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Deubiquitinases as novel therapeutic targets in colorectal cancer

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Abstract

Colorectal cancer (CRC) is one of the leading causes of cancer-related mortality and is the third most prevalent malignant tumor in the world. In recent years, the key role of protein post-translational modifications, especially ubiquitination and deubiquitination modifications, in tumorigenesis and progression has gradually been revealed. Deuubiquitinating Enzymes (DUBs) play an important role in CRC cell proliferation, apoptosis, autophagy, immune escape, and chemotherapy resistance by removing ubiquitin chains from proteins, regulating protein stability, activity, and subcellular localization. Research has shown that DUBs such as USP7, USP10, and USP22 promote the progression and metastasis of CRC by stabilizing key tumor associated proteins such as β-catenin, p53, and c-Myc, activating signaling pathways such as Wnt/β-catenin and ERK/MAPK. In addition, DUBs exacerbate malignancy in the tumor microenvironment (TME) by regulating inflammatory responses, immune escape, and polarization of tumor associated macrophages. Meanwhile, DUBs are closely related to chemotherapy resistance, leading to decreased drug sensitivity by maintaining the stability of drug targets or enhancing anti-apoptotic protein function. At present, small molecule inhibitors targeting DUBs have made certain progress, such as USP7 inhibitor P5091 and USP14 inhibitor IU1, providing new directions for the treatment of CRC. However, clinical applications still face challenges such as selectivity and safety concerns. In summary, in-depth research on the molecular mechanisms of DUBs in CRC, the development of more efficient and specific targeted inhibitors, and the exploration of their combined application with other therapeutic methods are expected to provide new strategies for the diagnosis and treatment of CRC.

Key words deubiquitinase, colorectal cancer, protein stability, tumor microenvironment, chemotherapy resistance, targeted therapy

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Introduction

Colorectal cancer (CRC) is the third most common malignant tumor in the world and the second leading cause of cancer related deaths. As a major hazard to human health, its incidence rate is rising every year. Global cancer data shows that there are roughly 935,000 CRC-related deaths and 1.93 million new cases per year [1, 2]. The prognosis for patients with late-stage or metastatic CRC remains poor, even with the ongoing advancements in diagnostic and treatment strategies, including comprehensive therapies like surgery, chemotherapy, radiotherapy, and targeted therapy, which have increased the survival rate in early diagnosed patients [3]. Major obstacles exist in the treatment of CRC when resistance arises during chemotherapy and when targeted therapy fails [4]. Therefore, further exploration of the molecular pathogenesis of CRC and development of novel treatment strategies have important clinical applications.

Modifications of proteins after translation are closely related to tumorigenesis and progression, therefore post-translational modification (PTM) of proteins has attracted increasing attention in recent years. In addition, protein stability and function are regulated by changes in ubiquitination and deubiquitination, as well as ubiquitin addition and removal are critical for biological processes such as cell cycle, apoptosis, autophagy and immune responses [5, 6]. Deubiquitinating enzymes (DUBs), have been discovered to be essential for maintaining protein structure and regulating diverse signaling pathways [7].

Deubiquitination alters ubiquitination modifications and removes ubiquitin molecules from target proteins via DUBs, thereby controlling protein degradation and subcellular localization. Over the past few years, studies have shown significant effects of ubiquitination and deubiquitination on the post-translational functions of proteins, especially some proteins are crucial for signal transduction, regulation of gene expression and cellular homeostasis, which has further stimulated the research interest [8, 9]. Ubiquitination modification is a process in which a number of enzymes (E1, E2, and E3) attach ubiquitin molecules to target proteins [10]. In addition to being essential for regular cellular physiological functions, DUBs are also intricately associated with the initiation and development of a number of illnesses, particularly cancer [11].

Research has shown a significant correlation between DUBs and the development and incidence of a number of malignancies, such as CRC and other tumors of the digestive system [12]. In CRC, DUBs promote tumor invasion and metastasis by maintaining the equilibrium of cancer cell proliferation, apoptosis, autophagy, and immune microenvironment. In addition, some DUBs are also associated with chemotherapy resistance, such as by maintaining the stability of drug target proteins or regulating apoptosis-related pathways, mediating a decrease in sensitivity of CRC cells to chemotherapy drugs [13, 14]. Therefore, DUBs are not only an important pathogenic factor for CRC, but also have the potential to become a novel therapeutic target. As the functions of DUBs are gradually revealed, their value as potential therapeutic targets for CRC is also receiving increasing attention. Low-molecular-weight inhibitors for DUBs, such as USP7, USP14, and WP1130 inhibitors, have made considerable headway in recent years, and have demonstrated strong anti-tumor effects in a variety of cancer models [15]. However, these inhibitors still face challenges in terms of selectivity, toxicity, and pharmacokinetic properties, limiting their widespread clinical applications.

Although many studies have demonstrated the role of DUBs in CRC, little is known about their molecular regulatory networks and mode of action. In addition, some side effects triggered in response to DUB treatment need to be urgently addressed. Here, we summarize the progress of DUBs in CRC research in recent years and the roles they play in tumorigenesis, drug resistance and immunomodulation, and discuss their potential applications in the treatment of CRC.

