its potential as a therapeutic target [31–34]. Recent evidence suggests that targeting the Notch pathway with γ-secretase inhibitors (GSIs) or monoclonal antibodies (mAbs) in combination with standard chemotherapy or immunotherapy enhances anti-tumor activity in preclinical and clinical studies. However, challenges remain, including therapy-related toxicities and the limited efficacy of Notch-targeting agents. These barriers emphasize the need for larger clinical trials to optimize Notch-targeted therapies and address these concerns [35].

This review provides an overview of Notch signaling's role in immune cell development and function, focusing on its regulatory influence within the CRC TME. Additionally, it explores recent preclinical and clinical efforts to target Notch signaling as a therapeutic strategy, highlighting its potential as both a biomarker and therapeutic target to improve patient outcomes.

Overview of Notch signaling pathway

The Notch signaling pathway operates through four primary receptors—Notch1, Notch2, Notch3, and Notch4—each comprising transmembrane glycoproteins with distinct extracellular, transmembrane, and intracellular domains [36–39]. The extracellular domain includes a negative regulatory region (NRR) and multiple epidermal growth factor (EGF) repeats critical for ligand binding and receptor stability. The intracellular region houses key signaling elements, such as the Recombination Signal-Binding Protein 1 for the J-kappa (RBP-J)-association molecule (RAM) domain, ankyrin (ANK) repeats, nuclear localization signals (NLS), a transactivation domain (TAD), and a proline/glutamine/serine/threonine-rich (PEST) sequence essential for signal modulation [40]. In humans, five Notch ligands are recognized—delta-like ligand 1 (DLL1), DLL3, DLL4, Jagged-1 (JAG1), and JAG2—which, like the Notch receptors, are transmembrane proteins with comparable structural features [41].

The activation of Notch receptors begins with ligand binding, initiating a series of proteolytic cleavages necessary for signal transduction [42–45]. The first cleavage (S1) occurs in the Golgi apparatus, producing a mature Notch heterodimer that is transported to the cell surface. Upon ligand engagement, the receptor undergoes an S2 cleavage by metalloproteases from the disintegrin and metalloproteases (ADAM) family (e.g., ADAM17 or ADAM10), separating the extracellular subunit and generating the membrane-bound intermediate Notch extracellular truncated (NEXT). Subsequently, the γ-secretase complex—comprising presenilin 1 (PSEN1) or PSEN2, nicastrin (NCT), presenilin enhancer 2 (PEN2), and anterior pharynx-defective 1 (APH1)—executes the S3 cleavage, releasing the Notch intracellular domain (NICD) into the cytoplasm [46–48]. The NICD then translocates into the nucleus, where it associates with the CSL (CBF1/RBPJ) transcriptional regulator, converting a co-repressor complex into an activator complex. This complex includes NICD, CSL, mastermind-like protein (MAML; a transcriptional coactivator), SKIP (Ski-interacting protein as a CBF1-binding protein), and p300, facilitating the transcription of canonical Notch target genes [49, 50]. Notch target genes, predominantly from the Hairy/Enhancer of Split (HES) and Hairy/Enhancer of Split related to YRPW motif (HEY) families, are instrumental in governing cell differentiation, proliferation, and survival [51–53]. Precise regulation of the Notch pathway is critical to developmental and cellular homeostasis, with its dysregulation implicated in various pathologies, including cancers such as CRC [18, 54–56].

Role of Notch signaling in immune cell development and regulation

The Notch signaling pathway is integral to the development and function of immune cells, orchestrating both lymphoid and myeloid lineages within the hematopoietic

system [57, 58]. During embryogenesis, Notch-driven processes facilitate the transition of endothelial cells into hematopoietic cells, initiating the first population of hematopoietic stem cells (HSCs) [59]. Originating from HSCs within the bone marrow, Notch signaling directs their progression through various differentiation stages, giving rise to T cells, B cells, granulocytes, and myeloid cells, including macrophages and dendritic cells (Fig. 1). This pathway is indispensable in guiding immune cell lineage decisions, thereby supporting a balanced and adaptive immune system [60–62].

T cell and B cell development and adaptive immunity

In the early stages of hematopoietic progenitor cell (HPC) development, the absence of Notch1 or the transcription factor CSL disrupts thymic T cell maturation, leading to B cell accumulation. Notch signaling is crucial for T cell lineage specification within the thymus, driving key processes in T cell commitment [63–65]. Additionally, mesenchymal cells in the bone marrow can interact with HPCs *via* surface-bound Notch ligands, further promoting T cell lineage differentiation [66, 67]. Once transplanted into the thymus, these progenitors complete their differentiation into mature T cells, emphasizing

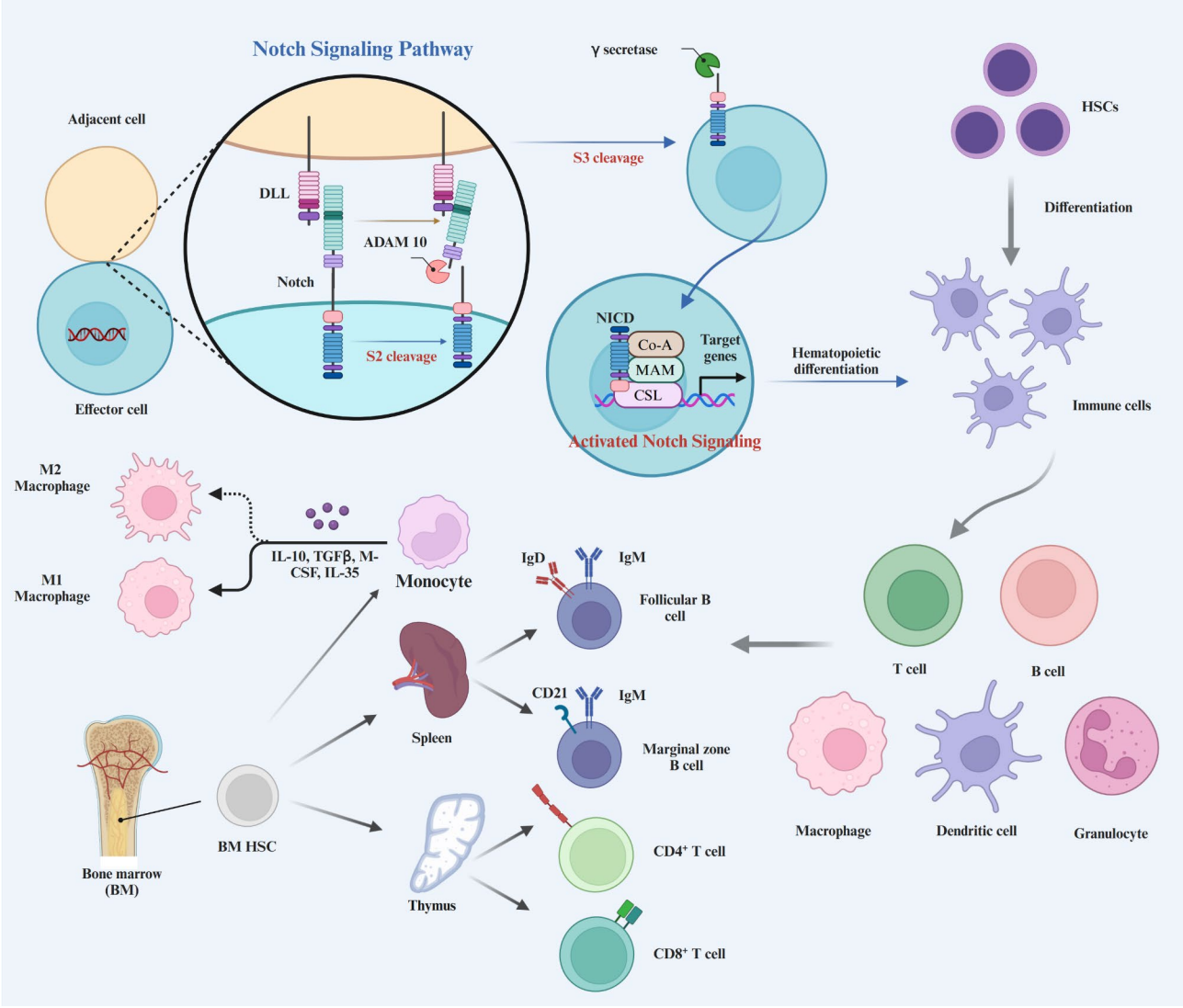

Fig. 1 Overview of the Notch Signaling Pathway and Its Role in Immune Cell Differentiation and Function. Upon binding of the Delta-like ligand (DLL) from an adjacent cell, the Notch receptor undergoes sequential cleavages first by ADAM10 and subsequently by γ-secretase, resulting in the release of the Notch intracellular domain (NICD). NICD translocates to the nucleus, where it engages transcriptional regulators such as CSL and MAML, initiating the transcription of target genes. Within hematopoiesis, Notch signaling is essential for directing hematopoietic stem cells (HSCs) toward specific immune lineages, influencing the differentiation and maturation of T cells, B cells, and myeloid cells (including monocytes, dendritic cells, and granulocytes). Through its role in guiding immune cell fate and function, Notch signaling is vital for maintaining immune homeostasis and supporting effective immune responses

Notch's role in T cell maturation [68, 69]. Notch receptor-ligand engagements not only influence T cell lineage commitment but also regulate the divergence of αβ and γδ T cell subsets, as well as β-selection and positive selection processes [70–73]. Notch signaling provides critical prethymic cues, enabling early T cell progenitors (ETPs) to commence T cell differentiation upon entering the thymus [74]. B cell subset differentiation is also highly Notch-dependent [75–77]. Notch2 is essential for the development of splenic marginal zone B (MZB) cells, even in the absence of CD19, with the DLL1-Notch2 interaction facilitating the transition of follicular B cells into MZB cells [78–80]. This adaptability reflects the dynamic nature of mature B cell subsets in response to immunological demands [79, 81, 82]. Additionally, innate lymphoid cells (ILCs) situated near the marginal zone (MZ) integrate stromal and myeloid cues, stimulating MZB cells *via* DLL1 to enhance antibody production [83].

Myeloid cells and innate immunity

Notch signaling plays a pivotal role in innate immunity, directing myeloid lineage differentiation and modulating the function of macrophages, dendritic cells (DCs), and granulocytes, all of which are key components of the tumor immune microenvironment (TIME) [84, 85].

Macrophages and myeloid-derived suppressor cells (MDSCs)

Notch signaling regulates monocyte-to-macrophage differentiation and polarization into pro-inflammatory (M1) or anti-inflammatory (M2) phenotypes, directly influencing the immune-suppressive landscape of CRC [86–90]. Elevated Notch1 and Notch2 expression has been observed in circulating monocytes, and DLL1 activation in the presence of macrophage colony-stimulating factor (M-CSF) induces apoptosis, limiting monocyte-to-macrophage differentiation [91]. Additionally, DLL1 prevents monocyte differentiation into macrophages under granulocyte-macrophage CSF (GM-CSF) conditions, instead promoting dendritic cell (DC) differentiation, thereby influencing antigen presentation and T cell activation [92]. Notably, Notch4 is highly upregulated in tumor-associated macrophages (TAMs) upon Toll-like receptor (TLR) and interferon-γ (IFN-γ) activation, where it serves as a negative regulator of macrophage activation. By suppressing pro-inflammatory cytokines (IL-6, IL-12) and costimulatory molecules (CD80, CD86), Notch4 promotes an immunosuppressive macrophage phenotype within the CRC TME [93].

