Review

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# DUSP4 in Colorectal Cancer: A Mini Review of Expressions, Functions, Mechanisms

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**Mitogen-activated protein kinases (MAPKs) participate in signaling pathways triggered by diverse stimuli, including stress, growth factors, and autoantibodies. Activated MAPKs play essential roles in multiple cellular processes, such as cell proliferation, apoptosis, differentiation, and immune and stress responses. Dual-specificity phosphatases (DUSPs) belong to the family of protein tyrosine phosphatases and use MAPKs as the main substrates. DUSPs exhibit physiological and pathological activities by affecting cell growth, metastasis, and death. Increasing evidence has revealed that DUSPs play essential roles in tumor initiation, progression, and therapeutic resistance. As a vital member of DUSPs, DUSP4 has potent regulatory functions in tumors by mediating proliferation, growth, metastasis, autophagy, apoptosis, and therapeutic sensitivity. Recently, studies have suggested that DUSP4 is significantly altered in colorectal cancer (CRC) and is involved in its development. In this study, we will review the expression characteristics of DUSP4 in patients with CRC and will also summarize the associated cellular functions and molecular mechanisms. We hope this study provides a reference for developing novel therapeutic strategies against CRC.**

**Keywords:** DUSP4; colorectal cancer; progression; mechanism

## Introduction

Dual-specificity phosphatases (DUSPs) are a subfamily of protein tyrosine phosphatases (PTPs) that can dephosphorylate tyrosine and threonine residues on substrate kinases. Their primary substrates are mainly mitogen-activated protein kinases (MAPKs) [1]. DUSPs catalyze the dephosphorylation of MAPK activity and play important roles in regulating key biological processes such as immune stress, cell proliferation, and differentiation [2–4]. The phosphatase domain, which is composed of Asp, Cys, and Arg residues, is the conserved catalytic site of DUSPs. DUSPs contain MAP kinase binding motifs or kinase interaction motifs (KIMs). These motifs achieve enzyme–substrate interactions by docking with domains in MAPK. Based on the presence or absence of KIMs, DUSPs are classified into two categories: KIM-containing DUSPs are termed typical DUSPs (including DUSP1, 2, 4, 5, etc.), and KIM-deficient DUSPs are classified as atypical DUSPs (including DUSP3, 11, 12, etc.) [5]. Typical DUSPs exhibit distinct cellular localization characteristics. For example, DUSP1, DUSP2, DUSP4, and DUSP5 are localized primarily to the nucleus; DUSP6, DUSP7, and DUSP9 are cytoplasmic and exhibit ERK selectivity; and DUSP8, DUSP10, and DUSP16 are localized in both the cytoplasm and the nucleus, where they inactivate the JNK and p38 MAPK signaling pathways [6].

Numerous studies have demonstrated altered expression of DUSPs in tumors. DUSPs affect critical biological processes in tumor cells, including cell differentiation, proliferation, growth, metastasis, autophagy, and apoptosis. Hence, DUSPs play crucial roles in cancer initiation and progression. Additionally, DUSPs modulate therapeutic sensitivity. For example, DUSP1/MKP1 expression is lower in tumor tissues from glioma patients than in normal brain tissue. Lower expression of DUSP1 was associated with poorer prognosis in glioma patients. Functionally, overexpression of DUSP1 inhibited the growth of glioma U87 and U373 cells and attenuated the stemness of glioma stem cells. DUSP1 overexpression also increased the sensitivity of glioma stem cells to temozolomide [7]. Compared with that in normal tissues adjacent to cancer lesions, the level of DUSP2 was significantly lower in bladder cancer tissues. A lower DUSP2 level was also detected in bladder cancer cells than in ureteral epithelial cells. DUSP2 overexpression suppressed tumor cell proliferation and metastasis. DUSP2 had prominent effects on the tumor immune microenvironment [8]. In osteosarcoma (OS), DUSP3 expression is reduced, and lower DUSP3 expression is a possible predictor of poor prognosis in OS patients. Functionally, overexpression of DUSP3 significantly inhibited the migration, invasion, and stemness of OS cells. *In vivo* experiments revealed that overexpression of DUSP3 inhibited the growth of 143B OS cells [9]. Knockdown of DUSP5 can in-

hibit the proliferation and growth of gefitinib-resistant lung cancer cells [10]. In primary and recurrent glioblastoma (GBM) patient samples as well as GBM cells generated from *in vitro* radiation survival models, DUSP6 was significantly expressed in the nucleus. BCI, an allosteric chemical inhibitor of DUSP6, markedly repressed the proliferation and clonogenic survival rates of both parental and recurrent GBM cells. Inhibition of DUSP6 significantly enhances the radiosensitivity of GBM cells [11].

Globally, colorectal cancer (CRC) is the third most commonly diagnosed malignant tumor, and cancer-related mortality also ranks among the highest [12]. The World Health Organization (WHO) estimates that, in 2022, there would be approximately 1.9 million new CRC cases worldwide, with 904,000 CRC-related deaths. Among them, approximately 30% of CRC cases are in China [13]. By 2040, the number of new cases and deaths will increase to 3.2 million and 1.6 million, respectively [14]. Chronic inflammation is a key risk factor for the transformation of low-grade and high-grade dysplasia into CRC. Patients with chronic colonic inflammation caused by ulcerative colitis have an increased risk of developing CRC. Among patients with low-grade dysplasia, approximately 20% to 23% are found to have cancer [15]. An increasing number of studies have shown that DUSPs play a significant role in the development, prognosis, and drug resistance of CRC. The expression of DUSP1 and DUSP7 is increased in the tumor tissues of CRC patients compared with normal tissues [16,17]. Overall survival analysis revealed that increased DUSP7 expression is significantly associated with poor prognosis in CRC patients [17]. 5-FU is a conventional antitumor drug for CRC. In 5-FU-resistant CRC cells, the expression of DUSP4 is significantly increased, suggesting a role for DUSP4 in modulating the therapeutic sensitivity of CRC cells [18,19]. Additionally, several other DUSPs, such as DUSP5 [20], DUSP7 [21], and DUSP8 [22], are abnormally expressed in CRC (Fig. 1).