Risk factors

The etiology of OC encompasses a multifaceted display of risk factors that can be broadly classified into genetic and non-genetic categories. These non-genetic elements comprise various aspects, including an individual's reproductive history, the utilization of exogenous hormones, pre-existing medical conditions, lifestyle choices, and environmental influences. Each of these factors contributes to the overall risk profile of OC development [14]. Substantial evidence indicates that the primary risk factors for this pathology include a familial history of OC, mainly when a relative receives a diagnosis before 50 years of age, and germline BRCA1/BRCA2 mutations [15, 16] (**Figure 1**). Genetic alterations in MSH2, MSH6, MLH1, PMS2, and EPCAM, which are associated with Lynch syndrome, as well as mutations in BRIP1, PALB2, RAD51C, and RAD51D, have been implicated in increased susceptibility to OC. Research suggests that inherited genetic mutations are responsible for approximately 18% of epithelial malignancies, except high-grade serous carcinomas [17, 18].

The deubiquitinase family in CRC

DUB is an important enzyme that controls the stability, activity and function of proteins by removing ubiquitin modifications from them. Ubiquitin specific proteases (USPs) [16], Ubiquitin C-terminal hydrolases (UCHs) [17], deubiquitinases with OTU domains (OTUs) [18], deubiquitinases with MJD domains (MJDs), JAMM domains (JAMMs), and MINDY domains (MINDYs) are among the numerous subfamilies that make up the DUBs family [18]. Since different DUBs regulate different biological processes, including cell cycle, programmed cell death, autophagy, and inflammation, they could be crucial in the development and progression of tumors. In recent years, it has been found that DUBs play an important role in CRC development and progression as well.

(1) Ubiquitin specific protease family (USPs)

USPs constitute the largest subgroup of DUBs with diverse members involved in controlling the regulation of signaling pathways as well as maintaining protein homeostasis. It has been shown that USP7 is an important deubiquitinating enzyme in CRC, and its high expression is strongly associated with the unfavorable prognosis of CRC patients. In addition to USP7, the roles of USP10 and USP22 in CRC have also been thoroughly investigated. In addition, it regulates the expression of p53 or MDM2, thereby controlling cell division and death. According to Al Eidan, USP7 functions in CRC to control intercellular adhesion through AJUBA. The results of the study showed that when USP7 was knocked down, CRC cell survival and intercellular adhesion were significantly reduced [19]. Furthermore, according to Zhang et al, the results showed that USP7 ubiquitinates and modulates MyD88 expression, which improves the immune response. In addition, this study showed that USP7 promotes CRC tumor cell invasion and metastasis through the activation of the Wnt/β-catenin pathway via deubiquitinating β-catenin [20]. To investigate the relationship between USP7 and YY1 in CRC, Shao et al. found that USP7 accelerates the development of CRC by activating the Wnt/β-catenin pathway, thus revealing their intricate modes of action in CRC [21].

USP10 promotes CRC tumor growth through improving the

polarization of tumor-associated macrophages. According to Cao and Peng's research, USP10 and OTUB2 deubiquitinate NLRP7 and PKM2, speeding up the progression of CRC. Furthermore, the study focused at the potential prognostic role of these genes in the development and spread of CRC [22]. According to Kubaichuk's findings, patients with CRC who had high USP10 expression experienced significantly poorer overall and recurrence-free survival rates, implying that USP10 may play a role in tumor progression. Further research suggests that knocking out USP10 can alleviate the invasive phenotype of HCT116 colon cancer cells [23]. USP10 is also associated with p53, and studies have shown that it has anti-cancer properties in some cases by stabilizing wild-type p53, but it is more likely to have a pro-cancer effects in CRC [24].

Through controlling the stability of cell cycle proteins and c-Myc, USP22, a DUB that is abundantly expressed in CRC, stimulates tumor cell proliferation and advances the cell cycle. Furthermore, Liu Y's research has shown that low prognosis in advanced AJCC staging was substantially linked to CRCs, with elevated mRNA levels of USP22, BMI-1, c-Myc, and cyclin D2 [25]. USP22 also promotes the metastasis of CRC cells by regulating the expression of EMT (epithelial mesenchymal transition) related genes. Li et al. reported that overexpression of USP22 in CRC is associated with liver metastasis, and found that USP22 activates EMT via upregulating AP4 expression, thereby, enhancing the migration and invasion ability of CRC cells. They also pointed out that USP22 activates AP4 transcription by directly binding to its promoter region [26].

(2) Ubiquitin C-terminal hydrolase family (UCHs)

Members of the UCHs family include UCH-L1 and UCH-L3, which play important roles in tumor-related signaling pathway. Lee KC et al. analyzed the levels of expression of CHGA and UCH-L1 in CRC tissues using iTRAQ technology and found that the high expression of these two proteins is closely related to lymph node metastasis [27]. Furthermore, Ma Y's research indicated that UCH-L1 represents a functional protein that might be crucial for cell migration, in addition to being a biomarker for lymph node metastasis in CRC [28]. UCH-L1 exhibits a pro-cancer effect in CRC by stabilizing inflammatory factors in the tumor microenvironment (TME) or regulating the migration ability of cancer cells [29]. There are few reports on the function of UCH-UCH-L3 in CRC. According to Nam MJ's research, UCH-L3 antibodies were found in the serum of 19 out of 43 individuals with colon cancer. Nonetheless, they may have an impact on tumor cell survival by controlling the stability of proteins linked to apoptosis [30].