DCs and antigen presentation

Notch signaling is critical for DC maturation and function, as DLL-mediated Notch signaling drives the differentiation of both plasmacytoid DCs (pDCs) and conventional DCs (cDCs), which are essential for antigen presentation and T cell priming [94–96]. Notch2 specifically promotes the differentiation of CD11b + DCs in the spleen and intestine, directing their production of IL-23, a cytokine crucial for intestinal immunity and CRC progression [97–99]. Furthermore, Notch-RBP-J signaling is necessary for the maintenance of CD8 + DCs within the splenic marginal zone (MZ), as Notch2 deletion in DCs results in a significant reduction in CD8 + DC populations [100].

Granulocytes

For granulocytes, which include neutrophils, eosinophils, and basophils and are essential for inflammation and pathogen clearance. Notch signaling integrates external immune signals to regulate granulocyte differentiation and function [85, 101]. Eosinophils express Notch receptors and ligands under GM-CSF stimulation, impacting transendothelial migration and survival [102]. In CRC, increased Notch signaling in eosinophils has been linked to their recruitment into the tumor site, potentially influencing pro-tumorigenic inflammation. Similarly, basophil function and cytokine secretion are also regulated by Notch activity, as Notch inhibition has been shown to reduce basophil cytokine production upon stimulation, further supporting a role for Notch in shaping innate immune responses in the TME [103].

Given the prominent role of Notch in immune evasion mechanisms, targeting Notch signaling in innate immune cells presents a potential strategy to enhance anti-tumor immunity in CRC.

Clinical implications of abnormal Notch signaling and its regulatory mechanisms in CRC

Abnormal Notch signaling plays a pivotal role in shaping the TIME in CRC, influencing both tumor progression and therapeutic responses. Dysregulated Notch signaling modulates the differentiation and function of myeloid-derived suppressor cells (MDSCs) and tumor-associated macrophages (TAMs), which are crucial components of the TIME and contribute to immune suppression and tumor immune evasion (Fig. 2; Table 1) [104, 105]. High Notch activity in CRC has been correlated with advanced disease stages, poor prognosis, and resistance to therapy (Fig. 3; Table 2) [18, 29, 106].

In inflammatory bowel disease (IBD)-associated CRC, elevated Claudin-1 (Cld-1) levels activate Notch signaling, which in turn initiates the PI3K/Akt pathway, leading to β-catenin phosphorylation and subsequent hyperproliferation of CRC cells [107]. This process, validated in azoxymethane (AOM)/DSS mouse models, promotes TAM recruitment within the TIME and facilitates tumorigenesis.

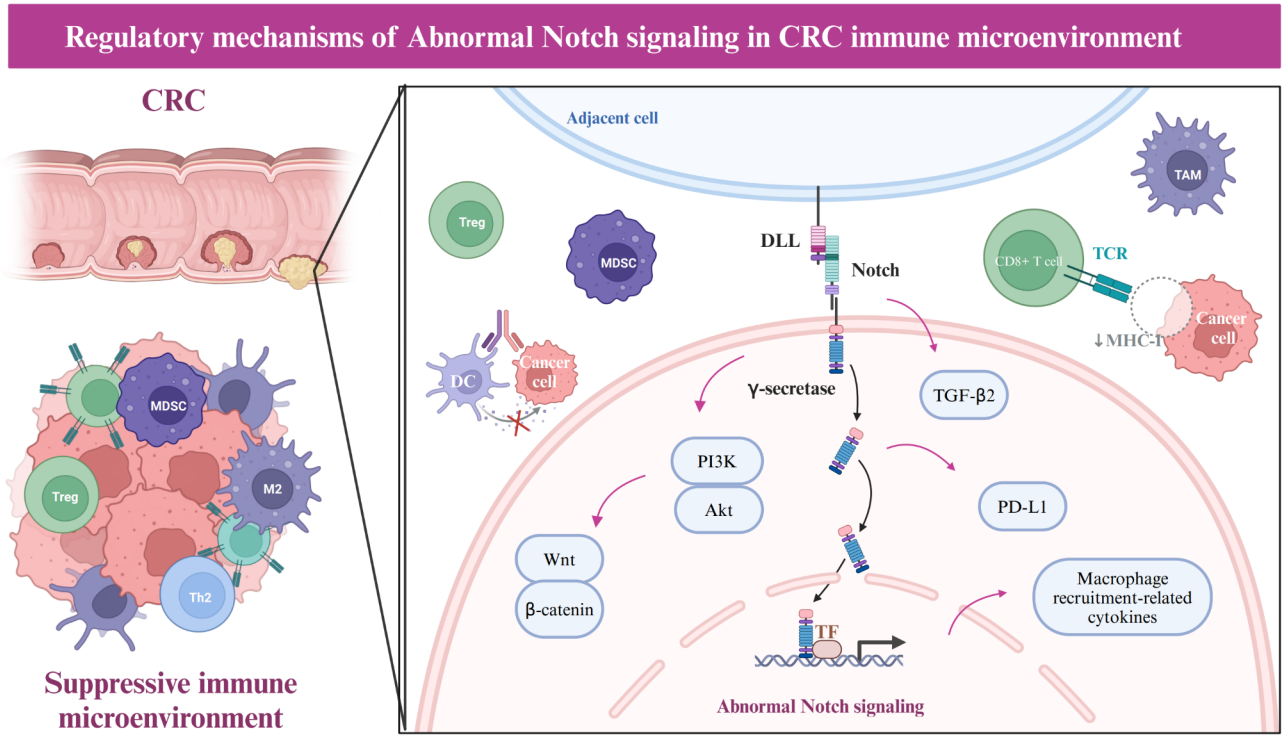

Fig. 2 Regulatory Mechanisms of Dysregulated Notch Signaling in the CRC Immune Microenvironment. Abnormal activation of Notch signaling within the CRC microenvironment impacts various immune cell populations, especially regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), and tumor-associated macrophages (TAMs). Dysregulated Notch signaling activates downstream pathways, notably PI3K/Akt, Wnt/β-catenin, and TGF-β2, which collectively establish an immunosuppressive tumor microenvironment. These pathways facilitate immune evasion by upregulating PD-L1 and cytokines that recruit tumor-promoting macrophages, while concurrently suppressing the activity of CD8 + T cells

Prognostic and predictive significance of Notch pathway in CRC

Recent transcriptomic analyses have established a Notch activity index as a strong predictor of overall survival (OS) and relapse-free survival (RFS) in CRC. Data from The Cancer Genome Atlas (TCGA)-CRC cohort show that high Notch index levels are associated with advanced AJCC/TNM staging and microsatellite stability (MSS). Notably, the CMS4 subtype, which is characterized by mesenchymal features and aggressive progression, exhibits the highest Notch activity. The NLncS model, an independent risk factor for CRC prognosis, demonstrates a correlation between high NLncS scores and increased tumor immunogenicity, including the enrichment of CD8 + T cells, macrophages, endothelial cells, and cancer-associated fibroblasts (CAFs) in the TME [108]. Additionally, Notch pathway mutations in the GSE108989 dataset are associated with enhanced anti-tumor immune responses, featuring elevated tumor-specific CD8 + T cells and a reduced regulatory T cell (Treg) population [109]. Analysis of TCGA-CRC and GSE108989 datasets further reveals that Notch pathway mutations contribute to an immune-activated tumor phenotype, characterized by higher expression of immune checkpoint molecules (PDCD1, GZMB, and PRF1) and inflammatory cytokines. These effects are particularly evident in microsatellite instability (MSI) CRC, where Notch pathway loss-of-function mutations are linked to heightened anti-tumor immunity through increased chemokine secretion in the TME [27].

Notch1, Notch2, and Notch3 as key prognostic markers in CRC

Notch1 overexpression has been implicated as an early biomarker for CRC recurrence and metastasis. In a study involving 47 CRC patients, Notch1 expression was upregulated in 80.8% of tumor samples, correlating with advanced histological grade, invasion depth, TNM stage, and lymph node metastasis [110]. Furthermore, epithelial Notch1 activation is enriched in aggressive CRC subtypes (CMS4 and CRIS-B), where it enhances TGF-β signaling, promoting neutrophil recruitment and immune suppression in the metastatic TME, particularly in KRASG12D-driven serrated CRC [106]. Spatial transcriptomics of primary and metastatic CRC samples reveal a cooperative immunosuppressive effect between Notch and TGF-β pathways, contributing to poor patient outcomes [111]. Single-cell and spatial transcriptome RNA sequencing of 27 samples from six patients with CRC has identified melanoma cell adhesion molecule (MCAM)-expressing

Table 1 Expression levels and regulatory mechanisms of Notch pathway in CRC

Type	Notch components	Expression/ Mutations	Major target	Regulatory pathways	Role	Cancer processes	Year	Ref.
Notch receptors	Notch1	upregulated	PI3K/AKT	Cld-1/Notch/ PI3K/AKT/ Wnt/β-Catenin	oncogenic	promote cell proliferation and TAM enrichment	2019	[109]
Notch receptors	Notch1	upregulated	/	/	oncogenic	promote CRC development	2015	[112]
Notch receptors	Notch1	upregulated	TGF-β2	Notch1/TGF-β2	oncogenic	promote neutrophil recruitment to drive metastasis	2019	[108]
Notch receptors	Notch1	upregulated	TGF-β2	Notch1/TGF-β2	oncogenic	promote abundance of regulatory T cells and neutrophils	2023	[113]
Notch receptors	Notch1	upregulated	/	/	oncogenic	/	2024	[30]
Notch receptors	Notch1	upregulated	PD-1	Notch1/PD-1		promote T-cell exhaustion-mediated immunosuppression	2019	[140]
Notch receptors	Notch2	deleted	CCR7	/	/	suppress conventional DC migration and cross-presentation	2021	[115]
Notch receptors	Notch3	upregulated	SMARCA4	NOTCH3/ SMARCA4/ MUC5AC/MUC2	oncogenic	/	2022	[139]
Notch receptors	Notch3	upregulated	/	AKT/Notch3	oncogenic	promote cell survival and invasion	2020	[116]
Notch receptors	Notch3	upregulated	CSF1	Notch3/ macrophage recruitment-related cytokines (CSF1, CXCL12, and CCL2)	oncogenic	promote infiltration of macrophages and MDSCs	2023	[117]
Notch signaling	Notch4	mutation	/	/	/	promote immunogenicity and anti-tumor immunity	2023	[138]
Notch ligands	JAG1	upregulated	/	/	/	promote CXCL13 + T cell generation	2023	[114]
Notch ligands	JAG1	upregulated	/	/	oncogenic	/	2023	[118]
Notch ligands	DLL4	upregulated	/	/	oncogenic		2022	[131]
Notch ligands	DLL4	upregulated	/	VEGF-A/DLL4	oncogenic	promote angiogenesis	2009	[135]
Notch ligands	DLL4	upregulated	/	SELENBP1/DLL4 /Notch1	oncogenic	promote angiogenesis	2022	[136]
Notch target genes	HES1	upregulated	PD-L1	ARID3B/KDM4C /HES1/PD-L1	oncogenic	promote stem-like features and immune escape of CRCSCs	2020	[120]
Notch target genes	HES1	loss	/	KRAS/HES1	oncogenic	promote matrix remodeling, EMT, M2 macrophage polarization, and immune suppression	2023	[123]
Notch target genes	HES1	loss	/	/	oncogenic	inhibit CD8 T cell cytotoxic function and gut barrier function	2017	[124]
Notch target genes	HES1	upregulated	genes associated with EMT	HES1/genes associated with EMT	oncogenic	promote cancer metastasis via inducing EMT	2015	[119]
Notch target genes	RBP-J	upregulated	/	RBP-J/Tiam1 /Rac1/p38 MAPK	oncogenic	promote cell proliferation, migration and invasion	2021	[137]
Notch cleavage enzymes	PSEN1	upregulated	PD-L1	PSEN1/PD-L1	oncogenic	promote immune evasion	2022	[128]
Notch cleavage enzymes	ADAM10	upregulated	Notch1	/	oncogenic	promote cell proliferation and tumor growth	2023	[141]
Notch cleavage enzymes	ADAM10	mutation	/	/	/	/	2021	[129]