As an essential member of the DUSP family, DUSP4 regulates the occurrence, progression, and treatment of various cancers [19,23,24]. This study aims to review the alterations in the expression of DUSP4 in CRC and its regulatory role in tumor cell biology and to summarize the specific mechanisms by which DUSP4 regulates CRC. DUSP4 may represent a promising therapeutic target for CRC.

## Expression of DUSP4 in CRC

Many studies have confirmed altered expression of DUSP4 in CRC (Table 1, Ref. [24–32]). Pei *et al.* [24] analyzed the expression of DUSP4 in normal colorectal tissues and CRC tissues via the online databases TIMER (http://timer.comp-genomics.org/) and TNMplot (https://tnmplot.com/analysis/). The results revealed that DUSP4 expression was significantly higher in CRC tissues than in normal tissues. In most cases, DUSP4 expression is higher in CRC tissues than in adjacent noncancer tissues [24].

Microsatellite instability (MSI) is a phenomenon of length variation in microsatellite sequences caused by defects in DNA mismatch repair function, manifested as insertions or deletions of repeat units in tumor tissues. Compared with microsatellite stability (MSS) CRC, MSI CRC presents unique clinicopathological and biological characteristics: (1) a high tumor mutation burden; (2) low tumor differentiation; (3) an increased frequency of mucinous adenocarcinoma; and (4) increased tumor-infiltrating lymphocytes [33,34]. DUSP4 is highly expressed in MSI-high CRC tissues compared with MSS CRC tissues. High expression of DUSP4 may be a risk factor for promoting the malignant progression of CRC [25].

Shalaby *et al.* [19] reported increased expression of DUSP4 in the cancer tissues of patients who received radiotherapy. The growth of Caco-2 cells was significantly inhibited by the chemotherapeutic drugs 5-FU and oxaliplatin, accompanied by increased expression of DUSP4 [19]. Compared with nintedanib (an angiogenesis inhibitor) alone, the combination of nintedanib and DUSP4 overexpression significantly reduced the inhibitory rate of CRC cells [35]. DUSP4 is associated with drug resistance in CRC cells.

Metastasis is a core mechanism for the poor prognosis of CRC patients. After resection of the primary tumor, 60% of patients experience metastatic progression. Approximately two-thirds of CRC patients have liver and peritoneal metastases. The expression of DUSP4 is significantly elevated in CRC-peritoneal metastases [26]. Sim *et al.* [27] examined the expression of DUSP4 in 23 normal colorectal tissues, 50 tubular adenomas (benign lesions), 439 adenocarcinomas, 56 lymph node metastases, and 53 distant metastases. In normal colorectal tissues, DUSP4 was positive in 2 patients (2/23), and in tubular adenomas, it was positive in 2 patients (2/50). In adenocarcinomas, DUSP4 was positive in 166 patients (166/439), 19 patients (19/56), and 32 patients (32/53) with distant metastases. The expression of DUSP4 in adenocarcinomas, lymph node metastases, and distant metastases was significantly greater than that in normal colorectal tissues. T staging represents the condition of the primary tumor, primarily considering the tumor size, depth of invasion, and involvement of adjacent tissues. The T stage was classified from low to high as T1, T2, T3, or T4. Clinically, higher DUSP4 expression has been detected in larger tissues with increased T stages [27].

Interestingly, Ichimanda *et al.* [28] reported that DUSP4 expression was reduced in the cancer tissues of CRC patients, with an increase in the superficial region of CRC and a decrease in the deep region. This regional expression difference suggests that DUSP4 may play a potential regulatory role in tumor invasion and progression. In summary, DUSP4 is significantly dysregulated in CRC tissues and is a potential tumor marker for CRC. However, the expression of DUSP4 is notably associated with the