(3) The deubiquitinase family (OTUs) and other families containing OTU domains

OTUs family fine-tunes diverse signaling pathways, and its members such as OTUB1 and OTUB2 have received widespread attention in the study of CRC. Wu's research found that OTUB1 stabilizes the expression of MSH2 by preventing its ubiquitin-mediated degradation, leading to affect the DNA mismatch repair process, and contributing to CRC cells' resistance to treatment [31]. In addition, Zhu D's research has shown that OTUB1 stimulates the proliferation of cancer cells and inhibits apoptosis by deubiquitinating specific substrates, suggesting its important role in tumor progression [32]. Wang D found that the expression of circSEC24B is elevated in CRC cell lines and tissues, and promotes CRC cell autophagy and proliferation. By controlling the protein stability of SRPX2, circSEC24B mechanistically stimulates the growth of CRC cells. As a scaffold, circSEC24B specifically facilitates OTUB1's binding to SRPX2, increasing OTUB1's protein stability. In summary, this study suggests that circSEC24B stimulates autophagy and triggers chemotherapy resistance in CRC by promoting OTUB1 mediated deacetylation of SRPX2 [33]. Zhu's research found that OTUB2 is significantly expressed in CRC tissues and is linked to a poor prognosis in patients. Functional experiments have shown that knocking down OTUB2 can weaken the stemness of CRC cells, enhance their sensitivity to oxaliplatin, inhibit EMT processes, and thus, reduce tumor metastatic ability. Mechanistic studies have shown that OTUB2, as a deubiquitinase, directly interacts with transcription factor SP1, inhibiting its K48 ubiquitination and stabilizing SP1 protein. SP1 further acts as a transcription regulator for GINS1, promoting its transcriptional activity and ultimately regulating the stemness, and antineoplastic drug refractoriness coupled with EMT dynamics in CRC [34].

The MJD family is mainly involved in the clearance of protein aggregates and degraded proteins. In CRC, there is limited research on the MJD family, but some preliminary studies suggest that it may function by regulating stress-related proteins [35]. For example, Chen, Y's research found that glucosidase I (GCS1) recruits the deubiquitinase USP10 to deubiquitinate GRP78, promoting its degradation and alleviating endoplasmic reticulum stress, thereby, promoting the progression of CRC [35]. The JAMMs family plays a role in DNA damage repair and signal transduction. For example, BRCC36 plays a key role in controlling cellular DNA damage response [36], though its specific mechanism in CRC is not yet clear. MINDYs is a newly discovered family of deubiquitinases that primarily recognize specific chain types of ubiquitin chains. In CRC, their potential functions and mechanisms still need further research.

Ubiquitination modification and protein homeostasis

One major post-translational modification of proteins that is crucial for preserving protein homeostasis is ubiquitination modification. Ubiquitination involves covalently linking ubiquitin molecules to lysine residues of target proteins, a process achieved via a three-step enzymatic cascade process. Ubiquitination regulates almost all aspects of eukaryotic organisms, from yeast to humans, expressing ubiquitinase catalyzed mechanisms for covalent modification of substrate proteins [37]. Ubiquitination has a significant impact on numerous biological processes, including cell signaling, protein degradation, DNA repair, cell cycle regulation, and immune responses. Ubiquitination is crucial for maintaining protein homeostasis by precisely regulating the integrity and amount of proteins. The diversity of ubiquitination sites and the extensive involvement of DUBs make the process complex, which plays diverse roles in the onset and progression of diseases [38]. The conservative, widespread and dynamic process of ubiquitin signaling involves the quick modification of protein substrates with ubiquitin, which can alter protein stability, function or location. For eliminating ubiquitin from various substrates, DUBs control this process by counteracting signals produced through ubiquitin conjugates and ligases [39]. In addition, the interaction between ubiquitination and SUMOylation, as well as their different associations in cancer, are also current research hotspots. By comparing the mechanisms of ubiquitination and SUMOylation and evaluating their interactions, we can better understand the similarities and differences between these two modifications in maintaining protein homeostasis [40].