Table 1 (continued)

Type	Notch components	Expression/ Mutations	Major target	Regulatory pathways	Role	Cancer processes	Year	Ref.
Notch cleavage enzymes	ADAM10	upregulated	/	/	/	promote immunoreactivity	2016	[130]
Notch signaling	Notch signaling	mutation	/	/	/	promote immunogenicity and immune-related characteristics	2023	[138]
Notch signaling	Notch signaling	mutation	/	/	/	increase CD8 + T cells and reduce Treg cells	2020	[111]
Notch signaling	Notch signaling	mutation	chemokine	/	/	upregulate the chemokine levels of the TIME	2022	[27]
General signaling	Notch-derived lncRNAs	upregulated	/	/	oncogenic	promote immunogenicity	2022	[110]

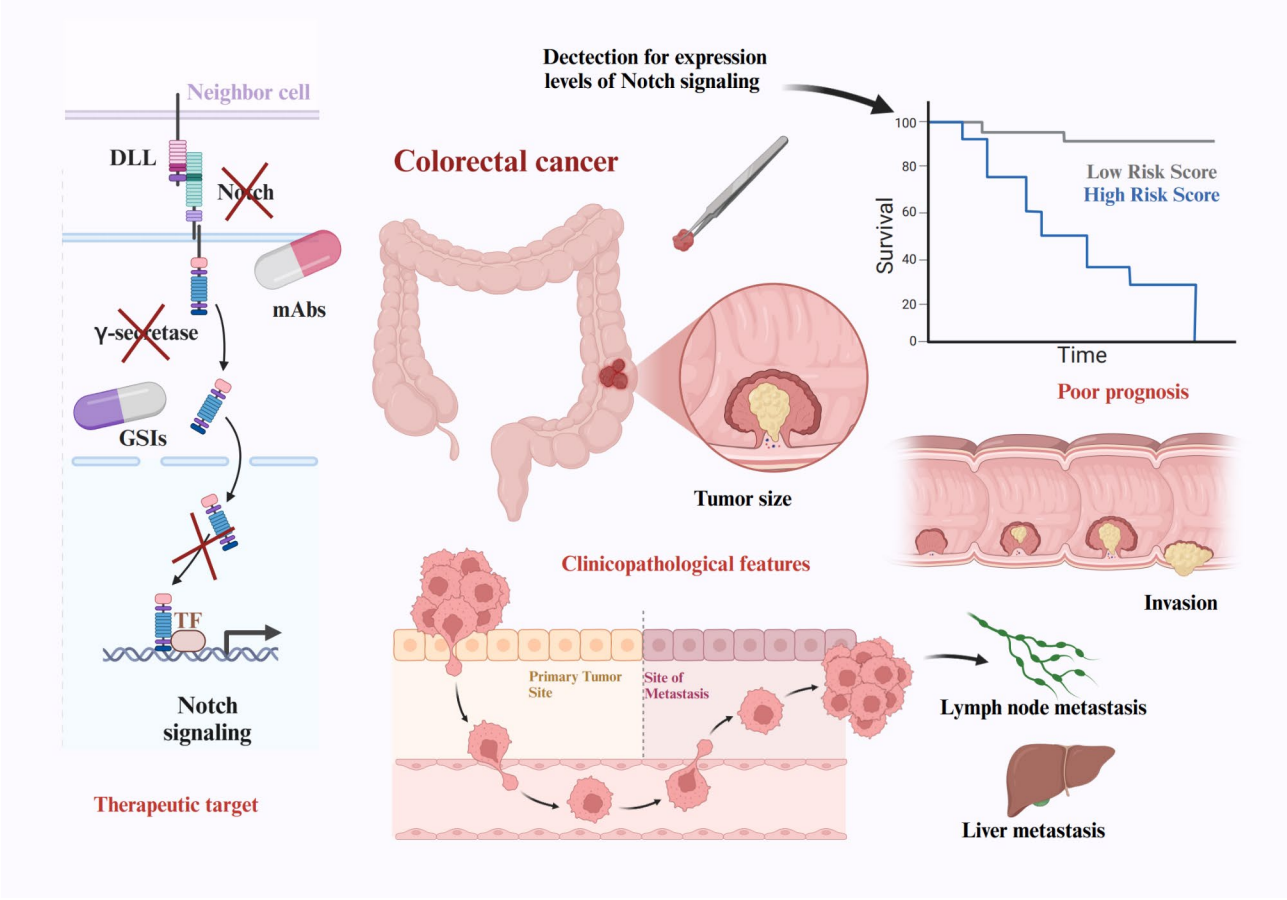

Fig. 3 Clinical Significance of Notch Signaling in CRC: Prognostic and Therapeutic Potential. Aberrant Notch pathway activation drives transcriptional changes that support key oncogenic processes, which correlate with adverse clinicopathological features, including increased tumor size, advanced tumor stage, and metastasis to lymph nodes and the liver. Elevated Notch pathway activity is also associated with poorer overall survival in patients with CRC, underscoring its prognostic relevance in CRC management. Therapeutically, inhibiting the Notch pathway with γ-secretase inhibitors (GSIs) and monoclonal antibodies (mAbs) is under active investigation, with some agents demonstrating enhanced efficacy when combined with other CRC treatments

fibroblasts, enriched in liver metastases, that promote CD8_CXCL13 + T cell generation within the TME *via* JAG1-Notch1 signaling [112].

Additionally, Notch2 plays a crucial role in anti-tumor immunity mediated by type 1 conventional dendritic cells (cDC1s). Notch2 deficiency impairs cDC migration and antigen presentation, which is directly linked to increased colitis-associated tumorigenesis [113]. Notch2 expression is positively correlated with macrophage infiltration in CRC, alongside higher levels of macrophage-recruiting

Table 2 Clinical values of abnormal Notch pathway in CRC

Type	NOTCH components	Role	Cell lines	In vivo model	Clinical samples	Clinical potential	Year	Ref.
Notch receptors	Notch1	oncogenic	/	/	47 CRC patients without receiving chemotherapy or radiotherapy	a biomarker for CRC recurrence and prognosis	2015	[112]
Notch receptors	Notch1	oncogenic	/	a $KRAS^{G12D}$-driven serrated mouse model, and organoids	46 CRC who underwent synchronous resection of colorectal primary tumor and liver metastases, GSE45270 ($n=13$) and GSE79460 ($n=16$), and TCGA-COAD dataset	therapeutic target	2019	[108]
Notch receptors	Notch1	oncogenic	/	a subcutaneous CRC tumor model	/	therapeutic target	2024	[30]
Notch receptors	Notch1	/	HT29 and HCT116 cell lines	subcutaneous CRC mouse model	Human CRC and its corresponding noncancer colon tissues	therapeutic target	2019	[140]
Notch receptors	Notch2	/	bone marrow-derived DCs	fucosylation deficiency (Fx-/- mice) reconstituted with Notch2-defective DCs	TCGA-CRC dataset	therapeutic target	2021	[115]
Notch receptors	Notch3	oncogenic	/	an AOM-treated $Trp53^{\Delta IEC}Akt^{E17K}$ mouse model (Subcutaneous, lung metastasis, and orthotopic mouse models) and organoids	TCGA-COAD dataset, GEO datasets GSE13067, GSE14333, GSE17536, GSE33113, and GSE39582, and 28 human CRC tissue samples	poor-prognosis (CMS4 subtype, lymphovascular invasion, lymphatic and distant metastasis)	2020	[116]
Notch receptors	Notch3	oncogenic	MC38, RAW264.7, HCT116, and HEK293T cell lines	subcutaneous CRC mouse model	TCGA-COAD dataset and human CRC tissue samples	poor prognosis	2023	[117]
Notch receptors	Notch3	oncogenic	HT29, SW480, SW620, and HCT116 cell lines	/	112 CRC and adjacent tissues, and Tissue microarray of 94 CRC patients, TCGA database, and 3806 patients/3953 samples in 10 studies (cBioPortal for Cancer Genomics)	differentiation of mucinous colorectal adenocarcinoma	2022	[139]
Notch receptors	Notch4	/	/	/	103 CRC samples, Samstein-CRC cohort, TCGA-COAD, and TCGA-READ cohorts	therapeutic target	2023	[138]
Notch ligands	JAG1	oncogenic	/	/	111 patients with metastatic CRC treated with bevacizumab and chemotherapy	poor prognosis	2023	[118]
Notch ligands	DLL4	oncogenic	/	/	289 CRC and adjacent normal tissues	poor prognosis (body mass index, greater tumor invasion, and metastasis)	2022	[131]
Notch ligands	DLL4	oncogenic	U87 cells	xenograft CRC mouse model	tissue microarrays containing 177 CRC patients	predictive biomarkers for therapy response (anti-VEGF therapies)	2009	[135]
Notch ligands	DLL4	oncogenic	HCT116 and HCT-15 cell lines	subcutaneous CRC mouse model	tissue microarrays containing COAD, READ, GSE104645, GSE21510, and GSE87211	therapeutic target	2022	[136]

Table 2 (continued)

Type	NOTCH components	Role	Cell lines	In vivo model	Clinical samples	Clinical potential	Year	Ref.
Notch target genes	HES1	oncogenic	/	a mouse model of fucosylation deficiency ($Fx^{-/-}$ mice) and mice with the full-length Fx gene (controls)	60 human CRC samples	epigenetic loss of MLH1 and right-sided CRCs	2017	[124]
Notch target genes	HES1	oncogenic	RKO, HCT8 and LOVO cell lines	nude mice model for liver metastasis	320 human CRC samples and ONCOMINE database	poor prognosis	2015	[119]
Notch target genes	HES1	oncogenic	SW620 cells	/	38 human CRC samples and TCGA-CRC dataset	poor prognosis and therapeutic target	2023	[123]
Notch target genes	HES1	oncogenic	HCT-15, HT-29, CaCo2, and SW480 cell lines	a subcutaneous CRC tumor model	GSE37892 and PETACC3 datasets, and two sets of tissue microarrays, one composed of samples from 130 CRC patients and the other containing 15 pairs of primary tumors with liver metastasis	poor prognosis and therapeutic target	2020	[120]
Notch target genes	RBP-J	oncogenic	HCT116, HCT8, HT29, LOVO, and SW480 cell lines	xenograft CRC mouse model	52 CRC tissues and normal adjacent tissues	poor prognosis (tumor size, advanced TNM stage, lymph node metastasis, and distant metastasis)	2021	[137]
Notch cleavage enzymes	PSEN1	oncogenic	/	/	TCGA-COAD dataset, HPA, and CPTAC	early stages of tumorigenesis	2022	[128]
Notch cleavage enzymes	ADAM10	/	/	/	plasma from 1,361 CRC matched case-control sets and 1,985 CRC cases and 2,220 controls	poor prognosis	2021	[129]
Notch cleavage enzymes	Immature ADAM10	/	LS180 and LoVo cell lines	/	sera and tissue samples from testing cohort containing 57 CRC patients and 39 healthy controls and serum samples from validation cohort containing 49 CRC patients and 52 healthy controls	favorable prognosis	2016	[130]
Notch cleavage enzymes	ADAM10	oncogenic	COLO205 and LIM1215 cell lines	xenograft CRC mouse model	/	therapeutic target (ADAM10 monoclonal antibody 1H5)	2023	[141]
Notch signaling	Notch signaling	/	/	/	GSE108989 and TCGA CRC datasets	poor prognosis (disease stage and metastasis) and therapeutic target	2020	[111]
Notch signaling	Notch signaling	/	/	/	103 CRC samples, Samstein-CRC cohort, TCGA-COAD, and TCGA-READ cohorts	prognosis and therapeutic target	2023	[138]
Notch signaling	Notch signaling	/	/	/	110 advanced solid tumor tissues	therapeutic target (RO4929097)	2012	[145]
Notch signaling	Notch signaling	/	/	/	20 advanced solid tumor tissues	therapeutic target (RO4929097 with cediranib)	2012	[145]
Notch signaling	Notch signaling	/	MC38 and HEK293T cell lines	/	TCGA-CRC dataset	therapeutic target	2022	[27]