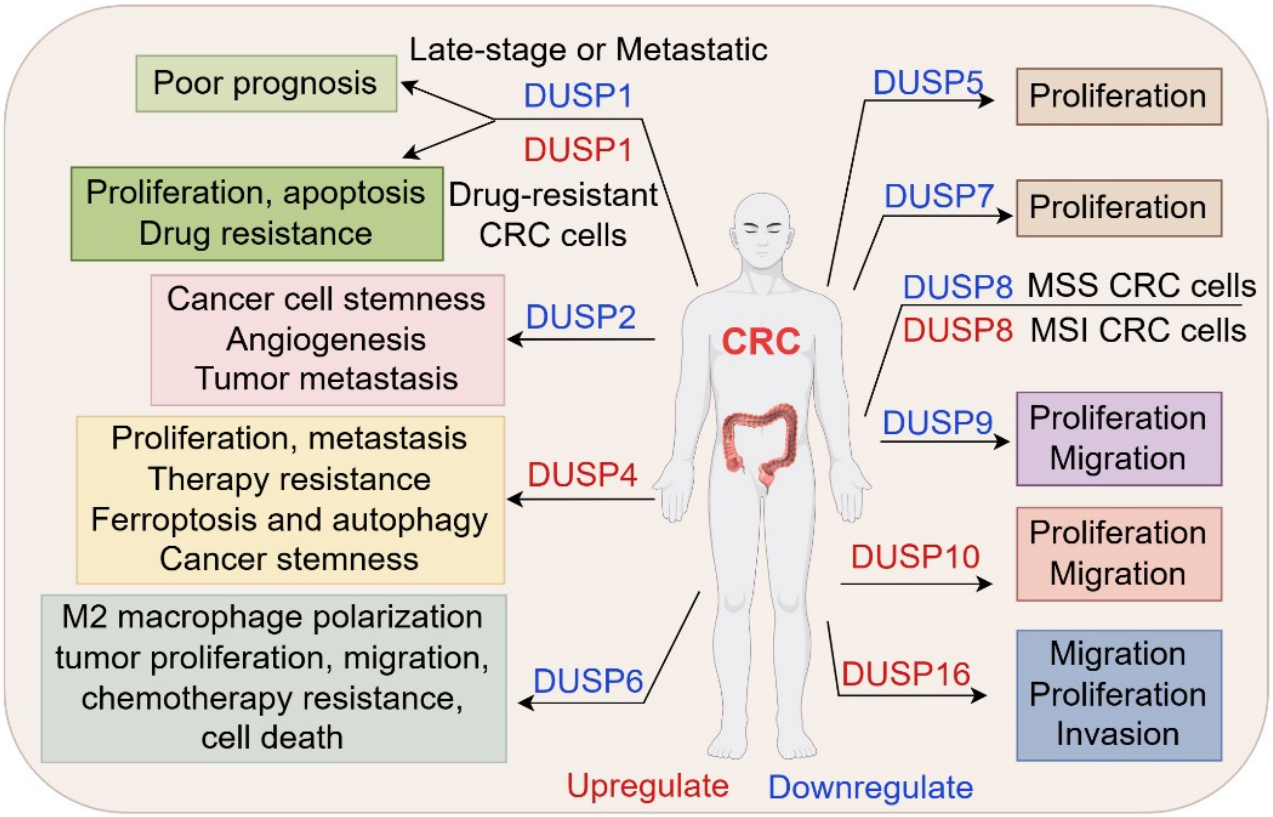


**Fig. 1. The expression and function of selected DUSPs in CRC.** There are multiple DUSPs, including DUSP1, DUSP2, DUSP4, DUSP5, DUSP6, DUSP7, DUSP8, DUSP9, DUSP10, and DUSP16, with alterations in CRC. These DUSPs also affect the malignant behaviors of CRC cells (By Figdraw, https://www.figdraw.com/). DUSPs, Dual-specificity phosphatase; CRC, Colorectal cancer.

anatomical location and subcellular localization of tumor tissues, which should be a key focus of subsequent research.

## Functions of DUSP4 in CRC

The regulatory effects of DUSP4 on CRC include proliferation and growth, migration, infiltration, metastasis, therapeutic resistance, the immune microenvironment, programmed cell death, autophagy, and ferroptosis (Fig. 2).

### *DUSP4 Exhibits Carcinogenic Activity in CRC*

DUSP4 can promote the proliferation and growth of CRC. Gröschl *et al.* [29] reported that in SW48 and HCT116 cells overexpressing DUSP4, the expression of the proliferation markers DC25A, CCND1, and MYC was upregulated. DUSP4 overexpression significantly promoted the proliferation of HCT116 cells on days 2, 3, 4, and 5, with a marked increase in colony formation. The expression of the proliferation markers CyclinD1 and PCNA was significantly greater than that in normal HCT116 cells [36]. DUSP4 affects cell cycle progression and reduces the number of S-phase cells, thereby inhibiting the proliferative capacity of tumor cells [24]. DUSP4 also exerts regulatory effects on CRC growth. Clinical pathology correlation analysis demonstrated that DUSP4 expression is significantly associated with tumor growth [26]. In CRC model mice, tumor volume was markedly reduced after DUSP4 knockdown. DUSP4 significantly inhibits tumor growth in CRC mice [30].

### *Migration, Invasion, and Metastasis*

Functional assays confirmed that DUSP4 plays a role in regulating the migration, invasion, and metastasis of CRC. Transwell experiments confirmed that knockdown of DUSP4 inhibited the migration of HCT116 cells [37]. Transwell and scratch assays were performed in LOVO and SW620 cell lines. DUSP4 knockdown inhibited migration in both cell lines [24]. In SW480 cells, DUSP4 knockdown significantly suppressed cell migration, as it effectively reduced the expression of N-cadherin, vimentin, and MMP9 while increasing E-cadherin expression [36]. Saigusa *et al.* [31] reported that elevated DUSP4 expression was detected in tumor tissues of advanced T stages and with remote metastasis. Reduced DUSP4 expression was an independent risk factor for synchronous distant metastasis ($p = 0.006$) and poorer prognosis ($p = 0.0162$) [31].

**Table 1. DUSP4 expression in CRC.**

| Control group | Experimental group | Method | Expression | Prognosis | References |
|---|---|---|---|---|---|
| Normal tissues | CRC tissues | IHC staining | Upregulation | NA | [24] |
| MSS CRC tissues | MSI CRC tissues | IHC staining | Upregulation | NA | [25] |
| Normal colon tissues | Colon adenocarcinoma tissues | ENCORI Pan-Cancer Analysis Platform, ONCOMINE | Upregulation | Poor | [30] |
| Normal tissues | CRC tissues | RT–qPCR | Upregulation | NA | [29] |
| MSS CRC tissues | MSI CRC tissues | RT–qPCR | Upregulation | NA | |
| CRC-liver metastasis | CRC-Peritoneal metastasis | IHC staining | Upregulation | NA | [26] |
| Normal tissues | CRC tissues (Superficial) | IHC staining | Upregulation | NA | [28] |
| CRC tissues (superficial) | CRC tissues (deep) | IHC staining | Downregulation | NA | |
| CRC (CTX resistant) | CRC (CTX-sensitive) | Khambata-Ford Analysis Platform | Downregulation | NA | [32] |
| Normal mucosa | CRC tissues | RT–qPCR | Upregulation | Poor | [31] |
| Primary CRC | Metastatic CRC | IHC staining | No change | | |
| Normal colorectal tissues | Adenocarcinomas and lymph node/distant metastases | IHC staining | Upregulation | Poor | [27] |

MSS, Microsatellite stability; CRC, Colorectal cancer; CTX, Cetuximab; MSI, Microsatellite instability; IHC, Immunohistochemistry.