The steady-state control of proteins linked to the onset and progression of CRC is directly affected by the ubiquitin proteasome system (UPs). It is made up of DUBs, the 26S proteasome, ubiquitin conjugating enzymes (E2), ubiquitin ligase enzymes (E3), ubiquitin activating enzyme (El) and the small

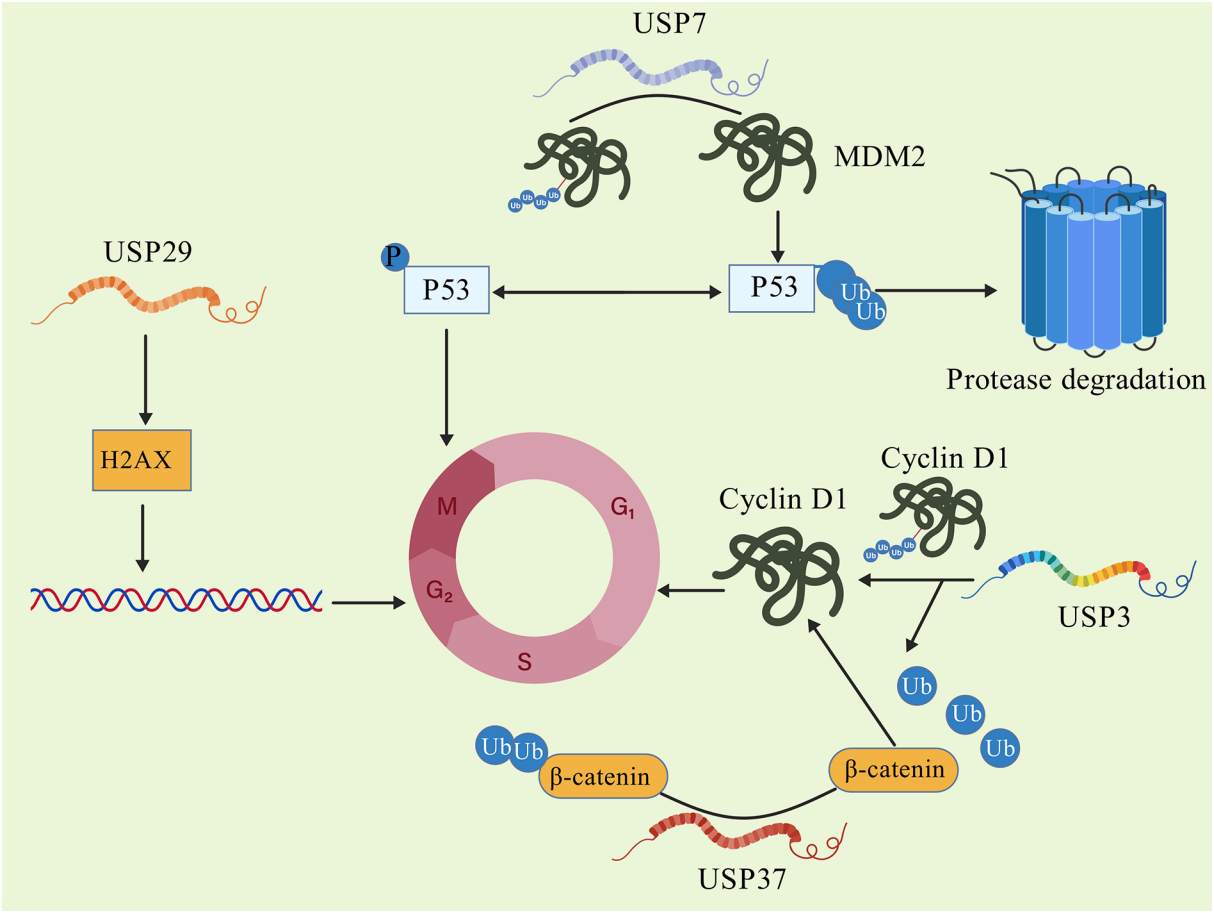

Figure 1. DUBs promote cell cycle progression.

molecule ubiquitin (Ub), which can control protein degradation and are key regulatory systems for protein function and stability [41]. Ub can covalently connect to the lysine residue's amino group of the receptor protein through its C-terminal glycine carboxyl group, a process involving enzymes E1, E2, and E3. E1 is activated by adenosylation of ATP at the C-terminus of protein Ub. The activated protein binds to E2 through a thioester bond, and finally E3 mediates the formation of an heteropeptide bond between the carboxyl terminus of protein Ub and the lysine of the substrate protein, completing the ubiquitination modification of the protein [42]. Through peptide/heteropeptide interactions, Ub's seven lysine residues (K6, K11, K27, K29, K33, K48, and K63) and N-terminal methionine residue (M1) can all form single, mixed, linear, or branching ubiquitin chains [43]. For instance, K63 connected ubiquitin chains primarily take part in processes like signal transduction and DNA repair, whereas K48 linked ubiquitin chains usually mark proteins for proteasomal breakdown [44]. In addition, the ubiquitin chain connected to K33 has been found to play a critical role in intracellular material transport. In addition, the diversity of ubiquitin chains is also reflected in their topological structure, including homogeneous (only one type of connection) and heterogeneous (multiple types of connections) chains, as well as linear and branched structures. This structural diversity enables ubiquitination modification to finely regulate various biological processes within cells [45]. Various ubiquitin chain types dictate the distinct outcomes of substrate proteins. Polyubiquitin chains connected through K48 and K11 are generally linked to proteasomal breakdown, whereas other kinds of polyubiquitin chains are implicated in autophagy, DNA damage response, and signal transduction [46].