Table 2 (continued)

Type	NOTCH components	Role	Cell lines	In vivo model	Clinical samples	Clinical potential	Year	Ref.
General signaling	Notch-derived lncRNAs	oncogenic	/	/	TCGA-CRC, GSE39582, GSE38832, and 115 pairs of CRC primary and normal tissues	poor prognosis (advanced clinical stages and microsatellite stability) and therapeutic target	2022	[110]

cytokines (CSF1, CXCL12, and CCL2). Inhibition of Notch2 signaling reduces macrophage infiltration and tumor burden in CRC xenograft models, reinforcing its potential as a therapeutic target [114, 115].

Notch3 is markedly overexpressed in CRC tissues compared to adjacent normal tissues, with strong correlations to poor prognosis and lymphovascular invasion. Multiarray analyses across GEO datasets associate high Notch3 expression with the CMS4 subtype, indicating its role in aggressive CRC progression [114]. In AOM-challenged Trp53ΔIEC/AktE17K mouse models, which closely resemble human CMS4 CRC, AKT-driven upregulation of Notch3 is essential for tumor cell survival and invasion, suggesting a rationale for targeting Notch3 in aggressive CRC subtypes [114]. Additionally, Notch2 and Notch3 expression correlates positively with macrophage infiltration in CRC, alongside increased expression of cytokines associated with macrophage recruitment (CSF1, CXCL12, and CCL2). Notably, inhibiting Notch3 significantly reduces macrophage proportions in human CRC tissues and suppresses tumor growth in CRC xenografts, further reinforcing the therapeutic potential of targeting Notch3 in CRC management [115].

Therapeutic implications of Notch signaling in CRC

High expression of NICD and JAG1 has been linked to reduced progression-free survival (PFS) in patients receiving anti-vascular endothelial growth factor (VEGF) therapy, indicating their potential as biomarkers of resistance to anti-VEGF-based treatments [116]. Furthermore, HES1 upregulation is associated with CRC metastasis, and public database analyses (ONCOMINE and CPTAC) suggest that HES1 overexpression predicts poorer OS [117]. A clinical analysis of 130 CRC samples shows that coexpression of AT-rich interaction domain-containing protein 3B (ARID3B) and HES1 is associated with lower 3-year survival rates in stage IV CRC, with similar patterns observed in the GSE12945 cohort [118]. In BRAF- and RAS-mutant CRCs, HES1 expression is frequently reduced, especially in KRAS-mutant tumors, where its loss is linked to extracellular matrix (ECM) remodeling and epithelial-mesenchymal transition (EMT) [119, 120]. This suggests a synergistic role between HES1 loss and KRAS mutations in promoting a tumor-supportive microenvironment [121]. Moreover, HES1 loss is particularly prevalent in right-sided CRC, where fucosylation deficiency disrupts Notch signaling, leading to altered epithelial proliferation and immune suppression [122]. Recent studies also underscore the role of colorectal cancer stem cells (CRCSCs) in evading immune surveillance [123–125]. Emerging evidence highlights the role of colorectal cancer stem cells (CRCSCs) in immune evasion through Notch activation. ARID3B-mediated HES1 activation via an NICD-independent mechanism facilitates PD-L1 upregulation in CRCSCs, suggesting a Notch-driven immune-evasive CRC subtype responsive to immune checkpoint inhibitors [118].

Potential biomarkers and future directions

In colorectal adenocarcinoma (COAD) from the Human Protein Atlas (HPA) dataset, PSEN1 overexpression is mutually exclusive with PD-L1 expression, suggesting that PSEN1-driven Notch activation may facilitate PD-L1 cleavage and nuclear translocation, thereby promoting immune evasion [126]. A multinational European cohort study also identified a single nucleotide polymorphism (SNP) within ADAM10, a Notch-processing enzyme, as a protective factor against CRC, with anti-ADAM10 antibodies correlating with prolonged relapse-free survival (RFS) in stage III CRC [127, 128].

High DLL4 expression is another potential marker of aggressive CRC, with strong correlations to BMI, metastasis, and poor prognosis [129–131]. DLL4 blockade enhances VEGF-targeted therapy responses, supporting its potential as a biomarker for anti-VEGF treatment efficacy in CRC [132–134]. Additionally, correlation analysis between RBP-J expression and clinicopathological features in patients with CRC indicates that elevated RBP-J levels are associated with larger tumor size, advanced TNM stage, lymph node metastasis, and distant metastasis, suggesting its role in aggressive disease phenotypes [135].

Targeting Notch signaling in combination with CRC immunotherapy and chemotherapy

The mutation status of the Notch pathway may serve as a valuable prognostic marker for patients with CRC undergoing immune checkpoint inhibitor (ICI) therapy. In a univariate Cox regression analysis of 109 ICI-treated patients with CRC, Notch pathway mutations (NOTCH-MT) were strongly associated with improved

clinical outcomes, with patients harboring NOTCH-MT exhibiting significantly prolonged OS. Multivariate Cox regression further identified NOTCH-MT as an independent protective factor in ICI-treated patients with CRC. Moreover, data from the TCGA-CRC cohort show that the NOTCH-MT group demonstrated enhanced immunogenicity, evidenced by increased levels of immune-activating cells and higher expression of immune checkpoint-related genes [136]. Notch4 mutations, frequently observed across various cancer types, including CRC, correlate with improved responses to ICI therapy. Multi-omics analyses reveal that Notch4 mutations are significantly linked to increased immunogenicity and activated anti-tumor immunity, characterized by elevated tumor mutation burden (TMB), increased co-stimulatory molecule expression, and enhanced infiltration of diverse immune cells [136]. Mucinous colorectal adenocarcinoma (mCA) typically shows lower responsiveness to chemotherapy and immunotherapy compared to non-mucinous CRC. The interaction between Notch3 and the transcription activator BRG1 (SMARCA4) drives the transcriptional activation of mucin-5AC (MUC5AC) and mucin-2 (MUC2) in CRC cells, with elevated levels of these mucins serving as key molecular markers distinguishing mCA from non-mucinous CRC. Targeted detection of Notch3 and its associated markers could facilitate early clinical diagnosis of mCA and support personalized interventions for improved patient outcomes [137]. Proprotein convertases (PCs) have emerged as significant regulators of PD-1 expression, representing a promising adjunct approach to enhance CRC immunotherapy. Recent research indicates that inhibiting PC activity prevents Notch cleavage and function, subsequently downregulating PD-1 expression and enhancing T-cell cytotoxicity against both MSI and MSS CRC cells. Targeting PCs in T cells thus presents a novel strategy to counteract T-cell exhaustion and immune suppression in CRC immunotherapy [138]. Additionally, a TME-responsive injectable hydrogel has been developed as a cascade gene delivery system for the targeted delivery of plasmid DNA encoding short hairpin RNAs against Notch1 (shNotch1) into CRC cells. In a subcutaneous CRC tumor model, hydrogels loaded with PAMAM-F/shNotch1 effectively suppressed Notch1 activity, resulting in significant tumor growth inhibition while preserving Notch signaling in surrounding normal tissues, highlighting the potential for Notch-targeted gene therapy in CRC treatment [30]. Furthermore, 1H5, a human anti-ADAM10 mAb designed to inhibit Notch1 cleavage, in combination with the chemotherapeutic agent irinotecan, demonstrated effective tumor growth suppression without evident toxicity in a CRC preclinical model, underscoring its promise as a targeted therapeutic strategy in CRC management [139].

Currently, GSIs and large-molecule mAbs targeting Notch ligands and receptors represent the primary agents in clinical development aimed at inhibiting the Notch pathway to curtail CRC progression [22]. These agents, largely advancing from preclinical research to early clinical trials, are being evaluated for various cancers, including CRC, breast cancer, pancreatic cancer, leukemia, and glioblastoma [22]. Dietary supplements with low toxicity profiles, such as curcumin, genistein, and resveratrol, also offer promising alternatives for Notch pathway inhibition [140].

The S3 cleavage of Notch receptors, catalyzed by γ-secretase, is critical for Notch pathway activation, positioning GSIs as a focal point in Notch-targeted therapy research. Numerous preclinical studies have shown that combining GSIs with other treatment modalities, including chemotherapy and immunotherapy, can yield synergistic anti-tumor effects in CRC. For instance, chemotherapeutic agents such as oxaliplatin, 5-fluorouracil (5-FU), and SN-38 (the active metabolite of irinotecan) are known to activate the Notch pathway in CRC cells. Blocking Notch-1 signaling with the sulfonamide-based GSI (GSI34) sensitizes CRC cells to chemotherapy, demonstrating a synergistic effect when combined with oxaliplatin, 5-FU, and SN-38 [141]. Furthermore, GSIs show potential in overcoming taxane resistance in CRC, as they enhance taxane-induced mitotic arrest and apoptosis in CRC cells, both in vitro and in vivo, despite having limited impact on cell growth and apoptosis when used as monotherapy [142].

The competitive oral GSI RO4929097 (Roche) has progressed to phase I clinical trials, showing partial antitumor activity as a monotherapy in a patient with CRC exhibiting neuroendocrine features among a cohort of 110 patients with advanced solid tumors [143]. Administered using both intermittent and continuous dosing regimens, RO4929097 was generally well tolerated, with the most frequently observed side effects being skin reactions, gastrointestinal (GI) events, and fatigue. Most treatment-related toxicities (95%) were mild to moderate (grade 1 or 2), with no grade 4 toxicities, and treatment discontinuations due to adverse events were infrequent (2%) [143]. A multicenter, dose-escalation phase I trial (NCT01158274) is underway to determine the response and maximum tolerated dose (MTD) of the combination of RO4929097 with the chemotherapeutic agent capecitabine for advanced solid tumors, including metastatic CRC. In another phase I study with 20 patients with advanced solid tumors, including 6 CRC cases, the combination of RO4929097 and cediranib (a VEGFR multi-kinase inhibitor) demonstrated preliminary antitumor activity, with stable disease achieved in 11 patients. This combination was well tolerated, with manageable side effects [144]. Another phase I trial (NCT01198535)

is evaluating dose-escalation, efficacy, and tolerability of RO4929097 in combination with cetuximab for metastatic CRC. Further, an open-label phase II trial (NCT01116687) is assessing the objective radiographic response of RO4929097 in patients with metastatic CRC who have undergone at least two prior systemic chemotherapy regimens. Additionally, a phase II study (NCT01270438) is investigating the clinical benefit of RO4929097 combined with mFOLFOX6 (modified infusional fluorouracil, leucovorin, and oxaliplatin) and the anti-VEGF monoclonal antibody bevacizumab for metastatic CRC treatment. Another GSI, MK-0752 (Merck), a non-competitive oral inhibitor, is being studied in several phase I/II trials with promising preclinical activity in T-ALL and breast cancer. However, in a phase I trial cohort involving 103 patients treated with MK-0752, only patients with glioma exhibited a modest response, while the 16 patients with CRC in the study showed no discernible antitumor activity with MK-0752 as a monotherapy [145].