### *Therapy Resistance*

Alterations in DUSP4 expression are significantly associated with reduced therapeutic drug sensitivity in CRC cells. DUSP4 is highly expressed in CRC patients undergoing chemotherapy. Compared with that in the untreated group, the expression of DUSP4 in CRC cells treated with 5-FU and oxaliplatin increased with increasing drug dosage. Upregulated DUSP4 expression is correlated with decreased sensitivity of CRC cells to 5-FU [19].

Nintedanib is a tyrosine kinase inhibitor whose primary mechanism of action involves inhibiting the activity of platelet-derived growth factor receptor (PDGF-R), fibroblast growth factor receptor (FGFR), and vascular endothelial growth factor receptor (VEGF-R). Studies have demonstrated that nintedanib significantly inhibits tumor growth, reduces angiogenesis, promotes vascular normalization, and improves oxygenation and drug delivery potential [38]. Cheng *et al.* [35] verified that miR-429 can increase the sensitivity of CRC cells to nintedanib. DUSP4 is a target gene of miR-429. Forced DUSP4 overexpression reversed the inhibitory effect of miR-429 on CRC cells. Overexpression of DUSP4 reduces the expression of the apoptotic markers BCL and cleaved caspase-3. In conclusion, DUSP4 overexpression inhibited the sensitivity of CRC cells to nintedanib [35].

Cetuximab (CTX) is a targeted antibody against epidermal growth factor receptor (EGFR). It is used for the treatment of metastatic CRC [32]. Park *et al.* [32] reported that in an RNA-seq dataset (GSE5851), DUSP4 expression was upregulated in the drug-resistant group compared with the nondrug-resistant group. Analysis of gene expression data from 155 cell lines (GSE59857) revealed increased DUSP4 expression in the CTX-resistant cell groups compared with the control groups. Further validation of the role of DUSP4 in CRC was conducted by treating all the groups with CTX, which resulted in increased death in CRC cells with DUSP4 knockdown compared with that in the control groups, and low DUSP4 expression could synergize with CTX [32]. DUSP4 inhibitors can enhance drug sensitivity in cancer cells, potentially serving as novel therapeutic targets for future cancer treatment.

### *Immune Microenvironment*

The tumor immune microenvironment (TIME) is a complex environment comprising tumor cells, immune cells, secreted mediators, extracellular matrix components, and metabolic molecules [39]. The immunosuppressive properties of the CRC TIME promote immune evasion by tumor cells, thereby facilitating the occurrence, progression, recurrence, and metastasis of CRC, ultimately leading to treatment resistance [40]. CRC is infiltrated by multiple TIICs, including macrophages, T cells, B cells, and neutrophils [41]. Single-cell RNA sequencing analysis revealed that DUSP4 was enriched in $CD4^+$ T cells and $CD8^+$ T cells. Compared with the low DUSP4 expression group, the high DUSP4 expression group presented greater proportions of $CD8^+$ T cells, neutrophils, dendritic cells, B cells, and $CD4^+$ T cells, with DUSP4 expression significantly correlated with TIIC infiltration [42].

Cell cyclin-dependent kinases (CDKs) are key regulators of the cell cycle, and abnormal cell cycle progression can promote tumor initiation and progression. CDKs are associated with cell cycle progression and tumor cell growth [43]. Phosphorylation at the Thr170 site is correlated with CDK7 kinase activity. Zhang *et al.* [25] reported that DUSP4 binds to and dephosphorylates the Thr170 site of CDK7, leading to CDK7 inactivation. CXCL16, a member of the CXC chemokine family, plays a significant role