Protein ubiquitination is a highly dynamic process. In contrast to the E1-E2-E3 ubiquitin ligase system, DUB can remove ubiquitins or polyubiquitin chains from the target proteins, thereby counteracting the ubiquitination process, and reversing protein fate and related physiological processes [47, 48]. The altered expression and activity of DUBs are closely related to cell cycle and immune regulation disorders, contributing to the initiation and advancement of CRC. The known DUBs in humans can currently be divided into 8 families. Understanding how these DUBs mediate cellular life activities can offer novel approaches for treating diseases such as CRC.

The mechanism of action of deubiquitinase in CRC

One of the worst malignancies is CRC. Its mortality and incidence rate have increased dramatically on a global scale in recent years. There is mounting evidence that DUBs are important in the development and incidence of CRC [49, 50]. DUBs directly or indirectly drive the initiation, progression, and metastasis of tumors by participating in and regulating a series of key cellular events, such as cell cycle dysregulation, dysregulation of signaling pathways, EMT, and activation of immune escape mechanisms. The following subsections provide a detailed description of the close association between cellular abnormal events related to DUBs in CRC.

Promoting cell cycle progression

The process of the cell cycle is a highly controlled process, divided into four stages: G1, S, G2, and M phases. The cell cycle is driven by regulatory mechanisms in the nucleus, which rely on the orderly activation of multiple cell cycle proteins (cyclins) and cyclin dependent kinases (CDKs) [51]. Cell cycle dysregulation is one of the main characteristics of cancers, including CRC. Abnormal activation of cell cycle-related proteins in cancer leads to uncontrolled cell proliferation, ultimately resulting in the development of tumors [52]. Various DUBS exhibit abnormal activity in CRC, promoting cell proliferation and inhibiting apoptosis by regulating the cell cycle progression, becoming an indispensable driving force for the occurrence and development of CRC (**Figure 1**).

USP1 is markedly increased in the tumors tissues of CRC patients, Xu X et al. found that knocking down USP1 increases the level of phosphorylated p53 in HCT116 cells, leading to increased expression of downstream target protein, cyclin dependent kinase inhibitor p21, ultimately resulting in cell cycle G/M arrest [53]. Montalto et al. found that cyclin D1 can regulate the progression from the G phase to the S phase of the cell cycle [54]. Notably, USP2 stabilizes cyclin D1 directly through deubiquitinase activity, and knocking down USP2 significantly reduces the half-life of cyclin D1 and inhibits cell proliferation in HCT116 cells [55]. Xu et al. found that USP5 is highly expressed in CRC where it directly deubiquitinates and upregulates the expression of Tu translation elongation factor (TUFM)., In turn, TUFM upregulates cyclin D1 and promotes cell proliferation. Knocking down USP5 can lead to HCT116 cell growth inhibition [56]. As a unique deubiquitinase targeting both p53 and Mdm2, the protease HAUSP plays a crucial role in the regulation of p53 and is an essential part of the p53/Mdm2 pathway. Another important regulator of the p53 pathway is USP7 which deubiquitinates and promotes the stability of the ubiquitin ligase MDM2. MDM2 raises p53 ubiquitination levels, causing its destruction and, resulting in cell cycle progression and aberrant tumor cell growth [57]. Dai X's study has shown that USP7 inhibitors increase the expression of programmed death ligand 1 (PD-L1) in tumors, reprogram tumor-associated macrophages, and effectively inhibit programmed death protein 1 (PD-1) to control immune response against tumors [58]. The Al Eidan study revealed the role of USP7 as a cell adhesion regulator in CRC, indicating that USP7 regulates cell adhesion through targeting AJUBA [19].

USP29 is overexpressed in tumor tissues of CRC patient. Chandrasekaran knocked out USP29 in HCT116 cells, leading to an increase in the amount of DNA damage marker, phosphorylated histone H2AX (yH2AX), triggering genomic integrity impairment via bicentenary lesions with mitotic phase arrest, thereby reducing cell proliferation ability [59]. In various cancers, cell cycle progression is accelerated, cell proliferation is enhanced, and the cell cycle transition from the G phase to the S phase is facilitated by dysregulation of CDK4 [60]. Tong et al. found that USP37 is upregulated in the tumor tissues of CRC patients. Knocking down USP37 in HCT116 and T84 cells results in a reduction of cyclin D1 levels. Furthermore, it was found that USP37 participates in regulating the cell cycle by stabilizing the level of B-junction protein and upregulating the expression of cyclin D1, thereby promoting cell proliferation and leading to CRC progression [61].

Impact on signal pathways

In recent years, the abnormal activation of DUBs in CRC and their impact on signaling pathways have become research hotspots. DUBs regulate protein stability and function through the removal of ubiquitin molecules from proteins, thereby affecting cellular processes including proliferation, apoptosis, and migration. In CRC, abnormal expression or activity of DUBs can lead to dysregulation of multiple signaling pathways, promoting the occurrence and development of tumors [62].