The most significant toxicity associated with GSIs is gastrointestinal, notably nausea, vomiting, fatigue, and persistent diarrhea, particularly prevalent with continuous dosing schedules, which limits their clinical utility [146–148]. To alleviate these side effects, in vivo models have been used to investigate strategies for reducing toxicity and enhancing efficacy through intermittent dosing regimens and the co-administration of corticosteroids. Additionally, GSIs as monotherapy often show limited efficacy, underscoring the need for further research into combination strategies with chemotherapy or immunotherapy to improve CRC outcomes [141, 145].

Due to the treatment-related toxicities and complex dosing schedules associated with GSIs, several innovative mAbs are now undergoing clinical investigation. These mAbs have demonstrated potential in effectively inhibiting Notch signaling while minimizing severe gastrointestinal side effects [18, 22]. For example, OMP-21M18, a humanized mAb targeting DLL4, disrupts the interaction of DLL4 with Notch1 and Notch4. In an ongoing phase Ib trial (NCT01189942) with 32 patients with metastatic CRC, OMP-21M18 is being tested in combination with FOLFIRI (folinic acid, bolus/continuous fluorouracil, and irinotecan) to determine the optimal dosing regimen. Another fully humanized mAb, OMP-59R5, targets Notch2/3 receptors and has shown prolonged stable disease in patients with CRC in a phase I open-label dose-escalation trial (NCT01277146). These studies highlight the promise of mAbs as a more tolerable and effective alternative to GSIs in CRC therapy, although the limited efficacy, stability, and production costs of mAbs present challenges to their widespread clinical application [19, 149]. Notably, pharmacodynamic monitoring to assess Notch pathway activity levels is essential in optimizing dosing and achieving the desired degree of Notch inhibition in CRC. This approach ensures that the therapeutic effect on the Notch pathway is maximized while minimizing adverse effects [150, 151].

Conclusions

The Notch pathway, a highly evolutionarily conserved signaling mechanism, is essential for the proliferation, differentiation, and functional regulation of immune cells. Mounting evidence indicates that dysregulated Notch signaling contributes to various malignancies, including CRC, where its abnormal activation supports an immunosuppressive TME. Elevated expression of Notch components correlates with unfavorable clinicopathological characteristics and poor prognosis in patients with CRC. Given the pivotal role of Notch signaling in CRC progression, targeted inhibition through small molecule inhibitors (primarily GSIs) and mAbs is under evaluation across multiple clinical trials. Moreover, combining Notch inhibitors with chemotherapy, anti-VEGF therapies, or immunotherapy presents promising potential for overcoming immune evasion and metastatic progression in CRC.

However, dose-limiting gastrointestinal side effects have challenged the clinical advancement of GSIs, and monotherapy with GSIs has shown limited efficacy in CRC based on current clinical data. Despite these hurdles, Notch signaling remains a validated and actionable target with significant therapeutic promise in CRC. To optimize Notch-targeted therapies, prioritizing the identification and application of efficacy biomarkers for pharmacodynamic monitoring is essential during clinical development. Additionally, minimizing off-target toxicities associated with prolonged Notch inhibition should be a research focus, with an emphasis on developing more specific Notch inhibitors or compounds. Another critical avenue for drug development lies in addressing the extensive crosstalk between Notch and other major oncogenic pathways, such as PI3K/AKT, which may unveil further therapeutic opportunities for targeting Notch in CRC. Larger clinical trials are warranted to evaluate the efficacy of Notch-targeted therapies in combination with existing CRC treatment regimens, potentially enhancing outcomes for patients with CRC.

Abbreviations

CRC	Colorectal cancer
TME	Tumor microenvironment
MDSCs	Myeloid-derived suppressor cells
TAMs	Tumor-associated macrophages
GSIs	γ-secretase inhibitors
mAbs	Monoclonal antibodies
CMS	Consensus molecular subtypes
NRR	Negative regulatory region
EGF	Epidermal growth factor
RAM	Recombination signal-binding protein 1 for the J-kappa (RBP-J)-association molecule

ANK	Ankyrin
NLS	Nuclear localization signals
TAD	Transactivation domain
PEST	Proline/glutamine/serine/threonine-rich
DLL1	Delta-like ligand 1
JAG1	Jagged-1
ADAM	Disintegrin and metalloproteases
NEXT	Notch extracellular truncated
PSEN1	Presenilin 1
NCT	Nicastrin
PEN2	Presenilin enhancer 2
APH1	Anterior pharynx-defective 1
NICD	Notch intracellular domain

Acknowledgements
Not applicable.

Author contributions
PHL conceived and designed the manuscript. JCS wrote and revised the manuscript. YC and ZYX designed the figures. WZW revised the manuscript. All authors read and approved the final version of the manuscript.

Funding
Not available.

Data availability
Not available.

Declarations

Ethical approval and consent to participate
Not available.

Consent for publication
Not available.

Competing interests
The authors declare no conflict of interest.

Received: 29 November 2024 / Accepted: 20 February 2025
Published online: 12 March 2025

References

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024;74:229–63. https://doi.org/10.3322/caac.21834
2. Malki A, ElRuz RA, Gupta I, Allouch A, Vranic S, Al Moustafa AE. Molecular mechanisms of Colon cancer progression and metastasis: recent insights and advancements. Int J Mol Sci. 2020;22. https://doi.org/10.3390/ijms22010130
3. Dekker E, Tanis PJ, Vleugels JLA, Kasi PM, Wallace MB. Colorectal cancer. Lancet. 2019;394:1467–80. https://doi.org/10.1016/s0140-6736(19)32319-0
4. Ni JJ, Li XS, Zhang H, Xu Q, Wei XT, Feng GJ, et al. Mendelian randomization study of causal link from gut microbiota to colorectal cancer. BMC Cancer. 2022;22:1371. https://doi.org/10.1186/s12885-022-10483-w
5. Li G, Yao Q, Liu P, Zhang H, Liu Y, Li S et al. Critical roles and clinical perspectives of RNA methylation in cancer. MedComm (2020). 2024;5:e559. https://doi.org/10.1002/mco2.559
6. Eng C, Jácome AA, Agarwal R, Hayat MH, Byndloss MX, Holowatyj AN, et al. A comprehensive framework for early-onset colorectal cancer research. Lancet Oncol. 2022;23:e116–28. https://doi.org/10.1016/s1470-2045(21)00588-x
7. Dienstmann R, Vermeulen L, Guinney J, Kopetz S, Tejpar S, Tabernero J. Consensus molecular subtypes and the evolution of precision medicine in colorectal cancer. Nat Rev Cancer. 2017;17:79–92. https://doi.org/10.1038/nrc.2016.126
8. Fontana E, Eason K, Cervantes A, Salazar R, Sadanandam A. Context matters-consensus molecular subtypes of colorectal cancer as biomarkers for clinical trials. Ann Oncol. 2019;30:520–7. https://doi.org/10.1093/annonc/mdz052
9. Joanito I, Wirapati P, Zhao N, Nawaz Z, Yeo G, Lee F, et al. Single-cell and bulk transcriptome sequencing identifies two epithelial tumor cell States and refines the consensus molecular classification of colorectal cancer. Nat Genet. 2022;54:963–75. https://doi.org/10.1038/s41588-022-01100-4
10. Linnekamp JF, Wang X, Medema JP, Vermeulen L. Colorectal cancer heterogeneity and targeted therapy: a case for molecular disease subtypes. Cancer Res. 2015;75:245–9. https://doi.org/10.1158/0008-5472.Can-14-2240
11. Lenz HJ, Ou FS, Venook AP, Hochster HS, Niedzwiecki D, Goldberg RM, et al. Impact of consensus molecular subtype on survival in patients with metastatic colorectal cancer: results from CALGB/SWOG 80405 (Alliance). J Clin Oncol. 2019;37:1876–85. https://doi.org/10.1200/jco.18.02258
12. Lam M, Roszik J, Kanikarla-Marie P, Davis JS, Morris J, Kopetz S, et al. The potential role of platelets in the consensus molecular subtypes of colorectal cancer. Cancer Metastasis Rev. 2017;36:273–88. https://doi.org/10.1007/s10555-017-9678-9
13. Li J, Ma X, Chakravarti D, Shalapour S, DePinho RA. Genetic and biological hallmarks of colorectal cancer. Genes Dev. 2021;35:787–820. https://doi.org/10.1101/gad.348226.120
14. Koveitypour Z, Panahi F, Vakilian M, Peymani M, Seyed Forootan F, Nasr Esfahani MH, et al. Signaling pathways involved in colorectal cancer progression. Cell Biosci. 2019;9:97. https://doi.org/10.1186/s13578-019-0361-4
15. Yuan C, Zhao X, Wangmo D, Alshareef D, Gates TJ, Subramanian S. Tumor models to assess immune response and tumor-microbiome interactions in colorectal cancer. Pharmacol Ther. 2022;231:107981. https://doi.org/10.1016/j.pharmthera.2021.107981
16. Fan A, Wang B, Wang X, Nie Y, Fan D, Zhao X, et al. Immunotherapy in colorectal cancer: current achievements and future perspective. Int J Biol Sci. 2021;17:3837–49. https://doi.org/10.7150/ijbs.64077
17. Picard E, Verschoor CP, Ma GW, Pawelec G. Relationships between immune landscapes, genetic subtypes and responses to immunotherapy in colorectal Cancer. Front Immunol. 2020;11:369. https://doi.org/10.3389/fimmu.2020.00369
18. Vinson KE, George DC, Fender AW, Bertrand FE, Sigounas G. The Notch pathway in colorectal cancer. Int J Cancer. 2016;138:1835–42. https://doi.org/10.1002/ijc.29800
19. Tyagi A, Sharma AK, Damodaran C. A review on Notch signaling and colorectal Cancer. Cells. 2020;9. https://doi.org/10.3390/cells9061549
20. Shi Q, Xue C, Zeng Y, Yuan X, Chu Q, Jiang S, et al. Notch signaling pathway in cancer: from mechanistic insights to targeted therapies. Signal Transduct Target Ther. 2024;9:128. https://doi.org/10.1038/s41392-024-01828-x
21. Zhou B, Lin W, Long Y, Yang Y, Zhang H, Wu K, et al. Notch signaling pathway: architecture, disease, and therapeutics. Signal Transduct Target Ther. 2022;7:95. https://doi.org/10.1038/s41392-022-00934-y
22. Takebe N, Nguyen D, Yang SX. Targeting Notch signaling pathway in cancer: clinical development advances and challenges. Pharmacol Ther. 2014;141:140–9. https://doi.org/10.1016/j.pharmthera.2013.09.005
23. Hasan SS, Fischer A. Notch signaling in the vasculature: angiogenesis and angiocrine functions. Cold Spring Harb Perspect Med. 2023;13. https://doi.org/10.1101/cshperspect.a041166
24. Meurette O, Mehlen P. Notch signaling in the tumor microenvironment. Cancer Cell. 2018;34:536–48. https://doi.org/10.1016/j.ccell.2018.07.009
25. Su X, Wang X, Lai J, Mao S, Li H. Unraveling a novel hippo-associated immunological prognostic signature: the contribution of SERPINE1 in facilitating colorectal cancer progression via the Notch signaling pathway. Genomics. 2024;116:110794. https://doi.org/10.1016/j.ygeno.2024.110794
26. Qiao L, Wong BC. Role of Notch signaling in colorectal cancer. Carcinogenesis. 2009;30:1979–86. https://doi.org/10.1093/carcin/bgp236
27. Wang F, Huang C, Long J, Zhao ZB, Ma HQ, Yao XQ, et al. Notch signaling mutations increase intra-tumor chemokine expression and predict response to immunotherapy in colorectal cancer. BMC Cancer. 2022;22:933. https://doi.org/10.1186/s12885-022-10032-5
28. Ruland J. Colon cancer: epithelial Notch signaling recruits neutrophils to drive metastasis. Cancer Cell. 2019;36:213–4. https://doi.org/10.1016/j.ccell.2019.08.010
29. Brisset M, Mehlen P, Meurette O, Hollande F. Notch receptor/ligand diversity: contribution to colorectal cancer stem cell heterogeneity. Front Cell Dev Biol. 2023;11:1231416. https://doi.org/10.3389/fcell.2023.1231416
30. Lu Y, Cao Y, Guo X, Gao Y, Chen X, Zhang Z, et al. Notch-Targeted therapeutic in colorectal Cancer by Notch1 Attenuation via tumor Microenvironment-Responsive cascade DNA delivery. Adv Healthc Mater. 2024;13:e2400797. https://doi.org/10.1002/adhm.202400797