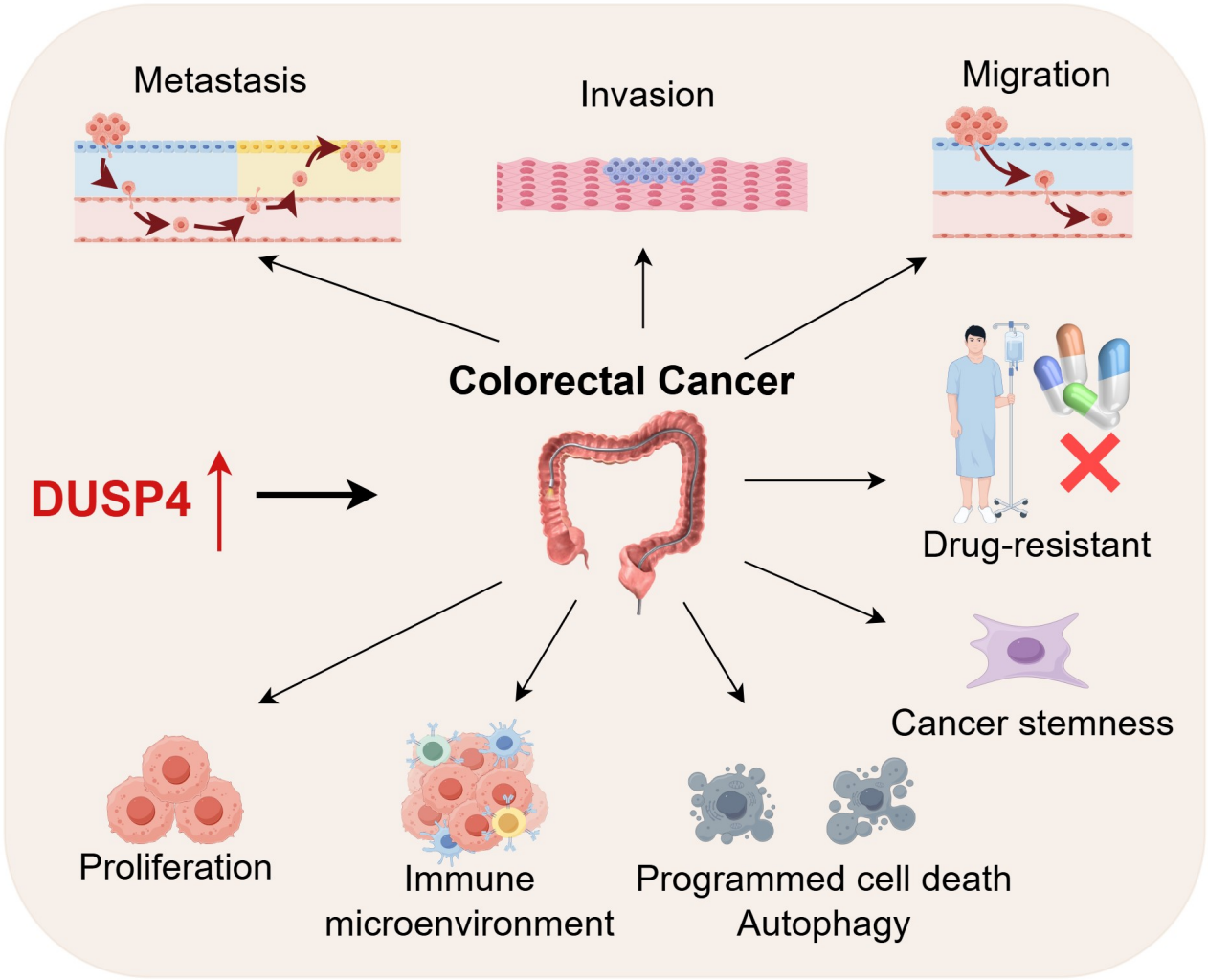


**Fig. 2. Functions of DUSP4 in CRC.** DUSP4 can regulate multiple cellular processes in CRC, including proliferation and growth, migration, infiltration and metastasis, therapeutic resistance, the immune microenvironment, programmed cell death, and autophagy (By Figdraw, https://www.figdraw.com/).

in driving immune cell infiltration into the tumor microenvironment. Studies have shown that high expression of DUSP4 inhibits CDK7 activity in MSI-high CRC cells, promotes CXCL16 expression, and increases $CD8^+$ T-cell infiltration [25]. DUSP4 can regulate the tumor microenvironment, enhance immune cell infiltration, and exert protumor effects.

### *Programmed Cell Death, Autophagy, and Ferroptosis*

Autophagy is essential for maintaining cellular homeostasis and is characterized by the lysosomal degradation of long-lived proteins and unnecessary organelles through autophagosomes [44]. Apoptosis is the most common form of programmed cell death (PCD). During cancer development, cancer cells are shaped to withstand stressors such as oncogene-induced stress, hypoxia, nutrient deprivation, and anticancer immune attacks. Those stimulations have been reported to trigger apoptosis and disturb cancer progression [45]. DUSP4 silencing enhanced apoptosis, increased BCL2 phosphorylation, and promoted LC3II expression. Overexpression of DUSP4 had the opposite effects [37]. In summary, DUSP4 can inhibit autophagy and apoptosis, thereby increasing the survival capacity of CRC cells.

Ferroptosis, a unique mechanism of programmed cell death, was proposed in 2012 by the laboratory of Brent R. Stockwell [46]. It is characterized by the accumulation of iron-dependent lethal lipid peroxides on the cell membrane, ultimately leading to cell death. This novel iron-dependent form of programmed cell death is distinct from apoptosis, necrosis, and autophagy [47,48]. DUSP4 overexpression significantly reduces the levels of the ferroptosis markers MDA, $Fe^{2+}$, and 4HNE. Erastin and RSL3 are often used as ferroptosis inducers. Erastin or RSL3 treatment in CRC cells contributes to elevated lipid per-

oxidation, which can be significantly inhibited by DUSP4 overexpression. *DUSP4* gene knockout leads to mitochondrial shrinkage and increased mitochondrial density, which are typical morphological changes induced by ferroptosis. DUSP4 inhibits the transcription of TFRC via the proto-oncogene c-MYC, thereby exerting anti-ferroptotic effects. Additionally, DUSP4 overexpression reduces intracellular $Fe^{2+}$ levels in cells. DUSP4 may serve as a negative regulator of ferroptosis [25]. The role of DUSP4 in the key regulatory axis of the GPX4/SLC7A11/ROS ferroptosis pathway remains unclear and requires further investigation in the future.

### *Cancer Stemness*

Owing to the unlimited self-renewal capacity, cancer stem cells (CSCs) play prominent roles in the occurrence and maintenance of CRC. CSCs also mediate drug resistance during chemotherapy [49]. Traditional anticancer drugs have short-term effects on tumor cell proliferation but fail to eradicate highly malignant CSCs, leading to cancer recurrence [50]. LINC01315 knockdown inhibits the survival, proliferation, spheroid formation, and migration of CRC CSCs while increasing the expression of the stem cell markers Oct-4, Prominin, and SOX2. These results indicate that LINC01315 promotes the progression of CRC. Additionally, bioinformatics analysis revealed a negative correlation between LINC01315 and DUSP4 expression, suggesting that LINC01315 may regulate CRC progression through DUSP4 and play a critical role in maintaining the stemness of CRC cells [51]. A study has demonstrated that DUSP4 knockdown significantly reduces the expression of the stem cell markers CD44, OCT4, C-MYC, and NANOG in CRC cells and inhibits colony formation and cell proliferation [30]. DUSP4 appears to promote the characteristics of cancer stem cells.