The occurrence of CRC is significantly influenced by Wnt/β-catenin signaling pathway. Zhu, W.'s research found that USP4 improves the stemness of CRC cells through activating the Wnt/β-catenin pathway and facilitating the nuclear localization of β-catenin by deubiquitination [34]. Abnormal Wnt signaling pathway is strongly associated with tumor development, and can be classified into classical pathway and non-classical pathway based on whether it depends on β-catenin or not. The classical pathway, also known as the Wnt/β-catenin pathway, involves the entry of β-catenin into the nucleus and the binding of transcription factor TCF/LEF to initiate downstream target gene transcription, participating in the regulation of cell proliferation. In addition, Sun H et al. found that USP11 stabilizes its expression by deubiquitinating protein phosphatase PPP1CA, thereby. activating the ERK/MAPK signaling pathway and promoting the growth and metastasis of CRC cells [63].

Non-classical pathways such as the Wnt/Ca^{2+} pathway mainly regulate cell polarity and migration. In CRC, various DUBs directly intervene or indirectly affect the stability of intracellular β-catenin and nuclear aggregation, causing aberrant Wnt/β-catenin signaling activation, which encourages the migration and proliferation of cancer cells [64] (**Figure 2**).

The impact of deubiquitinase on drug resistance

Chemotherapy resistance in CRC remains a major hurdle in clinical treatment, significantly reducing patient survival rates and treatment outcomes. In recent years, studies have found that DUBs, as important regulatory factors in the ubiquitin proteasome system, participate in the formation of chemotherapy resistance through various mechanisms and are essential for the survival and adaptability of cancer cells.

DUBs play a significant role in regulating cancer cells to evade chemotherapy induced cell death. Taking USP9X as an example, Schwickart M research found that it stabilizes the pro-survival protein Mcl-1 through ubiquitination, inhibits the apoptosis pathway caused by chemotherapy drugs, and enhances the chemotherapy tolerance of cancer cells. The stability of Mcl-1 is crucial for the survival of chemotherapy resistant cancer cells, which not only involves the direct effects of chemotherapy drugs, but is also closely related to the cancer cells' ability to adapt to endogenous stress [65]. Small molecule inhibitors targeting USP9X have shown significant anti-tumor effects in experimental models, indicating that targeting DUBs may become a new strategy to overcome drug resistance. Harris DR used homologous recombination technology to disrupt the USP9X gene and found that CRC cells lacking USP9X were more sensitive to the chemotherapy drug 5-fluorouracil (5-FU). Inhibiting USP9X may increase the effectiveness of chemotherapy, as it may contribute to CRC cells' resistance to it [66]. In addition, the Cao Y study found that tanshinone IIA inhibits the Akt/WEE1/CDK1 signaling pathway, leading to downregulation of survivin phosphorylation and disruption of the interaction between USP1 and survivin, thereby inhibiting tumor growth in CRC and overcoming chemotherapy resistance [67].

DUBs directly affect the accumulation and action of drugs in cells by regulating the stability of drug efflux related proteins, such as P-glycoprotein and chemotherapy drug targets. For example, USP14 has been found to regulate the expression level of P-glycoprotein through the ubiquitin proteasome pathway. Overexpression of USP14 can significantly increase the activity of P-glycoprotein, thereby expelling chemotherapy drugs to the extracellular space and reducing intracellular drug concentration [68]. In addition, some DUBs indirectly weaken the efficacy