31. Wang M, Tang L, Chen S, Wang L, Wu J, Zhong C, et al. ZNF217-activated Notch signaling mediates sulforaphane-suppressed stem cell properties in colorectal cancer. J Nutr Biochem. 2024;125:109551. https://doi.org/10.1016/j.jnutbio.2023.109551
32. Irshad S, Bansal M, Guarnieri P, Davis H, Al Haj Zen A, Baran B, et al. Bone morphogenetic protein and Notch signalling crosstalk in poor-prognosis, mesenchymal-subtype colorectal cancer. J Pathol. 2017;242:178–92. https://doi.org/10.1002/path.4891
33. Zhang Z, Li G, Qiu H, Yang J, Bu X, Zhu S, et al. The novel Notch-induced long noncoding RNA LUNAR1 determines the proliferation and prognosis of colorectal Cancer. Sci Rep. 2019;9:19915. https://doi.org/10.1038/s41598-019-56536-2
34. Seyfinejad B, Jouyban A. Importance of method validation in the analysis of biomarker. Curr Pharm Anal. 2022;18:567–9. https://doi.org/10.2174/1573412918666211213142638
35. Goruganthu MUL, Shanker A, MM Dikov, DP Carbone. Specific targeting of Notch Ligand-Receptor interactions to modulate immune responses: A review of clinical and preclinical findings. Front Immunol. 2020;11:1958. https://doi.org/10.3389/fimmu.2020.01958
36. Kopan R, Ilagan MX. The canonical Notch signaling pathway: unfolding the activation mechanism. Cell. 2009;137:216–33. https://doi.org/10.1016/j.cell.2009.03.045
37. Wang H, Zang C, Liu XS, Aster JC. The role of Notch receptors in transcriptional regulation. J Cell Physiol. 2015;230:982–8. https://doi.org/10.1002/jcp.24872
38. Luxán G, D'Amato G, MacGrogan D, de la Pompa JL. Endocardial Notch signaling in cardiac development and disease. Circ Res. 2016;118:e1–18. https://doi.org/10.1161/circresaha.115.305350
39. Bi P, Kuang S. Notch signaling as a novel regulator of metabolism. Trends Endocrinol Metab. 2015;26:248–55. https://doi.org/10.1016/j.tem.2015.02.006
40. Kovall RA, Gebelein B, Sprinzak D, Kopan R. The canonical Notch signaling pathway: structural and biochemical insights into shape, sugar, and force. Dev Cell. 2017;41:228–41. https://doi.org/10.1016/j.devcel.2017.04.001
41. Vázquez-Ulloa E, Lin KL, Lizano M, Sahlgren C. Reversible and bidirectional signaling of Notch ligands. Crit Rev Biochem Mol Biol. 2022;57:377–98. https://doi.org/10.1080/10409238.2022.2113029
42. Lefort K, Dotto GP. Notch signaling in the integrated control of keratinocyte growth/differentiation and tumor suppression. Semin Cancer Biol. 2004;14:374–86. https://doi.org/10.1016/j.semcancer.2004.04.017
43. Luna-Escalante JC, Formosa-Jordan P, Ibañes M. Redundancy and Cooperation in Notch intercellular signaling. Development. 2018;145. https://doi.org/10.1242/dev.154807
44. Nowell CS, Radtke F. Notch as a tumour suppressor. Nat Rev Cancer. 2017;17:145–59. https://doi.org/10.1038/nrc.2016.145
45. Bray SJ, Gomez-Lamarca M. Notch after cleavage. Curr Opin Cell Biol. 2018;51:103–9. https://doi.org/10.1016/j.ceb.2017.12.008
46. Suarez Rodriguez F, Sanlidag S, Sahlgren C. Mechanical regulation of the Notch signaling pathway. Curr Opin Cell Biol. 2023;85:102244. https://doi.org/10.1016/j.ceb.2023.102244
47. Zanotti S, Canalis E. Notch signaling and the skeleton. Endocr Rev. 2016;37:223–53. https://doi.org/10.1210/er.2016-1002
48. Friedrich T, Ferrante F, Pioger L, Nist A, Stiewe T, Andrau JC, et al. Notch-dependent and -independent functions of transcription factor RBPJ. Nucleic Acids Res. 2022;50:7925–37. https://doi.org/10.1093/nar/gkac601
49. Kageyama R, Ohtsuka T. The Notch-Hes pathway in mammalian neural development. Cell Res. 1999;9:179–88. https://doi.org/10.1038/sj.cr.7290016
50. Iso T, Kedes L, Hamamori Y. HES and HERP families: multiple effectors of the Notch signaling pathway. J Cell Physiol. 2003;194:237–55. https://doi.org/10.1002/jcp.10208
51. Medina E, Perez DH, Antfolk D, Luca VC. New tricks for an old pathway: emerging Notch-based biotechnologies and therapeutics. Trends Pharmacol Sci. 2023;44:934–48. https://doi.org/10.1016/j.tips.2023.09.011
52. Redmond L, Ghosh A. The role of Notch and Rho GTPase signaling in the control of dendritic development. Curr Opin Neurobiol. 2001;11:111–7. https://doi.org/10.1016/s0959-4388(00)00181-1
53. Grotek B, Wehner D, Weidinger G. Notch signaling coordinates cellular proliferation with differentiation during zebrafish fin regeneration. Development. 2013;140:1412–23. https://doi.org/10.1242/dev.087452
54. Fortini ME, Bilder D. Endocytic regulation of Notch signaling. Curr Opin Genet Dev. 2009;19:323–8. https://doi.org/10.1016/j.gde.2009.04.005
55. Yan M, Plowman GD. Delta-like 4/notch signaling and its therapeutic implications. Clin Cancer Res. 2007;13:7243–6. https://doi.org/10.1158/1078-0432.Ccr-07-1393
56. Thomas MM, Zhang Y, Mathew E, Kane KT, Maillard I. Pasca Di Magliano M. Epithelial Notch signaling is a limiting step for pancreatic carcinogenesis. BMC Cancer. 2014;14:862. https://doi.org/10.1186/1471-2407-14-862
57. Yuan JS, Kousis PC, Suliman S, Visan I, Guidos CJ. Functions of Notch signaling in the immune system: consensus and controversies. Annu Rev Immunol. 2010;28:343–65. https://doi.org/10.1146/annurev.immunol.021908.132719
58. Radtke F, Fasnacht N, Macdonald HR. Notch signaling in the immune system. Immunity. 2010;32:14–27. https://doi.org/10.1016/j.immuni.2010.01.004
59. Maillard I, Adler SH, Pear WS. Notch and the immune system. Immunity. 2003;19:781–91. https://doi.org/10.1016/s1074-7613(03)00325-x
60. Robey EA, Bluestone JA. Notch signaling in lymphocyte development and function. Curr Opin Immunol. 2004;16:360–6. https://doi.org/10.1016/j.coi.2004.03.009
61. Osborne BA, Minter LM. Notch signalling during peripheral T-cell activation and differentiation. Nat Rev Immunol. 2007;7:64–75. https://doi.org/10.1038/nri1998
62. Sandy AR, Maillard I. Notch signaling in the hematopoietic system. Expert Opin Biol Ther. 2009;9:1383–98. https://doi.org/10.1517/14712590903260777
63. Benne C, Lelievre JD, Balbo M, Henry A, Sakano S, Levy Y. Notch increases T/NK potential of human hematopoietic progenitors and inhibits B cell differentiation at a pro-B stage. Stem Cells. 2009;27:1676–85. https://doi.org/10.1002/stem.94
64. Tanigaki K, Honjo T. Regulation of lymphocyte development by Notch signaling. Nat Immunol. 2007;8:451–6. https://doi.org/10.1038/ni1453
65. Radtke F, Wilson A, Mancini SJ, MacDonald HR. Notch regulation of lymphocyte development and function. Nat Immunol. 2004;5:247–53. https://doi.org/10.1038/ni1045
66. Yu VW, Saez B, Cook C, Lotinun S, Pardo-Saganta A, Wang YH, et al. Specific bone cells produce DLL4 to generate thymus-seeding progenitors from bone marrow. J Exp Med. 2015;212:759–74. https://doi.org/10.1084/jem.20141843
67. Jenkinson EJ, Jenkinson WE, Rossi SW, Anderson G. The thymus and T-cell commitment: the right niche for Notch? Nat Rev Immunol. 2006;6:551–5. https://doi.org/10.1038/nri1883
68. Guidos CJ. Synergy between the pre-T cell receptor and Notch: cementing the alphabeta lineage choice. J Exp Med. 2006;203:2233–7. https://doi.org/10.1084/jem.20060998
69. Ikawa T, Kawamoto H, Goldrath AW, Murre C. E proteins and Notch signaling cooperate to promote T cell lineage specification and commitment. J Exp Med. 2006;203:1329–42. https://doi.org/10.1084/jem.20060268
70. Ciofani M, Knowles GC, Wiest DL, von Boehmer H, Zúñiga-Pflücker JC. Stage-specific and differential Notch dependency at the alphabeta and gammadelta T lineage bifurcation. Immunity. 2006;25:105–16. https://doi.org/10.1016/j.immuni.2006.05.010
71. Schmitt TM, Ciofani M, Petrie HT, Zúñiga-Pflücker JC. Maintenance of T cell specification and differentiation requires recurrent Notch receptor-ligand interactions. J Exp Med. 2004;200:469–79. https://doi.org/10.1084/jem.20040394
72. Garbe AI, von Boehmer H. TCR and Notch synergize in alphabeta versus gammadelta lineage choice. Trends Immunol. 2007;28:124–31. https://doi.org/10.1016/j.it.2007.01.004
73. Ciofani M, Zúñiga-Pflücker JC. Notch promotes survival of pre-T cells at the beta-selection checkpoint by regulating cellular metabolism. Nat Immunol. 2005;6:881–8. https://doi.org/10.1038/ni1234
74. Chen ELY, Thompson PK, Zúñiga-Pflücker JC. RBPJ-dependent Notch signaling initiates the T cell program in a subset of thymus-seeding progenitors. Nat Immunol. 2019;20:1456–68. https://doi.org/10.1038/s41590-019-0518-7
75. Gaudette BT, Roman CJ, Ochoa TA, Gómez Atria D, Jones DD, Siebel CW, et al. Resting innate-like B cells leverage sustained Notch2/mTORC1 signaling to achieve rapid and mitosis-independent plasma cell differentiation. J Clin Invest. 2021;131. https://doi.org/10.1172/jci151975
76. Mesini N, Fiorcari S, Atene CG, Maffei R, Potenza L, Luppi M, et al. Role of Notch2 pathway in mature B cell malignancies. Front Oncol. 2022;12:1073672. https://doi.org/10.3389/fonc.2022.1073672
77. Babushku T, Lechner M, Ehrenberg S, Rambold U, Schmidt-Supprian M, Yates AJ et al. Notch2 controls developmental fate choices between germinal center and marginal zone B cells upon immunization. Nat Commun. 2024;15:1960. https://doi.org/10.1038/s41467-024-46024-1