## Mechanisms

DUSP4 participates in the progression of CRC through multiple pathways, such as the BCL2-Beclin1/Bax and CREB/PRKACB pathways (Fig. 3).

### *BCL2-Beclin1/Bax Signaling*

Beclin-1 is one of the key components involved in autophagosome formation, and its expression levels are typically elevated during autophagy. The autophagy-promoting function of Beclin-1 can be inhibited by interactions with proteins of the Bcl-2 family (e.g., Bcl-2), thereby forming the Beclin-1+Bcl-2 complex. Phosphorylation of Bcl-2 disrupts the interaction between Beclin-1 and Bcl-2, releasing Beclin-1 to promote cellular autophagy [52]. In externally stimulated protective autophagy, JNK activation upregulates Beclin-1 expression and mediates the phosphorylation of Bcl-2, leading to the dissociation of the apoptotic molecule Bax and the autophagy molecule Beclin-1 from the BCL2–Bax and BCL2–Beclin-1 complexes. The resulting free molecules promote apoptotic signal transduction and entry into the autophagic stream to activate autophagy, thereby increasing cell survival [53]. Xu *et al*. [37] reported that the Beclin1 inhibitor spautin-1 can partially reverse the increased cellular autophagy level induced by the downregulation of DUSP4 expression, whereas the BCL2 inhibitor ABT-737 is able to completely reverse the inhibitory effect of DUSP4 overexpression on cellular autophagy and apoptosis processes. DUSP4 promotes CRC cell survival and disease progression by stabilizing the BCL2+Beclin1 and BCL2+Bax complexes through the inhibition of JNK-mediated BCL2 phosphorylation, thereby suppressing Beclin1-dependent autophagy and Bax-associated apoptosis.

### *CREB/PRKACB Pathway*

CREB is a nuclear protein that regulates gene transcription through phosphorylation regulation. Recent studies have demonstrated that CREB is closely associated with cellular biological functions such as cell growth, proliferation, differentiation, and cell cycle regulation. Research indicates that CREB plays a significant role in the development, progression, and metastasis of melanoma, prostate cancer, hepatocellular carcinoma, breast cancer, and other malignancies [54]. PRKACB is the coding gene for a subunit (catalytic subunit) of PKA, which mediates cAMP-dependent signal transduction. The activation of PKA kinase is implicated in various critical cellular processes, including the regulation of chromatin condensation and decondensation, cell proliferation, cell differentiation, and the cell cycle [55]. Pei *et al*. [24] reported that overexpression of DUSP4 increased the phosphorylation level of CREB and the expression of PRKACB. Conversely, the results of the knockdown of DUSP4 verified these findings. A dual-luciferase reporter gene assay confirmed the regulatory effects of DUSP4 and CREB on the target gene PRKACB. These results indicate that DUSP4 regulates PRKACB expression by promoting CREB activation, thereby mediating the progression of CRC. A specific CREB inhibitor (666-15) can inhibit the phosphorylation and activation of CREB. Compared with oe-NC, DUSP4 overexpression upregulated PRKACB expression in cells treated with 666-15, but this effect was significantly weakened. Compared with the untreated 666-15 group, 666-15 attenuated the malignant phenotypes of CRC cells induced by DUSP4 overexpression, such as proliferation and migration. These results suggest that DUSP4 mediates the malignant phenotypes of CRC through CREB-dependent activation [24].

In summary, DUSP4 is a nuclear-specific phosphatase. It regulates the transcriptional control of the downstream target gene PRKACB by binding to CREB and activating CREB. The DUSP4/CREB/PRKACB pathway promotes cell proliferation and migration and inhibits apoptosis by mediating cell cycle progression. As PRKACB is