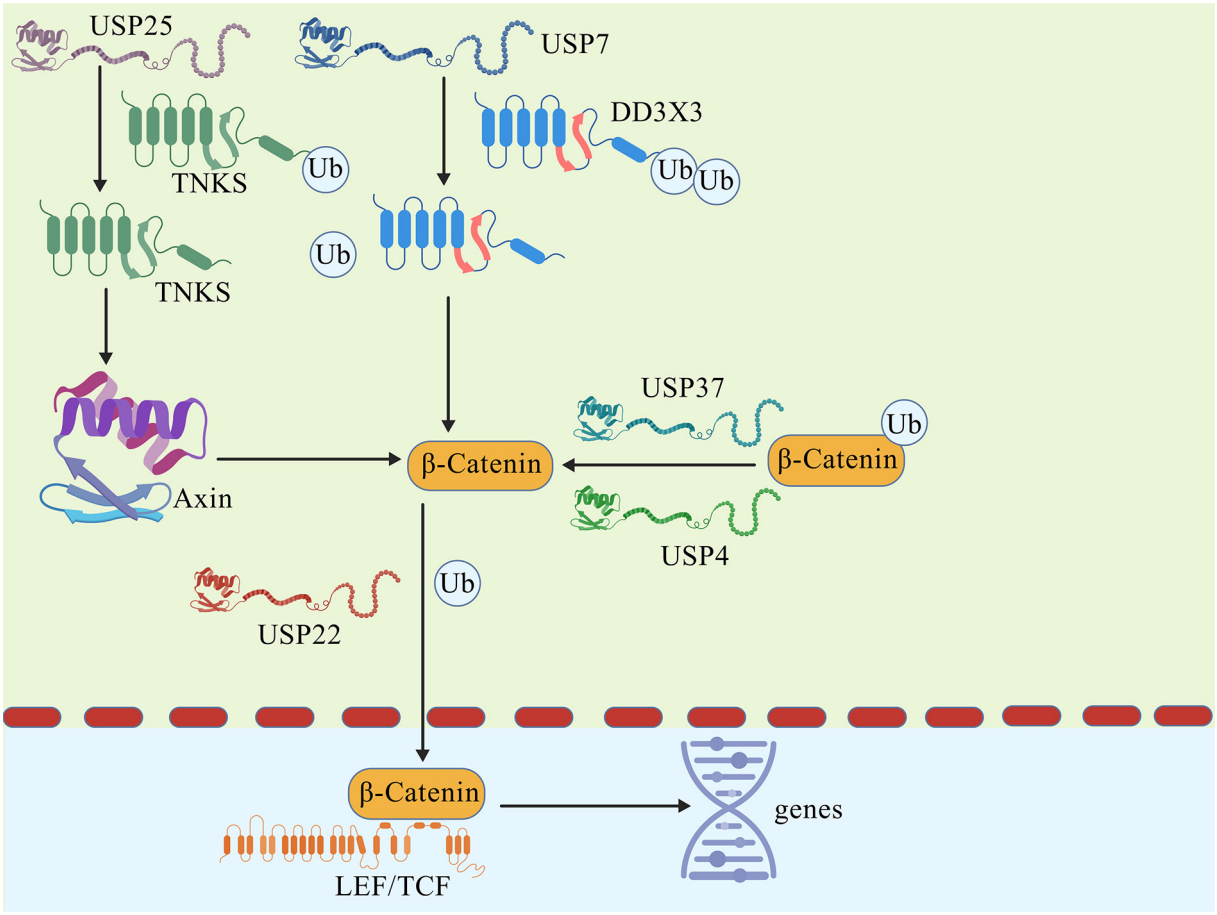

Figure 2. DUBs affect the quantity of β-catenin and the transcription of target genes.

of drugs by regulating the ubiquitination state of drug targets, enhancing their stability.

De ubiquitination and TME

The dynamic characteristics of TME have a pivotal role in various stages of tumor occurrence and development, among which DUBs profoundly affect the structure and function of TME by regulating the ubiquitination status of signaling molecules and metabolic pathways. Lately, there has been an increasing number of research reports revealing the specific mechanisms and potential therapeutic targets of DUBs in TME.

Chuang et al. highlighted the involvement of T lymphocytes in the pathophysiology and the advancement of CRC, along with the makeup of the tumor immune microenvironment in CRC, and also discussed the current T-cell related immunotherapy methods, emphasizing the importance of TME in CRC treatment [69]. On the other hand, Guo Xw analyzed the gene expression data of CRC, constructed the TME score (TMEscore), and divided the samples into different TME patterns. The results indicated that TMEscore was strongly correlated with clinical characteristics, prognosis, immune score, gene mutations, and immune checkpoint inhibitor response in patients. This indicates that TME features can be used to predict the prognosis and immune therapy response in CRC patients [70]. Wu et al. comprehensively characterized the TME of CRC, including the functional status, immune and stromal characteristics, and alterations in metabolic reprogramming of tumor cells. As a result, the study successfully classified CRC into four subtypes based on 61 TME related features. Comprehensive analysis showed that these subtypes have significant differences in histopathology, molecular characteristics, treatment efficacy, and prognosis [71].

Chronic inflammation in TME is an important driving factor for tumor development. Li B's study found that USP10 stabilizes the protein level of NLRP7 by deubiquitinating it, encouraging the growth and spread of CRC cells. In addition, NLRP7 overexpression is linked to tumor-promoting M2 macrophage polarization, revealing the important role of the USP10-NLRP7 axis in the CRC TME [14]. Wang XM's research shows that USP25 is crucial to colitis and bacterial infections, and its upregulation can promote the development of CRC. Inhibition of USP25 can enhance immune response, promote bacterial clearance and inflammation resolution, and weaken Wnt and SOCS3-pSTAT3 signaling, thereby inhibiting the occurrence of colon tumors [72]. Zhou Y's research found that USP4 is upregulated in microsatellite stable CRC and negatively regulates immune response against tumors. USP4 inhibits the nuclear localization of IRF3, suppresses interferon response and antigen presentation, and weakens pattern recognition receptor signaling-mediated cell death by deubiquitinating TRAF6 and IRF3. Knocking down USP4 can enhance T cell infiltration and overcome immune checkpoint blockade resistance [13].

Given the crucial role of DUBs in TME, the development of drugs targeting DUBs has become a potential direction for anti-tumor therapy. For example, USP7 inhibitor, P22077, and USP14 inhibitor, IU1, have shown the potential to inhibit TME pro-tumor function in multiple tumor models [73]. In addition, by combining DUBs targeting with inhibitors of other TME components, such

Table 1. The role of DUBs in colorectal cancer.