78. Hampel F, Ehrenberg S, Hojer C, Draeseke A, Marschall-Schröter G, Kühn R, et al. CD19-independent instruction of murine marginal zone B-cell development by constitutive Notch2 signaling. Blood. 2011;118:6321–31. https://doi.org/10.1182/blood-2010-12-325944
79. Descatoire M, Weller S, Irtan S, Sarnacki S, Feuillard J, Storck S, et al. Identification of a human Splenic marginal zone B cell precursor with NOTCH2-dependent differentiation properties. J Exp Med. 2014;211:987–1000. https://doi.org/10.1084/jem.20132203
80. Pillai S, Cariappa A. The follicular versus marginal zone B lymphocyte cell fate decision. Nat Rev Immunol. 2009;9:767–77. https://doi.org/10.1038/nri2656
81. Lechner M, Engleitner T, Babushku T, Schmidt-Supprian M, Rad R, Strobl LJ, et al. Notch2-mediated plasticity between marginal zone and follicular B cells. Nat Commun. 2021;12:1111. https://doi.org/10.1038/s41467-021-21359-1
82. Wang H, Morse HC 3rd, Bolland S. Transcriptional control of mature B cell fates. Trends Immunol. 2020;41:601–13. https://doi.org/10.1016/j.it.2020.04.011
83. Magri G, Miyajima M, Bascones S, Mortha A, Puga I, Cassis L, et al. Innate lymphoid cells integrate stromal and immunological signals to enhance antibody production by Splenic marginal zone B cells. Nat Immunol. 2014;15:354–64. https://doi.org/10.1038/ni.2830
84. Huang F, Zhao JL, Wang L, Gao CC, Liang SQ, An DJ, et al. miR-148a-3p mediates Notch signaling to promote the differentiation and M1 activation of macrophages. Front Immunol. 2017;8:1327. https://doi.org/10.3389/fimmu.2017.01327
85. Schroeder T, Just U. Notch signalling via RBP-J promotes myeloid differentiation. Embo J. 2000;19:2558–68. https://doi.org/10.1093/emboj/19.11.2558
86. Lin Y, Zhao JL, Zheng QJ, Jiang X, Tian J, Liang SQ, et al. Notch signaling modulates macrophage polarization and phagocytosis through direct suppression of signal regulatory protein α expression. Front Immunol. 2018;9:1744. https://doi.org/10.3389/fimmu.2018.01744
87. Wang YC, He F, Feng F, Liu XW, Dong GY, Qin HY, et al. Notch signaling determines the M1 versus M2 polarization of macrophages in antitumor immune responses. Cancer Res. 2010;70:4840–9. https://doi.org/10.1158/0008-5472.Can-10-0269
88. Zhou D, Huang C, Lin Z, Zhan S, Kong L, Fang C, et al. Macrophage polarization and function with emphasis on the evolving roles of coordinated regulation of cellular signaling pathways. Cell Signal. 2014;26:192–7. https://doi.org/10.1016/j.cellsig.2013.11.004
89. Keewan E, Naser SA. Notch-1 signaling modulates macrophage polarization and immune defense against Mycobacterium avium paratuberculosis infection in inflammatory diseases. Microorganisms. 2020;8. https://doi.org/10.3390/microorganisms8071006
90. Huang YH, Cai K, Xu PP, Wang L, Huang CX, Fang Y, et al. CREBBP/EP300 mutations promoted tumor progression in diffuse large B-cell lymphoma through altering tumor-associated macrophage polarization via FBXW7-NOTCH-CCL2/CSF1 axis. Signal Transduct Target Ther. 2021;6:10. https://doi.org/10.1038/s41392-020-00437-8
91. Ohishi K, Varnum-Finney B, Flowers D, Anasetti C, Myerson D, Bernstein ID. Monocytes express high amounts of Notch and undergo cytokine specific apoptosis following interaction with the Notch ligand, Delta-1. Blood. 2000;95:2847–54.
92. Ohishi K, Varnum-Finney B, Serda RE, Anasetti C, Bernstein ID. The Notch ligand, Delta-1, inhibits the differentiation of monocytes into macrophages but permits their differentiation into dendritic cells. Blood. 2001;98:1402–7. https://doi.org/10.1182/blood.v98.5.1402
93. López-López S, Romero de Ávila MJ, de Hernández NC, Ruiz-Marcos F, Baladrón V, Nueda ML, et al. NOTCH4 exhibits Anti-Inflammatory activity in activated macrophages by interfering with Interferon-γ and TLR4 signaling. Front Immunol. 2021;12:734966. https://doi.org/10.3389/fimmu.2021.734966
94. Cheng P, Nefedova Y, Corzo CA, Gabrilovich DI. Regulation of dendritic-cell differentiation by bone marrow stroma via different Notch ligands. Blood. 2007;109:507–15. https://doi.org/10.1182/blood-2006-05-025601
95. Olivier A, Lauret E, Gonin P, Galy A. The Notch ligand delta-1 is a hematopoietic development cofactor for plasmacytoid dendritic cells. Blood. 2006;107:2694–701. https://doi.org/10.1182/blood-2005-03-0970
96. Zhou J, Cheng P, Youn JI, Cotter MJ, Gabrilovich DI. Notch and wingless signaling cooperate in regulation of dendritic cell differentiation. Immunity. 2009;30:845–59. https://doi.org/10.1016/j.immuni.2009.03.021
97. Lewis KL, Caton ML, Bogunovic M, Greter M, Grajkowska LT, Ng D, et al. Notch2 receptor signaling controls functional differentiation of dendritic cells in the spleen and intestine. Immunity. 2011;35:780–91. https://doi.org/10.1016/j.immuni.2011.08.013
98. Satpathy AT, Briseño CG, Lee JS, Ng D, Manieri NA, Kc W, et al. Notch2-dependent classical dendritic cells orchestrate intestinal immunity to attaching-and-effacing bacterial pathogens. Nat Immunol. 2013;14:937–48. https://doi.org/10.1038/ni.2679
99. Aychek T, Mildner A, Yona S, Kim KW, Lampl N, Reich-Zeliger S, et al. IL-23-mediated mononuclear phagocyte crosstalk protects mice from Citrobacter rodentium-induced colon immunopathology. Nat Commun. 2015;6:6525. https://doi.org/10.1038/ncomms7525
100. Caton ML, Smith-Raska MR, Reizis B. Notch-RBP-J signaling controls the homeostasis of CD8- dendritic cells in the spleen. J Exp Med. 2007;204:1653–64. https://doi.org/10.1084/jem.20062648
101. Liu LY, Wang H, Xenakis JJ, Spencer LA. Notch signaling mediates granulocyte-macrophage colony-stimulating factor priming-induced transendothelial migration of human eosinophils. Allergy. 2015;70:805–12. https://doi.org/10.1111/all.12624
102. Radke AL, Reynolds LE, Melo RC, Dvorak AM, Weller PF, Spencer LA. Mature human eosinophils express functional Notch ligands mediating eosinophil autocrine regulation. Blood. 2009;113:3092–101. https://doi.org/10.1182/blood-2008-05-155937
103. Webb LM, Oyesola OO, Früh SP, Kamynina E, Still KM, Patel RK, et al. The Notch signaling pathway promotes basophil responses during helminth-induced type 2 inflammation. J Exp Med. 2019;216:1268–79. https://doi.org/10.1084/jem.20180131
104. Zhao JL, Ye YC, Gao CC, Wang L, Ren KX, Jiang R, et al. Notch-mediated lactate metabolism regulates MDSC development through the Hes1/MCT2/c-Jun axis. Cell Rep. 2022;38:110451. https://doi.org/10.1016/j.celrep.2022.110451
105. Wang SH, Lu QY, Guo YH, Song YY, Liu PJ, Wang YC. The blockage of Notch signalling promoted the generation of polymorphonuclear myeloid-derived suppressor cells with lower immunosuppression. Eur J Cancer. 2016;68:90–105. https://doi.org/10.1016/j.ejca.2016.08.019
106. Jackstadt R, van Hooff SR, Leach JD, Cortes-Lavaud X, Lohuis JO, Ridgway RA, et al. Epithelial NOTCH signaling rewires the tumor microenvironment of colorectal Cancer to drive Poor-Prognosis subtypes and metastasis. Cancer Cell. 2019;36:319–36.e7.
107. Gowrikumar S, Ahmad R, Uppada SB, Washington MK, Shi C, Singh AB, et al. Upregulated claudin-1 expression promotes colitis-associated cancer by promoting β-catenin phosphorylation and activation in Notch/p-AKT-dependent manner. Oncogene. 2019;38:5321–37. https://doi.org/10.1038/s41388-019-0795-5
108. Dang Q, Liu Z, Liu Y, Wang W, Yuan W, Sun Z, et al. LncRNA profiles from Notch signaling: implications for clinical management and tumor microenvironment of colorectal cancer. Front Immunol. 2022;13:953405. https://doi.org/10.3389/fimmu.2022.953405
109. Wang F, Long J, Li L, Zhao ZB, Wei F, Yao Y, et al. Mutations in the Notch signalling pathway are associated with enhanced anti-tumour immunity in colorectal cancer. J Cell Mol Med. 2020;24:12176–87. https://doi.org/10.1111/jcmm.15867
110. Zheng CG, Chen R, Xie JB, Liu CB, Jin Z, Jin C. Immunohistochemical expression of Notch1, Jagged1, NF-κB and MMP-9 in colorectal cancer patients and the relationship to clinicopathological parameters. Cancer Biomark. 2015;15:889–97. https://doi.org/10.3233/cbm-150533
111. Wood CS, Pennel KAF, Leslie H, Legrini A, Cameron AJ, Melissourgou-Syka L, et al. Spatially resolved transcriptomics deconvolutes prognostic histological subgroups in patients with colorectal Cancer and synchronous liver metastases. Cancer Res. 2023;83:1329–44. https://doi.org/10.1158/0008-5472.Can-22-2794
112. Wang F, Long J, Li L, Wu ZX, Da TT, Wang XQ, et al. Single-cell and Spatial transcriptome analysis reveals the cellular heterogeneity of liver metastatic colorectal cancer. Sci Adv. 2023;9:eadf5464. https://doi.org/10.1126/sciadv.adf5464
113. Wang L, Yu S, Chan ER, Chen KY, Liu C, Che D, et al. Notch-Regulated dendritic cells restrain Inflammation-Associated colorectal carcinogenesis. Cancer Immunol Res. 2021;9:348–61. https://doi.org/10.1158/2326-6066.Cir-20-0428
114. Varga J, Nicolas A, Petrocelli V, Pesic M, Mahmoud A, Michels BE, et al. AKT-dependent NOTCH3 activation drives tumor progression in a model of mesenchymal colorectal cancer. J Exp Med. 2020;217. https://doi.org/10.1084/jem.20191515
115. Huang K, Luo W, Fang J, Yu C, Liu G, Yuan X, et al. Notch3 signaling promotes colorectal tumor growth by enhancing immunosuppressive cells infiltration in the microenvironment. BMC Cancer. 2023;23:55. https://doi.org/10.1186/s12885-023-10526-w