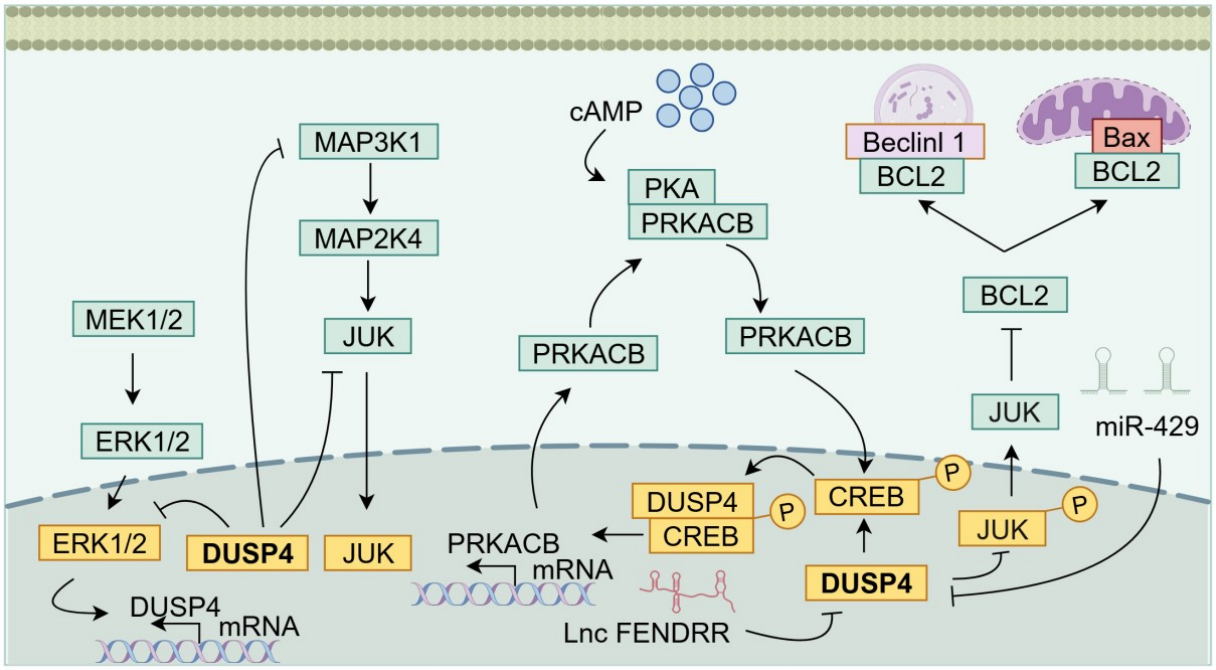


**Fig. 3. Mechanism of DUSP4 in CRC.** DUSP4 participates in the progression of CRC through multiple pathways, such as the BCL2-Beclin1/Bax pathway, the CREB/PRKACB pathway, and the MAPK-ERK pathway (By Figdraw).

the catalytic subunit of PKA kinase, the upregulation of PRKACB expression can lead to the recruitment of more cAMP, further enhancing CREB activation. This forms a positive feedback loop, ultimately driving the progression of CRC.

### *MAPK-ERK Pathway*

ERK is a key member of the MAPK family and is often associated with the MAPK/ERK pathway. DUSP4 is an inducible nuclear phosphatase that can specifically dephosphorylate MAPK family members such as ERK1/2, thereby inhibiting their kinase activity. Moreover, downstream target transcription factors of MAPKs, including EGR1, E2F1, HOXA10, and TP53, activate the transcription of DUSP4. These findings suggest that DUSP4, a key component of the negative feedback regulatory loop in the MAPK signaling pathway, can antagonize the activation process of MAP kinases [29,56].

In CRC, oncogenes such as KRASG12V and BRAFV600E can cause persistent activation of ERK, thereby promoting the phosphorylation and activation of ERK1/2 in the cytoplasm. Activated ERK1/2 can translocate into the cell nucleus, where the phosphorylation level of ERK1/2 is difficult to sustain, and ERK1/2 is rapidly dephosphorylated and inactivated. Activated ERK1/2 induces the transcription and protein expression of DUSP4, which in turn dephosphorylates and inactivates phosphorylated ERK, thereby terminating the signal transduction of ERK in the nucleus [56]. In contrast, when the MEK-ERK signaling pathway is inhibited, the JNK-JUN signaling pathway is activated by downregulating the expression of DUSP4. The MAP3K1-MAP2K4-JNK cascade can activate JUN, which then binds to FOS to form the activated protein-1 transcriptional activator complex, regulating various processes, such as cell differentiation, proliferation, and apoptosis [57]. DUSP4 specifically dephosphorylates and inactivates MAPK, inhibiting downstream signaling proteins such as CCND1, MYC, and CDC25A while upregulating the cell cycle inhibitor CDKN1A, thereby forming a negative feedback regulatory mechanism to prevent signal overactivation [2,29,58].

### *Upstream Mechanisms of DUSP4 Regulation*

Studies have reported that non-coding RNA, such as microRNAs (miRNAs), can target DUSP4 and modulate its expression. miRNAs play crucial roles in the initiation and progression of malignant tumors, with mechanisms of gene silencing mediated by miRNAs including (1) translation initiation inhibition and posttranslational initiation inhibition and (2) miRNA-mediated mRNA degradation [59]. Cheng *et al.* [35] identified DUSP4 as a target gene of miR-429 via ENCORI software. They further demonstrated that miR-429 enhances the sensitivity of CRC cells to nintedanib by downregulating DUSP4, thus inhibiting the JNK signaling pathway [35].

LncRNAs, another large group of non-coding RNAs, are involved in various biological processes through multiple mechanisms, such as interactions with miRNAs and proteins [60]. LncRNA FENDRR is found to reverse EMT by downregulating the DUSP4/CREB/PRKACB signaling

pathway, thereby inhibiting CRC growth [23]. LncRNA LINC01315 promotes malignant behavior in CRC cells, which may contribute to CRC development through interaction with DUSP4 [51].

In addition to regulations by non-coding RNAs, DNA methylation and histone modification (two other epigenetic mechanisms), also play essential roles in DUSP4 expression [61,62]. The downregulation of DUSP4 in deep regions of CRC tissues may be associated with epigenetic modifications. However, the underlying mechanism appears to be complex. Studies have revealed that genomic deletions of the DUSP4 gene located on chromosome 8p lead to downregulation of DUSP4 expression in pancreatic cancer. In pancreatic cancer, DUSP4 is upregulated in carcinoma *in situ* through a positive feedback loop involving ERK phosphorylation, with no abnormalities detected on chromosome 8p in carcinoma *in situ*; however, in the invasive region of pancreatic cancer, DUSP4 is downregulated due to 8p deletion [63]. Chromosomal 8p deletions are detected in 29% of CRC cases [64]. Compared with untreated cells, CRC cells treated with epigenetic modifiers such as 5-azacytosine and triphenylmethane presented increased DUSP4 expression, but no hypermethylation was detected in the promoter regions of DUSP4 in CRC cell lines. The downregulation of DUSP4 in deep regions of CRC may involve mechanisms other than epigenetic silencing, which requires further investigation [28].