DUBs	Effect	References
USP1	Gene knockout increases the level of phosphorylated p53 and downregulates the levels of Cy cyclin Al, Dl, and El	[53]
USP2	Cell Cycle Protein D1 and PD-L1 Stabilization	[74]
USP9X	Stabilization of FBW7	[75]
USP29	Deletion activates the expression of y-H2AX	[59]
USP47	Promote EMT, Stabilize TCEA3 and regulate YAP protein stability	[74, 75]
UCHL1	Stabilize β-catenin directly	[76]
UCHL3	Promote EMT	[77]
OTUB1	Promote EMT	[78]
OTUB2	Inhibit PKM2 ubiquitination and promote glycolysis	[12]
PSMD14	Stabilize ALK2 and promote efflux of anticancer drugs	[79]
USP20	Directly stabilizing β- catenin protein and participating in immune regulation	[82, 83]
USP25	The increase in TNKS expression negatively regulates the level of Axin protein, thereby enhancing the accumulation of β - catenin	[84]

as, immune checkpoint inhibitors, the therapeutic effect may be further improved.

Discussions

DUBs are integral to the initiation and development of CRC through multiple mechanisms [53][74][75][12][59][76, 77][78][79][80][81][82, 83][84], including stabilizing key tumor associated proteins, regulating the immune microenvironment, and mediating chemotherapy resistance (**Table 1**). These findings provide new perspectives on molecular mechanisms and developing targeted treatments for CRC. Firstly, DUBs stabilize key proteins and regulate cell cycle and signaling pathways by removing ubiquitin chains. For example, USP7 enhances the growth and invasion of CRC cells by maintaining β-catenin stability and activating the Wnt/β-catenin signaling pathway. In addition, USP22 enhances cell cycle progression and tumor invasion ability by regulating the expression of c-Myc and cyclins [25]. These results indicate that abnormal expression or activation of specific DUBs is an important driving factor in the development of CRC.

TME plays a crucial role in the occurrence and development of CRC, and DUBs profoundly affect the function of TME by regulating immune-related signaling pathways. For example, USP4 weakens tumor immune response by inhibiting the nuclear localization of IRF3, leading to immune escape in CRC [13]. In addition, USP10 promotes polarization of tumor associated macrophages by stabilizing NLRP7, further exacerbating the invasion and metastasis of CRC [14]. These findings reveal the key role of DUBs in regulating TME immune escape, providing new ideas for targeting DUBs to improve anti-tumor immunotherapy.
Chemotherapy resistance is a significant obstacle in the treatment of CRC and DUBs play a central role in this process. For example, USP9X stabilizes the Mcl-1, an anti-apoptotic protein, inhibits chemotherapy induced apoptosis, and leads to chemotherapy resistance [65, 66]. In addition, USP14 regulates P-glycoprotein expression, promotes drug efflux, and significantly reduces intracellular chemotherapy drug concentration. These research findings suggest that targeting DUBs may be an effective strategy to overcome chemotherapy resistance.

At present, specific inhibitors targeting DUBs have shown significant anti-tumor potential in preclinical studies. For example, USP7 inhibitor P5091 and USP14 inhibitor IU1 showed good anti-tumor effects in the CRC model. However, these inhibitors still face challenges in terms of selectivity and pharmacokinetic properties. In addition, inhibition of DUBs may cause non-specific toxic side effects, limiting their clinical application. Therefore, future research needs to focus on improving the selectivity and safety of DUBs inhibitors, exploring the clinical feasibility of combination with immunotherapy or targeted therapy. Although the important role of DUBs in CRC has gradually been revealed, their molecular mechanisms and regulatory networks still need further in-depth research. Future research directions should include (1) revealing the specific functions of DUBs in different subtypes of CRC; (2) developing efficient and specific DUBs inhibitors, and evaluating their clinical efficacy; (3) exploring the combinationof DUBs with TME targeting and immunotherapy. In summary, DUBs have significant clinical application value as potential targets for CRC treatment. By conducting in-depth research on the mechanism of action of DUBs and optimizing targeted treatment strategies against DUBs, it is expected to provide more precise and efficient treatment plans for CRC patients.

Conclusion

In recent years, the key role of DUBs in the occurrence and development of CRC has gradually been revealed. DUBs affect the occurrence, development, and prognosis of CRC by regulating various mechanisms such as protein stability, cell cycle

progression, TME, and chemotherapy resistance. Specifically, DUBs such as USP7, USP10, USP22, etc. promote cancer cell proliferation, invasion, and metastasis by stabilizing key tumor associated proteins such as β-catenin, p53, and Mcl-1, activating multiple signaling pathways. In addition, DUBs further accelerate tumor progression in the immune microenvironment by regulating inflammatory responses, polarization of tumor associated macrophages, and immune escape pathways. Targeted inhibitors for DUBs, such as USP1 inhibitor ML323, USP7 inhibitor P5091, and USP14 inhibitor IU1, have shown certain therapeutic potential in CRC models, but issues such as insufficient selectivity and significant toxic side effects still need to be further addressed. Future research should focus on improving the specificity and safety of DUBs inhibitors, exploring their role in different molecular subtypes and their combination with immunotherapy and targeted drugs, providing more precise treatment strategies for CRC patients, and ultimately achieving the goal of improving clinical outcomes in CRC patients.

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Ethics approval

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Data availability

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Authors' contribution

Noor Al Shukri contributed to the conception, design, writing of this review article and figures drawing. Razik Bin Abdul Momin revised the review and submitted the final version of the manuscript.

Competing interests

The authors declare no competing interests.

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