116. Negri F, Bottarelli L, Pedrazzi G, Maddalo M, Leo L, Milanese G, et al. Notch-Jagged1 signaling and response to bevacizumab therapy in advanced colorectal cancer: A glance to radiomics or back to physiopathology? Front Oncol. 2023;13:1132564. https://doi.org/10.3389/fonc.2023.1132564
117. Yuan R, Ke J, Sun L, He Z, Zou Y, He X, et al. HES1 promotes metastasis and predicts poor survival in patients with colorectal cancer. Clin Exp Metastasis. 2015;32:169–79. https://doi.org/10.1007/s10585-015-9700-y
118. Liao TT, Lin CC, Jiang JK, Yang SH, Teng HW, Yang MH. Harnessing stemness and PD-L1 expression by AT-rich interaction domain-containing protein 3B in colorectal cancer. Theranostics. 2020;10:6095–112. https://doi.org/10.7150/thno.44147
119. Sanchez JA, Krumroy L, Plummer S, Aung P, Merkulova A, Skacel M, et al. Genetic and epigenetic classifications define clinical phenotypes and determine patient outcomes in colorectal cancer. Br J Surg. 2009;96:1196–204. https://doi.org/10.1002/bjs.6683
120. Ahadi M, Andrici J, Sioson L, Sheen A, Clarkson A, Gill AJ. Loss of Hes1 expression is associated with poor prognosis in colorectal adenocarcinoma. Hum Pathol. 2016;57:91–7. https://doi.org/10.1016/j.humpath.2016.07.010
121. Wang L, Gu W, Zou B, Kalady M, Xin W, Zhou L. Loss of HES1 expression is associated with extracellular matrix remodeling and tumor immune suppression in KRAS mutant colon adenocarcinomas. Sci Rep. 2023;13:15999. https://doi.org/10.1038/s41598-023-42234-7
122. Wang Y, Huang D, Chen KY, Cui M, Wang W, Huang X, et al. Fucosylation deficiency in mice leads to colitis and adenocarcinoma. Gastroenterology. 2017;152:193–e20510. https://doi.org/10.1053/j.gastro.2016.09.004
123. O'Brien CA, Pollett A, Gallinger S, Dick JE. A human colon cancer cell capable of initiating tumour growth in immunodeficient mice. Nature. 2007;445:106–10. https://doi.org/10.1038/nature05372
124. Beck B, Blanpain C. Unravelling cancer stem cell potential. Nat Rev Cancer. 2013;13:727–38. https://doi.org/10.1038/nrc3597
125. Todaro M, Alea MP, Di Stefano AB, Cammareri P, Vermeulen L, Iovino F, et al. Colon cancer stem cells dictate tumor growth and resist cell death by production of interleukin-4. Cell Stem Cell. 2007;1:389–402. https://doi.org/10.1016/j.stem.2007.08.001
126. Wei W, Zhang Y. PSEN1 is associated with colon cancer development via potential influences on PD-L1 nuclear translocation and tumor-immune interactions. Front Immunol. 2022;13:927474. https://doi.org/10.3389/fimmu.2022.927474
127. Aglago EK, Rinaldi S, Freisling H, Jiao L, Hughes DJ, Fedirko V, et al. Soluble receptor for advanced glycation End-products (sRAGE) and colorectal Cancer risk: A Case-Control study nested within a European prospective cohort. Cancer Epidemiol Biomarkers Prev. 2021;30:182–92. https://doi.org/10.1158/1055-9965.Epi-20-0855
128. Álvarez-Fernández SM, Barbariga M, Cannizzaro L, Cannistraci CV, Hurley L, Zanardi A, et al. Serological immune response against ADAM10 pro-domain is associated with favourable prognosis in stage III colorectal cancer patients. Oncotarget. 2016;7:80059–76. https://doi.org/10.18632/oncotarget.11181
129. Zhang Z, Li X, Yan X, Qiu H, Li G, Guo X, et al. Delta-like ligand 4 level in colorectal cancer is associated with tumor aggressiveness and clinical outcome. Cancer Biomark. 2022;33:415–22. https://doi.org/10.3233/cbm-200986
130. Zhou B, Wang H, Liu R, Wang M, Deng H, Giglio BC, et al. PET imaging of Dll4 expression in glioblastoma and colorectal Cancer xenografts using (64)Cu-Labeled monoclonal antibody 61B. Mol Pharm. 2015;12:3527–34. https://doi.org/10.1021/acs.molpharmaceut.5b00105
131. Kim G, Jung J, Kim JW, Kim JY. Low HES-1 and positive DLL4 expression predicts poor prognosis of colorectal cancers. Pathology. 2023;55:52–7. https://doi.org/10.1016/j.pathol.2022.07.008
132. Badenes M, Trindade A, Pissarra H, Lopes-da-Costa L, Duarte A. Delta-like 4/notch signaling promotes apc (Min/+) tumor initiation through angiogenic and non-angiogenic related mechanisms. BMC Cancer. 2017;17:50. https://doi.org/10.1186/s12885-016-3036-0
133. Jubb AM, Turley H, Moeller HC, Steers G, Han C, Li JL, et al. Expression of delta-like ligand 4 (Dll4) and markers of hypoxia in colon cancer. Br J Cancer. 2009;101:1749–57. https://doi.org/10.1038/sj.bjc.6605368
134. Zhang X, Hong R, Bei L, Yang J, Zhao X, Hu Z, et al. Selenium binding protein 1 inhibits tumor angiogenesis in colorectal cancers by blocking the Delta-like ligand 4/Notch1 signaling pathway. Transl Oncol. 2022;18:101365. https://doi.org/10.1016/j.tranon.2022.101365
135. Li F, Zhou YD, Liu J, Cai JD, Liao ZM, Chen GQ. RBP-J promotes cell growth and metastasis through regulating miR-182-5p-mediated Tiam1/Rac1/p38 MAPK axis in colorectal cancer. Cell Signal. 2021;87:110103. https://doi.org/10.1016/j.cellsig.2021.110103
136. Lin A, Yao J, Cheng Q, Liu Z, Luo P, Zhang J. Mutations status of NOTCH signaling pathway predict prognosis of immune checkpoint inhibitors in colorectal Cancer. J Inflamm Res. 2023;16:1693–709. https://doi.org/10.2147/jir.S394894
137. Yan X, Cheng Y, Zhang X, Hu Y, Huang H, Ren J, et al. NICD3 regulates the expression of MUC5AC and MUC2 by recruiting SMARCA4 and is involved in the differentiation of mucinous colorectal adenocarcinoma. Mol Oncol. 2022;16:3509–32. https://doi.org/10.1002/1878-0261.13296
138. Tomé M, Pappalardo A, Soulet F, López JJ, Olaizola J, Leger Y, et al. Inactivation of proprotein convertases in T cells inhibits PD-1 expression and creates a favorable immune microenvironment in colorectal Cancer. Cancer Res. 2019;79:5008–21. https://doi.org/10.1158/0008-5472.Can-19-0086
139. Saha N, Baek DS, Mendoza RP, Robev D, Xu Y, Goldgur Y, et al. Fully human monoclonal antibody targeting activated ADAM10 on colorectal cancer cells. Biomed Pharmacother. 2023;161:114494. https://doi.org/10.1016/j.biopha.2023.114494
140. Espinoza I, Miele L. Notch inhibitors for cancer treatment. Pharmacol Ther. 2013;139:95–110. https://doi.org/10.1016/j.pharmthera.2013.02.003
141. Meng RD, Shelton CC, Li YM, Qin LX, Notterman D, Paty PB, et al. gamma-Secretase inhibitors abrogate oxaliplatin-induced activation of the Notch-1 signaling pathway in colon cancer cells resulting in enhanced chemosensitivity. Cancer Res. 2009;69:573–82. https://doi.org/10.1158/0008-5472.Can-08-2088
142. Akiyoshi T, Nakamura M, Yanai K, Nagai S, Wada J, Koga K, et al. Gamma-secretase inhibitors enhance taxane-induced mitotic arrest and apoptosis in colon cancer cells. Gastroenterology. 2008;134:131–44. https://doi.org/10.1053/j.gastro.2007.10.008
143. Tolcher AW, Messersmith WA, Mikulski SM, Papadopoulos KP, Kwak EL, Gibbon DG, et al. Phase I study of RO4929097, a gamma secretase inhibitor of Notch signaling, in patients with refractory metastatic or locally advanced solid tumors. J Clin Oncol. 2012;30:2348–53. https://doi.org/10.1200/jco.2011.36.8282
144. Sahebjam S, Bedard PL, Castonguay V, Chen Z, Reedijk M, Liu G, et al. A phase I study of the combination of ro4929097 and cediranib in patients with advanced solid tumours (PJC-004/NCI 8503). Br J Cancer. 2013;109:943–9. https://doi.org/10.1038/bjc.2013.380
145. Krop I, Demuth T, Guthrie T, Wen PY, Mason WP, Chinnaiyan P, et al. Phase I Pharmacologic and pharmacodynamic study of the gamma secretase (Notch) inhibitor MK-0752 in adult patients with advanced solid tumors. J Clin Oncol. 2012;30:2307–13. https://doi.org/10.1200/jco.2011.39.1540
146. Wei P, Walls M, Qiu M, Ding R, Denlinger RH, Wong A, et al. Evaluation of selective gamma-secretase inhibitor PF-03084014 for its antitumor efficacy and Gastrointestinal safety to guide optimal clinical trial design. Mol Cancer Ther. 2010;9:1618–28. https://doi.org/10.1158/1535-7163.Mct-10-0034
147. Jia H, Wang Z, Zhang J, Feng F. γ-Secretase inhibitors for breast cancer and hepatocellular carcinoma: from mechanism to treatment. Life Sci. 2021;268:119007. https://doi.org/10.1016/j.lfs.2020.119007
148. Schott AF, Landis MD, Dontu G, Griffith KA, Layman RM, Krop I, et al. Preclinical and clinical studies of gamma secretase inhibitors with docetaxel on human breast tumors. Clin Cancer Res. 2013;19:1512–24. https://doi.org/10.1158/1078-0432.Ccr-11-3326
149. Gocha T, Rao BM, DasGupta R. Identification and characterization of a novel Sso7d scaffold-based binder against Notch1. Sci Rep. 2017;7:12021. https://doi.org/10.1038/s41598-017-12246-1
150. Kummar S, Chen HX, Wright J, Holbeck S, Millin MD, Tomaszewski J, et al. Utilizing targeted cancer therapeutic agents in combination: novel approaches and urgent requirements. Nat Rev Drug Discov. 2010;9:843–56. https://doi.org/10.1038/nrd3216
151. Lee DP, Skolnik JM, Adamson PC. Pediatric phase I trials in oncology: an analysis of study conduct efficiency. J Clin Oncol. 2005;23:8431–41. https://doi.org/10.1200/jco.2005.02.1568

Publisher's note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.