## Future Perspectives

Studies have shown that DUSP4 plays a key role in inflammatory and immune-mediated diseases and appears to be associated with T-cell infiltration. For example, in experimental autoimmune encephalomyelitis (EAE) central nervous system (CNS) inflammation, Barbour *et al.* [65] reported that the severity of EAE was alleviated in DUSP4 knockout mice, with reduced infiltration of immune cells in the CNS, lower levels of proinflammatory factors, and decreased numbers of $CD4^+$ T cells and $CD8^+$ T cells in the spleen and lymph nodes. DUSP4 knockout mice exhibited impaired antigen presentation and T-cell activation [65]. Under persistent viral antigen stimulation, effector T cells induce differentiation into exhausted T cells [66]. Exhausted T cells show low proliferative capacities, reduced expression of proinflammatory factors, and elevated expression of inhibitory immune receptors. Therefore, the body's clearance of pathogens can be hindered. Tumor-infiltrating T cells typically exhibit specific phenotypes with weakened tumor-inhibiting ability [67,68].

Zhao *et al.* [69] used single-cell sequencing (GSE144735) and reported that DUSP4 expression is significantly upregulated in the exhausted T-cell subset of colorectal adenocarcinoma. DUSP4 negatively regulates T-cell activation by dephosphorylating key genes such as ERK and JNK downstream of the T-cell receptor (TCR) signaling pathway. Immune checkpoint inhibitors (ICIs), represented by targeting PD-1, exert good efficacy against tumors by promoting the functional recovery of exhausted $CD8^+$ T cells [70]. Anti-PD-1 therapy can downregulate the expression of DUSP4, and DUSP4 may serve as a potential target for reversing T-cell exhaustion [69]. DUSP4 is significantly overexpressed in different subtypes of CRC, such as MSI and MSS. Compared with MSS, DUSP4 is significantly more highly expressed in MSI [29]. Previous studies have demonstrated that increased immune infiltration ($CD8^+$ T-cell infiltration) is an important characteristic of MSI-H [71]. DUSP4 regulates $CD8^+$ T cells and promotes MSI-H malignant phenotypes [25]. The challenges for the clinical translational potential of DUSP4 as a biomarker or therapeutic target could be explored in greater detail, particularly the diagnostic and therapeutic complexity that may arise from its heterogeneous expression in different CRC subtypes (e.g., MSI-H vs. MSS). Additionally, clarifying the regulatory interactions among DUSP4+ T cells, $CD8^+$ T cells, and MSIs could help improve the efficacy of ICIs.

The development of small-molecule drugs targeting DUSP4 holds broad prospects in clinical cancer therapy. In a murine model of cholangiocarcinoma (CCA), plumbagin inhibited tumor growth and upregulated the expression of key pyroptosis-related genes, such as ROS, LDH, NLRP3, cleaved caspase-1, and GSDMD-N. Plumbagin suppressed the progression of cholangiocarcinoma by reducing DUSP4 expression [72]. DUSP4 functions differently in various tumors and sometimes functions as a tumor suppressor gene. In non-small cell lung cancer (NSCLC), DUSP4 is expressed at lower levels. Nimbolide upregulates DUSP4 expression, inhibits ERK1/2 activation, reduces the expression of MMP-3 and Snail, increases the expression of E-cadherin, and suppresses the invasion and migration of NSCLC cells [73]. DUSP4 plays a critical role in cancer development and treatment, and targeted intervention with DUSP4 provides a potential therapeutic strategy for CRC.

## Conclusion

This article reviews existing studies to explore the impact of DUSP4 on CRC and its regulatory mechanisms. The expression of DUSP4 is significantly altered in CRC. Differences in DUSP4 expression are correlated with tumor location, the clinical stage of CRC patients, and distant metastasis. Functionally, DUSP4 has been more frequently identified as an oncogene that promotes tumor proliferation, growth, migration, infiltration, and metastasis through multiple signaling pathways, such as the BCL2-Beclin1/Bax, CREB/PRKACB, and MAPK-ERK pathways. Additionally, DUSP4 can modulate the immune microenvironment and promote immune cell infiltration. Furthermore, DUSP4 confers therapeutic resistance by inhibiting cell death, including autophagy, apoptosis, and ferroptosis.

## Abbreviations

CCA, Cholangiocarcinoma; CDKs, Cyclin-dependent kinases; CNS, Central nervous system; CRC, Colorectal cancer; CTX, Cetuximab; DUSPs, Dual-specificity phosphatase; EAE, Experimental autoimmune encephalomyelitis; EGFR, Epidermal growth factor receptor; EMT, Epithelial–mesenchymal transition; GBM, Glioblastoma; GPX4, Glutathione peroxidase 4; KIM, Kinase interaction motif; LncRNA, Long noncoding RNA; ICIs, Immune checkpoint inhibitors; MAPKs, Mitogen-activated protein kinases; miRNA, microRNA; MKP, Mitogen-activated protein kinase phosphatase; MSI, Microsatellite instability; MSS, Microsatellite stability; NSCLC, Non-small cell lung cancer; OS, Osteosarcoma; PTPs, Protein Tyrosine Phosphatases; TCR, T-cell receptor; TIME, Tumor Immune Microenvironment; TIICs, Tumor-infiltrating immune cells.

## Availability of Data and Materials

Not applicable.

## Author Contributions

TG and JW designed the manuscript. TG and YZ conducted the literature search, generated the figures, and wrote the manuscript. JW supervised the review and made critical revisions and editing of the manuscript. All the authors agreed to be accountable for all aspects of the work. All the authors read and approved the final manuscript.

## Ethics Approval and Consent to Participate

Not applicable.

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## Conflict of Interest

The authors declare no conflict of interest.

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